Detection, Surveillance and Treatment of Pre-malignant Gastric Lesions related to *Helicobacter pylori* Infection

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Detectie, surveillance en behandeling van pre-maligne maagafwijkingen gerelateerd aan *Helicobacter pylori* infectie

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CHAPTER 1

Introduction and outline of the thesis

INTRODUCTION

Gastric cancer is the fourth most common cancer and second leading cause of cancer-related death worldwide. (1) The highest incidences are observed in Eastern Asia, Eastern Europe and South America, whereas the incidence in Western countries is much lower. For example, in Japan, the incidence of gastric cancer is approximately 44.1 cases/100 000 persons/year (world standardized rate, WSR). (1) In comparison, in the Netherlands, the incidence of gastric cancer is relatively low with approximately 6.9 cases/100 000 persons/year (WSR). (2) The incidence of gastric cancer is declining, in particular in Western countries. However, the absolute number of new cases per year increases, due to aging of the world population and expansion of the population in developing countries with a high gastric cancer incidence.

As symptoms are often absent or non-specific in patients with an early stage of disease, gastric cancer is usually diagnosed at an advanced stage. In advanced gastric cancer, curative options are frequently limited and in these cases only palliative treatment can be offered. During palliative treatment, most responses to chemotherapy are partial and of short duration, rendering a relatively small effect on survival. (3;4) Consequently, gastric cancer carries a poor prognosis, with an overall five-year survival rate of less than 20 percent. (2;5) In order to reduce its mortality, detection and intervention in an early stage are essential for gastric cancer prevention.

Gastric cancer is a heterogeneous disease with a complex pathogenesis. Proximal gastric carcinomas have probably a mixed etiology, partly related to the etiology of distal esophageal carcinomas and partly to the etiology of distal gastric cancer. (6;7) The vast majority of distal gastric malignancies are adenocarcinomas, which are commonly divided into intestinal type and diffuse (undifferentiated) type carcinomas. (8) Intestinal type gastric carcinomas account for at least 60 to 75 percent of cancers. (9;10)

In 1994, the International Agency for Research on Cancer classified *Helicobacter pylori* as a class I (definite) carcinogen, as *H. pylori* infection is considered an important trigger in the process of carcinogenesis of distal gastric cancer. (11) For the development of gastric cancer, the presence of *H. pylori* may even be a conditio sine qua non, as in more than 90% of gastric cancer patients current or past *H. pylori* colonization can be demonstrated. (12;13)

Infection with *H. pylori* results in chronic active gastritis, which persists lifelong in virtually all infected subjects. In a considerable number of subjects, this will eventually lead to loss of gastric glands and thus a reduction of gastric secretory function, commonly defined as atrophic gastritis. (14) Atrophic gastritis can subsequently progress to intestinal metaplasia and dysplasia. In intestinal metaplasia, gastric columnar epithelial cells are replaced by cells of intestinal morphology, whereas dysplasia is histologically characterized by a variation in size, shape, and orientation of epithelial cells and enlargement and atypia of nuclei. The hypothesis of a multi-step carcinogenic cascade of *H. pylori*-induced chronic active gastritis progressing through several pre-malignant stages, i.e. atrophic gastritis, intestinal metaplasia

and dysplasia, to eventually gastric cancer was originally proposed by Correa *et al.* and has later been supported by several prospective studies. (15-18) The progression of pre-malignant gastric lesions to gastric cancer generally takes decades and may thus provide a basis for cancer prevention by early intervention, in particular *H. pylori* eradication, and potentially also for early detection and treatment of advanced precursors and gastric carcinomas.

AIM

The general aim of this thesis is to explore the potential contribution of detection, surveillance and treatment of pre-malignant gastric lesions, i.e. atrophic gastritis, intestinal metaplasia and dysplasia, to the prevention of gastric cancer.

OUTLINE OF THE THESIS

Since symptoms are most frequently absent in patients with pre-malignant gastric lesions, epidemiology of these lesions is largely unknown, especially in regions with a relatively low incidence of gastric cancer. However, epidemiological data of pre-malignant gastric lesions are relevant as determinant in the evaluation of screening and surveillance practices. In this thesis, we therefore firstly aimed to evaluate the epidemiology of pre-malignant gastric lesions in the Netherlands (Chapter 3).

As gastric cancer incidence is low in Western countries, population-based screening for pre-malignant gastric lesions seems inappropriate. Therefore, a subpopulation at increased risk in comparison to the rest of the general population needs to be selected. As symptoms cannot predict the presence of pre-malignant gastric lesions, epidemiological risk factors need to identify this subpopulation. In Western countries, a possible risk factor may be migration from regions with a high *H. pylori* prevalence. Therefore, we investigated the prevalence of *H. pylori* infection and atrophic gastritis in a Dutch migrant population (Chapter 4).

In addition to the association of pre-malignant gastric lesions with subsequent development of gastric cancer, an association with other gastro-esophageal conditions has also been suggested in previous studies. Several studies claimed that pre-malignant gastric lesions in particular increased the risk for esophageal squamous cell carcinomas. In this thesis, we investigated the association between pre-malignant gastric lesions and the risk of esophageal squamous cell carcinomas (Chapter 5), and the risk of gastric cancer in patients with gastric MALT lymphomas (Chapter 6).

The need of endoscopic follow-up (surveillance) of patients after a diagnosis of pre-malignant gastric lesions is controversial. The most important reason for this controversy is that quantification of gastric cancer risk in these patients is unclear. In this thesis, we therefore

next assessed gastric cancer risk of patients with pre-malignant gastric lesions, and evaluated whether the current surveillance practice of patients with these pre-malignant gastric lesions matches their cancer risk (Chapter 8).

It can be assumed that only a minority of patients with atrophic gastritis and intestinal metaplasia will develop gastric cancer. Therefore, surveillance of these patients should preferably be limited to patients at high risk of gastric cancer. Previous studies have shown that the intragastric extent of intestinal metaplasia is an important indicator of gastric cancer risk. In this thesis, we therefore studied clinical characteristics, histological assessment of routine gastric biopsies, and serological markers as predictive parameters for extensive intestinal metaplasia at surveillance endoscopy (Chapter 9).

Although advanced endoscopic techniques may improve the detection of pre-malignant gastric lesions, current detection and surveillance in routine practice still relies on histological assessment of random biopsies, obtained during conventional endoscopy. However, the appropriate biopsy locations and number of biopsies, and the yield of random versus targeted biopsies are unclear. In order to determine the appropriate biopsy regimen for optimal detection of pre-malignant gastric lesions, we assessed the yield of endoscopic surveillance by standardized and targeted biopsy protocols in this thesis (Chapter 10).

With advancing insights into the pivotal role of *H. pylori* in gastric carcinogenesis, the prevention of gastric cancer by eradication of *H. pylori* seems increasingly important. A preventive effect of *H. pylori* eradication has been demonstrated in patients with *H. pylori*-induced chronic active gastritis, without pre-malignant gastric lesions. However, controversy remains whether eradication halts the progression or can even cause regression of pre-malignant gastric lesions. In this thesis, we evaluated the effect of *H. pylori* eradication in patients with pre-malignant gastric lesions in a systematic review of randomized controlled trials (Chapter 11) and a case report with long-term follow-up (Chapter 12).

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CHAPTER 2

Epidemiology of premalignant gastric lesions: implications for the development of screening and surveillance strategies

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ABSTRACT

Gastric cancer is one of the most common cancers worldwide; however, gastric cancer incidence varies greatly between different geographic areas. As gastric cancer is usually diagnosed at an advanced stage, the disease causes considerable morbidity and mortality. To detect gastric carcinomas at an early and curable stage, screening and surveillance seem necessary. Premalignant gastric lesions are well known risk factors for the development of intestinal type gastric adenocarcinomas. In a multistep cascade, chronic *Helicobacter pylori* –induced gastritis progresses through premalignant stages of atrophic gastritis, intestinal metaplasia and dysplasia, to eventually gastric cancer. Therefore, this cascade may provide a basis for early detection and treatment of gastric cancer. Epidemiology of gastric cancer and premalignant gastric lesions should guide the development of screening and surveillance strategies, as distinct approaches are required in countries with low and high gastric cancer incidences.

INTRODUCTION

The past 20 years have yielded an abundance of data and knowledge on the etiology of gastric cancer and its relation with *Helicobacter pylori* gastritis. The European Helicobacter Study Group has in its 20 years history greatly contributed to this understanding and aims to continue to do so in the coming decade, among others by repeated updates of the Maastricht guidelines on management of *H. pylori* infection, for example, as regards patients with gastric (pre)neoplastic lesions and their relatives (1). This is important because gastric cancer remains one of the most common forms of cancer worldwide with approximately 937,000 new cases per year, accounting for nearly 10% of all new cancers (2). In recent decades, the incidence of gastric cancer has declined rapidly in the Western world, but it remains high in many developing regions. As a result, the absolute annual number of new cases will undoubtedly increase, mainly because of the aging of the world population and the expansion of populations in developing countries with a high gastric cancer incidence.

The vast majority of gastric malignancies are adenocarcinomas, which are commonly divided into intestinal type and diffuse (undifferentiated) type carcinomas (3). Most gastric carcinomas are of the intestinal type. Both types of gastric adenocarcinoma are strongly associated with *H. pylori* infection. Colonization with this bacterium increases the risk of developing gastric cancer at least sixfold and is therefore considered an important carcinogenic trigger (4). Premalignant gastric lesions are well-known risk factors for the development of intestinal-type gastric adenocarcinomas. A multistep sequence of these recognizable precursor lesions generally precedes these tumors. In this cascade, *H. pylori* causes chronic inflammation of the gastric mucosa, which slowly progresses through the premalignant stages of atrophic gastritis, intestinal metaplasia and dysplasia to gastric adenocarcinoma (5). Estimates of progression rates of premalignant lesions are primarily based on historic cohort studies. Data from these studies generally suggest that among 100 *H. pylori* positive subjects, 50 will develop atrophic gastritis, 40 will develop intestinal metaplasia, eight will develop dysplasia, and one or two will eventually develop gastric cancer (6). Each of these subsequent steps in particular occurs in subjects who already have a previous lesion, and the risk of progression to the next step depends on the severity of the preexistent pathology, e.g. atrophic gastritis occurs mostly in subjects with more severe and diffuse chronic active gastritis, and intestinal metaplasia often in subjects with more severe and diffuse atrophic gastritis. Gastric cancer has a poor prognosis as it is usually diagnosed at an advanced stage. The progression of premalignant gastric lesions to gastric cancer generally takes decades and may thus provide a basis for early detection and treatment of gastric carcinomas, and furthermore potentially for cancer prevention by early intervention, such as *H. pylori* eradication.

Nationwide mass screening programs in Japan have resulted in the detection of more gastric carcinomas at an early stage. Several uncontrolled trials have suggested that cancer mortality has thereby been reduced (7–10), but nationwide data are lacking. In contrast to

these data from a country with a high gastric cancer incidence, an invasive mass-screening program in countries with a relatively low incidence of gastric cancer seems inappropriate, considering for instance the burden for the population, ethical objections, and costs. In these countries, a more targeted approach would be required to detect gastric cancer at an early and curable stage. In this approach, selection of a population sample from the general population that should be offered gastric cancer screening is needed. This selection should be based primarily on epidemiologic risk factors, as symptoms cannot predict the presence of premalignant lesions or early gastric cancer. In addition, serologic markers of the status of the gastric mucosa, such as pepsinogens I, II, and gastrin, for the identification of atrophic gastritis may be of great importance for population-based screening (11).

Apart from case finding, the necessity of reevaluation or surveillance of patients with premalignant gastric lesions is controversial (12–22). For the development of surveillance strategies, individuals with premalignant lesions at high risk of progression need to be identified, most likely based on epidemiologic factors and the severity and extent of the lesions.

However, premalignant gastric lesions presumably remain undetected in the majority of affected subjects. Therefore, epidemiologic observations of these lesions are scarce. In this review, we will provide an overview of current knowledge on the prevalence of premalignant gastric lesions and risk factors for the development and progression of these lesions. In addition, the implications of these epidemiologic observations for the development of screening and surveillance strategies will be described.

EPIDEMIOLOGY

The prevalence of premalignant gastric lesions shows considerable geographic differences and is clearly associated with the regional prevalence of *H. pylori* infection (23). Nonetheless, some reports describe regions with a low prevalence of gastric cancer and premalignant gastric lesions despite a high *H. pylori* infection rate (24). Therefore, other factors, including diet, *H. pylori* strain characteristics and host-immune response presumably also play a role in explaining the geographic variation in the prevalence of gastric cancer and its precursors.

The prevalence of premalignant gastric lesions has been investigated with both endoscopy and serologic markers. Reported prevalence rates vary widely, not only between populations but also within populations (25,26). These variations can probably be explained by a variety of factors such as the heterogeneity of selected populations, sample size, and variations in definitions of premalignant gastric lesions (27).

In the Western European population, *H. pylori* infection prevalence is approximately 30–40%. Atrophic gastritis is present in about 25–30% of *H. pylori* -infected individuals, and intestinal metaplasia in about 45% of *H. pylori* –infected individuals, whereas 5–10% of uninfected individuals are affected with these lesions (23,28,29). In Asia, the overall prevalence of

H. pylori infection is approximately 60% and is more often associated with pan-gastritis (30). Atrophic gastritis and intestinal metaplasia in these countries are thus also more common and present in a considerable proportion of *H. pylori* -positive subjects, compared to only 10% of uninfected individuals (31). Prevalence of dysplasia varies from 0.5 to 4% in Western populations and from 9 to 20% in high-risk areas for gastric carcinomas (26). Gastric cancer is more common in men than in women; however, differences in the prevalence of premalignant lesions by gender have rarely been observed (25,32).

The prevalence of premalignant gastric lesions increases with age, as has been demonstrated in several studies worldwide (23,33,34). Within a specific cohort, this is the result of progressive damage as a result of persistent *H. pylori* -induced gastritis. Furthermore, this increase with age is explained by a cohort phenomenon, as has been demonstrated by repeated cross-sectional investigations within the same population (35). This and other studies showed that the prevalence of chronic *H. pylori* -induced gastritis is lower in younger birth cohorts, whereas the prevalence of chronic *H. pylori* gastritis is stable over time within a specific birth cohort, as only a few adults become infected or spontaneously eradicate the infection (36). Thus, *H. pylori* infection rates in childhood can presumably predict the later incidence rates of premalignant lesions and gastric cancer within a specific birth cohort. This is supported by the observation that the decline in *H. pylori* prevalence over the past 20 years was accompanied by a steady decline in the prevalence of atrophic gastritis, intestinal metaplasia, and gastric dysplasia (37). This ongoing decline, both in men and in women, predicts that the gastric cancer incidence will further drop by at least 20–25% within a few decades without any specific intervention.

RELATION WITH *H. PYLORI* GASTRITIS

Infection with *H. pylori* results in persistent chronic gastritis lasting lifelong in virtually all infected subjects. In a considerable number of subjects, this will eventually lead to loss of gastric glands leading to atrophic gastritis. This is associated with a loss of specialized cells and thus a reduction of gastric secretory function (38). Atrophic gastritis can subsequently progress to intestinal metaplasia and dysplasia. In intestinal metaplasia, gastric columnar epithelial cells are replaced by cells of intestinal morphology, whereas dysplasia is histologically characterized by a variation in size, shape, and orientation of epithelial cells and enlargement and atypia of nuclei. The hypothesis of precursor lesions progressing to gastric cancer was originally proposed by Correa et al. and was later supported by several prospective analyses (5,23,39–42). This sequence explains the increased risk for gastric cancer in *H. pylori* -infected subjects, as has been shown in various cross-sectional and longitudinal studies (4,43).

The risk for progression of *H. pylori*-induced gastritis towards premalignant lesions and gastric cancer depends on the duration, distribution, and severity of chronic active *H. pylori*

gastritis. Prospective follow-up studies have shown that progression of *H. pylori* via premalignant lesions to gastric cancer takes several decades (23). A nested case-control study in a cohort of Japanese American men in Hawaii supported the concept that the earlier in life an individual becomes infected with *H. pylori* , the greater the probability that infection will progress to premalignant lesions and cancer (44).

In a Japanese cohort of 1526 patients, gastric cancers developed in 36 of 1246 *H. pylori* -positive patients as compared to none in the uninfected patients. In addition to the presence of severe atrophic gastritis and intestinal metaplasia at baseline, corpus-predominant gastritis was identified as an important risk factor for the development of intestinal-type gastric cancer (45). Similarly, patients with gastric ulcers, typically associated with atrophic gastritis and corpus-predominant gastritis, are at increased risk of gastric cancer, whereas patients with duodenal ulcers, commonly associated with few atrophic changes and antrum-predominant gastritis, are at low risk (46). It has been suggested that these differences in clinical outcome of *H. pylori* infection are caused by differences in local acid output between patients. Patients with increased acid output have antral-predominant gastritis, whereas patients with low acid output have widespread inflammation causing pan-gastritis (47). *H. pylori* –induced gastritis is most severe in zones between different types of gastric mucosa, in particular between the antrum and the corpus (48). The severity of gastritis determines the severity of mucosal damage, resulting in gastric pathology; therefore atrophy and intestinal metaplasia arise most often in this transitional zone. According to this transitional zone hypothesis, the border between different types of gastric glands will extend proximally with replacement of normal gastric mucosa as a result of inflammation (48). Therefore, the transitional zone between the antrum and the corpus moves upward in patients with low acid output and pan-gastritis. This continuous process predisposes to a further decrease in acid secretion as a result of the more proximal extension of inflammation, which further reinforces the process of proximal extension of inflammation associated with progressive gland loss.

The reversal of gastritis from antral-predominant to a corpus-predominant pan-gastritis in a low acid-producing stomach can also be induced by the use of profound acid suppressive medication (49). Increased corpus gastritis activity associated with long-term acid suppressive therapy can thus accelerate the development of atrophic gastritis in the corpus mucosa over a time frame of years. This hypothesis was supported by several longitudinal studies comparing cohorts of *H. pylori* -infected patients receiving or not receiving long-term acid suppression (50–52).

RISK FACTORS

H. pylori virulence

H. pylori strain variability plays an important role in determining the severity of gastritis and thus the risk for occurrence of clinically overt *H. pylori*-associated disease (53–55). Carriage of strains with the *cag* pathogenicity island (PAI), a large chromosomal region that encodes virulence genes, including the *cag* A gene, is associated with an increased risk of developing peptic ulcer disease as well as premalignant gastric lesions and gastric cancer (43,56). In Asian countries these associations are absent, as almost all *H. pylori* positive individuals carry *cag* A-positive strains (56–58). In addition, *vac* A- and *bab* A-positive *H. pylori* strains are also associated with an increased gastric cancer risk (59,60). A combination of different virulence genes adds to the risk of severe gastric inflammation, atrophic gastritis, and gastric adenocarcinoma (61).

Host genetics

Genetic susceptibility has also been shown to affect the risk of development of gastric cancer in the presence of *H. pylori* infection. Polymorphisms in a number of genes from the inflammatory cascade are involved, such as genes encoding cytokines IL-1, IL-10, IL-8, and TNF-α, each of which have been reported to affect the risk of gastric cancer in the presence of *H. pylori* (62–68). Functional polymorphisms in these genes affect the severity of the inflammatory process to *H. pylori*. For example, a significant association has recently been shown to exist between polymorphisms in the promoter region of the IL-8 gene and the development of dysplasia in a high-risk population (69). Future research studies will no doubt identify other genetic polymorphisms that increase the risk of premalignant gastric lesions.

Evidence from large epidemiologic studies shows a slight increase in the risk of gastric cancer in relatives of gastric cancer patients with intestinal-type carcinomas and a significantly increased risk of diffuse-type carcinoma (70). In addition, relatives of gastric cancer patients have an increased prevalence of premalignant gastric lesions in comparison to matched controls. To what extent this risk is independent from *H. pylori* infection status remains to be determined (71–73).

Environmental factors

Smoking has been associated with an increased risk of developing premalignant gastric lesions and gastric cancer (74). Among cigarette smokers the risk of developing intestinal metaplasia is increased fourfold compared to nonsmokers (33). In addition, cigarette smoking nearly doubles the risk of transition of intestinal metaplasia to dysplasia (75,76). A diet

high in nitrates, complex carbohydrates and salt, and low in fresh fruits and vegetables is also associated with an increased risk of premalignant gastric lesions (75,77,78). Moreover, alcohol use has been described as an independent risk factor for the progression of premalignant gastric lesions (79).

Interaction

As only approximately 50% of *H. pylori*-infected patients progress beyond chronic nonatrophic gastritis, the risk of premalignant lesions for each individual after infection is presumably determined to a large extent by a combination of the described factors previously mentioned (80). Indeed, interaction between *H. pylori* virulence, environmental, and host genetic factors has been described to strongly influence gastric cancer risk. For instance, in a case-control study the risk of gastric cancer increased from an odds ratio (OR) of 1.8 for the IL-1β-511T polymorphism in the human interleukin-1 beta (IL-1β) gene (IL-1β-511T) to an OR of 25 in *cag* A-positive/IL-1β-511T carriers, and an OR of 87 in *vac* As1-positive IL-1β-511T carriers (64,80). Similarly, an increased risk of development of dysplasia was described in Venezuelan subjects with a combined carriage of a *cag* A-positive *H. pylori* strain and a proinflammatory IL-8 genotype. The OR for the development of dysplasia was 1.34 and 2.0 in heterozygotic and homozygotic carriers of the IL8–251 A allele, respectively, as compared to the TT genotype. This was in particular true for subjects infected with a *cag* A-positive *H. pylori* strain, suggesting that the A-allele increased the risk of dysplasia only when *cag* A was present (69). This is in line with the concept that the host response to environmental triggers determines the susceptibility for progression of inflammation and the development of gastric adenocarcinomas. It seems that *H. pylori* in particular initiates the carcinogenic cascade and plays a role in the early progression of gastritis since development of atrophic gastritis and intestinal metaplasia is often associated with a decreased colonization density, and ultimately with a frequent loss of *H. pylori* colonization. This indicates that further progression of premalignant lesions is less dependent on *H. pylori* and more related to other environmental and host genetic factors.

DETECTION

Serology

Screening for *H. pylori* antibodies seems to be a suitable serologic test to noninvasively diagnose premalignant gastric lesions, given its central role in gastric carcinogenesis. However, the sensitivity of this test for the detection of (pre)malignant lesions is low, since the presence of *H. pylori* antibodies does not differentiate between chronic, nonatrophic gastritis and

(pre)malignant lesions. In addition, with longstanding, widespread atrophic gastritis or the presence of intestinal metaplasia, *H. pylori* colonization can disappear and therefore serology can ultimately become negative. Antibodies against specific, virulent strains of *H. pylori* containing *cag* A and *vac* A persist long after *H. pylori* eradication (81). Thus testing for these markers increases the sensitivity and specificity of *H. pylori* tests to detect (pre)malignant lesions (82). However, additional markers are needed for adequate diagnoses.

Serologic testing of pepsinogens I, II and gastrin provides valuable information on the status of the gastric mucosa. Pepsinogen I is produced by chief and mucous neck cells in the fundic glands, whereas pepsinogen II is produced throughout the whole stomach by mucous neck cells and also by cells in the pyloric glands and Brunner's glands. Gastric inflammation causes an increased release of both pepsinogens into the bloodstream, with a greater increase in pepsinogen II production in comparison to that of pepsinogen I. Atrophic gastritis causes a decreased production of both pepsinogens, with a more pronounced decrease in the production of pepsinogen I in comparison to that of pepsinogen II. As a result of these changes, chronic gastritis is associated with a reduced pepsinogen I/II ratio, and this ratio decreases even further when atrophic gastritis occurs (83). In addition, gastrin is synthesized and secreted almost solely from antral G-cells. *H. pylori* gastritis tends to raise the serum levels of gastrin, probably due to hyperplasia of the antral G-cells and also often due to an acid-suppressive effect of chronic gastritis when affecting the corpus mucosa. Increased production of gastrin also occurs in patients with atrophic gastritis in the corpus in response to reduced acid secretion, whereas in patients with antral-predominant atrophic gastritis the level of gastrin decreases (84). By using a combination of pepsinogens, gastrin levels and *H. pylori* serology, it is possible to establish the presence of gastritis, distinguish atrophic gastritis and locate atrophic changes with high sensitivity and specificity (85–87). In a prospective Japanese study a significantly higher risk of gastric cancer during follow-up was shown for patients with a pepsinogen status indicative of atrophic gastritis as compared to patients with normal pepsinogen levels (11). In this study, the gastric cancer risk was even higher in atrophic gastritis patients who were *H. pylori*-negative as compared to *H. pylori*-positive patients. As a result of this adequate predictive value, these tests have been implemented in gastric cancer screening in some regions in Japan. A Portuguese study reported high negative predictive values but low positive predictive values using pepsinogen and *H. pylori* antibody testing to diagnose extensive intestinal metaplasia and dysplasia in patients with previously diagnosed premalignant gastric lesions (88). Therefore, the value of these tests in high-risk populations in Western countries, i.e. during follow-up of patients with premalignant gastric lesions, seems limited to the exclusion of more advanced lesions, although further investigations are required.

Histology

Premalignant gastric lesions are often diagnosed on histologic examination of random biopsy samples. At present, the updated Sydney System is generally used both in clinical practice and research to grade gastritis (38). In this classification system several features of inflammation, atrophy and intestinal metaplasia are assessed separately and graded. Assessment of dysplasia is often difficult and interobserver agreement in grading dysplasia is poor. In addition, differences exist between Japanese and Western gastrointestinal pathologists concerning the classification of gastric dysplasia and cancer. Japanese pathologists diagnose cancer based on cellular and structural abnormalities, whereas Western pathologists focus on the presence of tissue invasion as a prerequisite for a diagnosis of cancer (27). In 2000, the unified Padova classification was proposed, which divided dysplasia and adenocarcinoma into 5 categories. The Vienna classification further subdivided the categories of low-grade dysplasia and high-grade dysplasia (89–91). It is unclear whether these renewed classifications improved the pre-existing lack of observer agreement for the diagnosis and grading of dysplasia.

Endoscopy

Although image quality of standard endoscopes has improved dramatically over the last decades, findings during conventional endoscopy still often correlate poorly with histologic diagnoses of premalignant gastric lesions (92–96). This is primarily due to the nonspecific macroscopic appearance of these lesions, but without a doubt the lack of experience in recognizing subtle macroscopic changes indicative of the presence of preneoplastic changes of the mucosa, and lack of attention during routine diagnostic endoscopy also contribute to the poor correlation between endoscopic and histologic findings. As a consequence, several alternative and supplementary strategies have been developed to overcome the limitations of standard endoscopic imaging. Magnification endoscopy has been shown to improve the correlation between the endoscopic findings and histology (97–102). Furthermore, several in-vivo staining techniques such as staining with methylene blue and indigo carmine, can be used as adjuncts to plain visualization of gastric mucosal lesions using conventional or magnifying endoscopy (103). In addition, several other endoscopic techniques have been suggested, including narrow band imaging and autofluorescence endoscopy, however, their value in the detection of premalignant gastric lesions has not yet been established (104,105).

SCREENING AND SURVEILLANCE

As suitable screening tests exist for (pre)malignant gastric lesions, effective screening seems feasible, although gastric cancer incidence, the burden for patients, costs and the availability of specific therapeutic interventions need to be taken into consideration (106).

As gastric cancer incidence varies largely between different geographic regions, development of uniform worldwide screening strategies seems inappropriate. In low incidence countries, a stepwise strategy with detailed selection criteria for screening is essential to meet all screening criteria, including cost-effectiveness (107). A high individual risk justifies invasive investigation by endoscopy, whereas in inhabitants of low-risk regions a more conservative approach is more appropriate and ethically acceptable. The initial selection of subjects for screening in low incidence countries should probably be based solely on epidemiologic factors, such as age, country of birth and socioeconomic class, as risk factors for *H. pylori* infection. Initial screening would consist of serologic testing with aforementioned specific gastric markers. A serologic diagnosis of atrophic gastritis, should be followed by endoscopy with histologic confirmation of the diagnosis. On the other hand, in high incidence countries, serologic and endoscopic screening could be offered to the general population, as has been common practice in Japan for several decades.

In addition, in countries with a high gastric cancer incidence, the cost of gastric cancer screening can be more easily balanced economically in relation to total expenditure on medical care compared to low incidence countries. Screening for gastric cancer by serology or endoscopy can potentially be cost-effective, however, the efficacy of early treatment needs to be established first (108–112).

H. pylori eradication therapy is frequently prescribed in patients with premalignant gastric lesions. In addition, adequate therapeutic options exist to treat severe dysplasia and early invasive cancers, since endoscopic alternatives to gastrectomy, such as endoscopic mucosal resection, have been developed over the past decades (113,114). Rokkas et al. provide a detailed overview of the influence of these treatment modalities on the progression of premalignant gastric lesions in another part of this issue. Clear conclusions on the efficacy to prevent gastric cancer of both *H. pylori* eradication and early endoscopic treatment in patients with premalignant gastric lesions are required to draw conclusions about the efficacy of gastric cancer screening (115).

Apart from screening, endoscopic surveillance of patients with premalignant lesions seems to be an important approach to reduce gastric cancer morbidity and mortality. It is surprising that clear guidelines are not available for the surveillance of patients with atrophic gastritis, intestinal metaplasia or gastric dysplasia, even more so since guidelines for surveillance of other gastrointestinal premalignant conditions have been widely developed, for instance for Barrett's esophagus or colonic adenomas. This is most likely due to the concept that preneoplastic gastric lesions are still associated with a low gastric cancer risk. However, this

concept is not supported by the published literature. Several studies have investigated the risk of malignant progression of premalignant lesions (107). The reported progression rates to gastric cancer vary between 0% and 2% per year for atrophic gastritis (22,116,117). For intestinal metaplasia and dysplasia, reported progression rates to gastric cancer vary greatly, from 0 to 10% per year for intestinal metaplasia and from 0 to 73% per year for dysplasia (22,116,118–120). These differences could be explained by geographic differences, variation in diagnostic criteria, or methodological flaws (107). Nevertheless, the gastric cancer risk seems very similar to the cancer risk of other preneoplastic lesions of the gastrointestinal tract for which follow-up guidelines have been widely introduced.

Follow-up guidelines are therefore needed to provide consistent management for patients with premalignant gastric lesions and to guide the clinician on how and when to perform surveillance endoscopies. In order to develop such guidelines, more research is needed to design the most optimal random biopsy schemes for the surveillance of premalignant gastric lesions. As previously mentioned, premalignant gastric lesions are most frequently localized in the antrum up into the transitional zone between the antrum and the corpus, with the exception of atrophic gastritis related to pernicious anemia which tends to be corpus-predominant. At present, the Sydney System recommends two biopsies from the corpus, two from the antrum and one from the incisura angularis during gastroscopy to classify and grade gastritis. However, this scheme is insufficient to reliably detect premalignant gastric lesions (121). As knowledge of the exact intragastric distribution of premalignant lesions should guide biopsy sampling during surveillance endoscopy, clarification of their distribution by further research is essential to develop tailored endoscopic guidelines for different geographic areas (26).

As only a minority of patients with premalignant lesions will eventually develop gastric cancer, selection of patients for surveillance based on sensitive progression markers seems attractive. In addition to the extent and severity of the lesions, a combination of *H. pylori* virulence factors and genetic polymorphisms of the host, as previously mentioned, may possibly identify high-risk subjects (11). These markers are probably only suited for the selection of subjects for screening in low incidence countries because high susceptibility markers are less discriminatory in populations at high risk of gastric cancer with a high proportion of individuals carrying the markers.

CONCLUSIONS

Early detection and treatment of gastric cancer are essential to improve survival. The cascade from *H. pylori* induced gastritis via premalignant stages to gastric cancer can provide the basis for gastric cancer prevention, especially in low incidence countries. The cancer risk associated with these premalignant lesions is often underestimated but, in fact, is very similar

to the cancer risk associated with other premalignant conditions of the gastrointestinal tract. Screening, surveillance and possible treatment of premalignant gastric conditions should therefore be carefully evaluated despite many limitations, such as the burden for patients and cost-effectiveness. To overcome these limitations, suitable screening and surveillance strategies should therefore be developed in relation to gastric cancer incidence in different geographic areas. At present, the lack of surveillance protocols leads to a lack of proper follow-up of patients once they are diagnosed with a preneoplastic condition of the stomach. The introduction of such guidelines, with adequate advice regarding follow-up intervals and endoscopic or serologic follow-up methods, would benefit these patients.

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CHAPTER 3

Epidemiological trends of pre-malignant gastric lesions: a long-term nationwide study in the Netherlands

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ABSTRACT

Background: The pre-malignant gastric lesions atrophic gastritis (AG), intestinal metaplasia (IM) and dysplasia (DYS) have long been identified as principal risk factors for gastric cancer.
Objective: To evaluate epidemiological time trends of pre-malignant gastric lesions in the Netherlands.
Methods: Patients with a first diagnosis of AG, IM or DYS between 1991 and 2005 were identified in the Dutch nationwide histopathology registry. The number of new diagnoses per year were evaluated relative to the total number of patients with a first gastric biopsy. Time trends were evaluated with age–period–cohort models using logistic regression analysis.
Results: In total, 23 278 patients were newly diagnosed with AG, 65 937 patients with IM, and 8517 patients with DYS. The incidence of AG declined similarly in men and women with 8.2% per year [95% CI 7.9% to 8.6%], and DYS with 8.1% per year [95% CI 7.5% to 8.6%]. The proportional number of new IM cases declined with 2.9% per year [95% CI 2.7% to 3.1%] in men and 2.4% [95% CI 2.2% to 2.6%] in women. With age–period–cohort models a cohort phenomenon was demonstrated for all categories of pre-malignant gastric lesions in men and in women with IM and DYS. Period phenomena with a larger decline in number of diagnoses after 1996 were also demonstrated for AG and IM.
Conclusions: The incidence of pre-malignant gastric lesions is declining. Period and cohort phenomena were demonstrated for diagnoses of AG and IM. These findings imply that a further decrease of at least 24% in the incidence of gastric cancer in the coming decade may be anticipated in Western countries without specific intervention.

INTRODUCTION

Gastric cancer represents the fourth most common cancer and second leading cause of cancer-related death worldwide. The estimated current incidence of gastric cancer is approximately 16.2/100 000 persons/year (world standardised rate, WSR), with highest incidences in Eastern Asia, Eastern Europe and South America. (1) For example, in Japan, the incidence of gastric cancer is approximately 44.1 cases/100 000 persons/year (WSR). In comparison, in the Netherlands, the incidence of gastric cancer is relatively low with approximately 6.9 cases/100 000 persons/year (WSR). (2) Although the incidence of gastric cancer has declined over the past decades, especially in Western countries, mortality remains high. As symptoms are frequently absent or only vague until the disease reaches an advanced stage, curative therapeutic options are usually limited at the time of diagnosis. (3)

The vast majority of gastric malignancies are adenocarcinomas, which can be divided into carcinomas of the intestinal and diffuse (undifferentiated) type. Intestinal type gastric carcinomas account for approximately 60% of cancers and are generally preceded by a sequence of precursor lesions. This multi-step model of gastric carcinogenesis is strongly associated with *Helicobacter pylori* colonisation; especially corpus-predominant *H. pylori*-induced gastritis has been identified as an important risk factor for gastric cancer development. (4) Chronic inflammation of the gastric mucosa can progress through the pre-malignant stages of atrophic gastritis, intestinal metaplasia and dysplasia to eventually gastric adenocarcinoma over a time frame of several years to decades. (5–8) The recognition of this long-term cascade may provide a basis for early detection, surveillance and treatment of advanced precursors and early gastric carcinomas and thereby improve survival.

The prevalence of *H. pylori* has declined significantly in Western countries during the past decades. (9) However, since symptoms are most frequently absent in patients with pre-malignant gastric lesions, epidemiology of these lesions is largely unknown, especially in regions with a relatively low incidence of gastric cancer. (10) Epidemiological data of pre-malignant gastric lesions are, however, relevant as an accurate predictor of gastric cancer incidence in the coming decade, and as determinant in the evaluation of screening and surveillance practices.

Therefore, the aim of the present study was to evaluate the incidence and time trends of atrophic gastritis, intestinal metaplasia and dysplasia in the Netherlands. As reliable incidence data are lacking, the prevalence of pre-malignant conditions as recorded in pathology reports was analysed alternatively.

METHODS

Histopathology database

In the Netherlands all histopathology and cytopathology reports are collected in a national archive (PALGA database), which has nationwide coverage since 1991. (11) Patients in this database are identified by date of birth, gender and the first four characters of their family name. Every record in the database contains a summary of a pathology report and diagnostic codes similar to the Systematized Nomenclature of Medicine (SNOMED) classification of the College of American Pathologists. (12) The diagnostic code contains a term indicating the anatomical location, type of sample, and a morphological term describing the finding, for example, "stomach*biopsy*intestinal metaplasia". Details about the number and intragastric location of biopsies and presence of *H. pylori* are not uniformly registered. After a report has been coded, it is submitted online to the central database. At present, the PALGA database contains 38 million records from approximately 10 million individuals. The present study was based on data recorded in the PALGA database between 1991 and 2005. The following items were made available for each report: gender, date of birth, date of pathology review, summary text and diagnostic code.

Incidence analysis

All patients with a histopathologically confirmed diagnosis of a pre-malignant gastric lesion were identified in the database. Pre-malignant gastric lesions were defined as atrophic gastritis, intestinal metaplasia or dysplasia. The SNOMED codes that were used to identify the lesions are described in the appendix. For each patient only the most severe pre-malignant lesion at baseline, that is, the first observation of a pre-malignant lesion, was evaluated. This means that patients with atrophic gastritis without a diagnosis of concomitant intestinal metaplasia were classified as having atrophic gastritis, patients with atrophic gastritis and intestinal metaplasia as intestinal metaplasia, and patients with gastric dysplasia as dysplasia.

Patients who had undergone gastric or oesophageal surgery, as far as could be determined from the database, or had been diagnosed with an oesophageal or gastric malignancy prior to or simultaneously with the first diagnosis of a pre-malignant gastric lesion were excluded from analysis.

In order to correct for possible changes in the frequency of upper gastrointestinal (GI) endoscopies with gastric biopsy sampling, rather than prevalence changes of pre-malignant gastric lesions, we also studied the trend in total number of patients with a first time biopsy of the stomach. The ratio of the number of new patients with a positive biopsy for pre-malignant gastric lesions to the number of new patients with a first time gastric biopsy was determined.

To evaluate the incidence of pre-malignant gastric lesions in different age classes, prevalence numbers in different periods were calculated within five-year age groups.

Statistical analysis

Age-standardised prevalence rates (WSR) of histopathologically confirmed pre-malignant lesions were calculated for the years 1991–2005. (13) Prevalence trends were evaluated with age–period–cohort models using logistic regression analysis. This analysis produces odds ratios (ORs) that quantify changes in time. Since these ORs (per year) are always close to 1.00 we present them as percentual annual changes (PAC). Calculations were corrected for age. In the age–period–cohort models, estimated drift parameters reproduce these PACs, which can be interpreted as linear period or cohort changes. For calculating non-linear period and cohort effects, linear splines were used. This means that to assess the presence of a period effect in the incidence of pre-malignant gastric lesions, the linear relationship between year and prevalence was replaced by a line consisting of three joined linear pieces, with knots at 1995 and 2000. For the estimation of cohort models a mean year of birth was calculated for each five-year age group and changes in prevalence were allowed to change in 1920, 1935, 1950 and 1965. Likelihood ratio tests (comparison of scaled deviances) showed whether significant non-linear period or cohort effects were present. (14, 15)

RESULTS

Between 1991 and 2005, 97 732 patients were newly diagnosed with a pre-malignant gastric lesion, with a 1:1 male:female ratio (Table 1). The study population consisted of 23 278 patients with a first diagnosis of atrophic gastritis as the most severe pre-malignant lesion at initial diagnosis, 65 937 patients with intestinal metaplasia and 8517 patients with gastric dysplasia. Significantly more women were present in the atrophic gastritis group (male:female 1.0:1.2) than in the group of patients with intestinal metaplasia (1.0:0.9) or dysplasia (1.0:0.8) ($p<0.001$). The median age at diagnosis was 65.7 years (10^{th}–90^{th} percentile 41.7–82.2 years); age at diagnosis was significantly higher with increasing severity of the categories of pre-

Table 1. Baseline characteristics.

	Total	Atrophic gastritis	Intestinal metaplasia	Dysplasia
Number of patients (n) (%)	97 732	23 278 (24%)	65 937 (67%)	8 517 (9%)
Male/ Female	1.0/ 1.0	1.0/ 1.2	1.0/ 0.9	1.0/ 0.8
Age				
median	65.7 yrs	60.8 yrs	66.5 yrs	69.2 yrs
10^{th}-90^{th} percentile	41.7 – 82.2 yrs	34.3 – 80.9 yrs	44.3 – 82.4 yrs	46.1 – 83.7 yrs

malignant gastric lesions (p<0.001). Within all categories of pre-malignant gastric lesions, female patients were significantly older than male patients (p<0.001).

Incidence

The number of patients with a first gastric biopsy increased by 3.7% per year over the study period, with a distinct maximum in 1998 (Figure 1). For all patients who were biopsied, the proportion of patients with a first time diagnosis of a pre-malignant gastric lesion, however, gradually declined (Figure 2). As expected, the proportion of patients with a diagnosis of a pre-malignant gastric lesion increased with age (Figure 3).

Figure 1. Number of patients with a first gastric biopsy during investigated period 1991-2005.

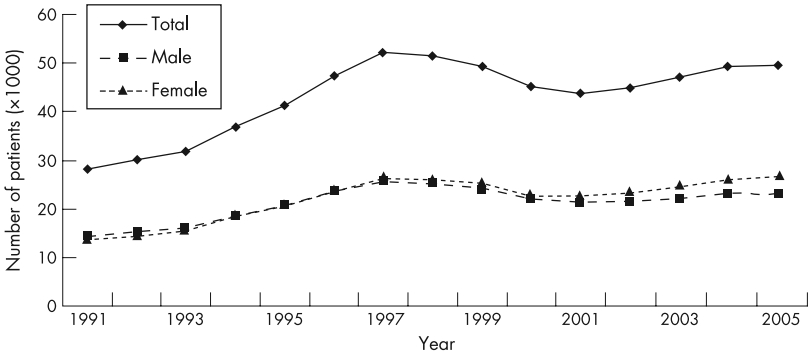
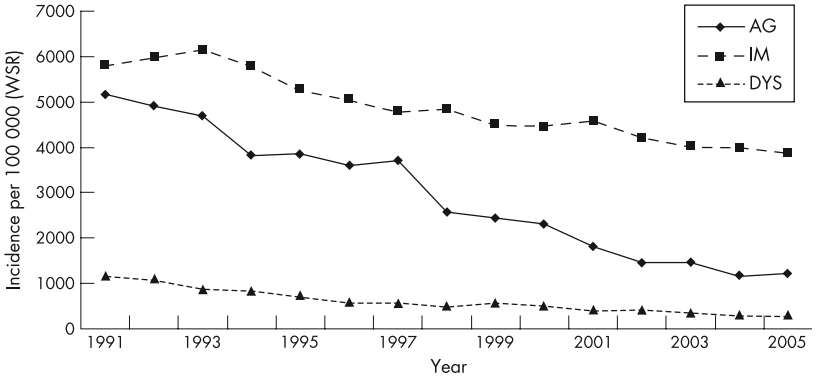
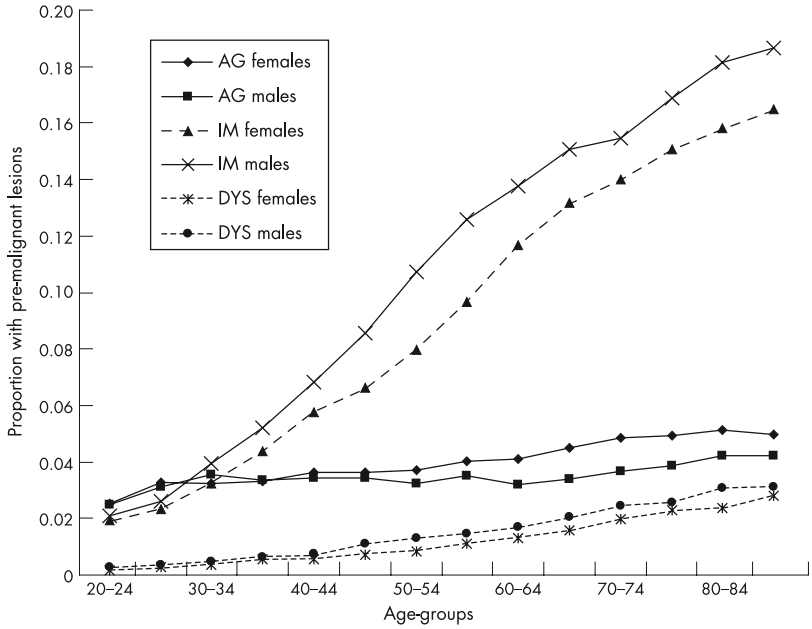


Figure 2. The prevalence of atrophic gastritis, intestinal metaplasia and dysplasia (WSR, world standardised rate) relative to total number of patients with a first gastric biopsy over time.



Legend: WSR: world standardised rate; AG: atrophic gastritis; IM: intestinal metaplasia; DYS: dysplasia

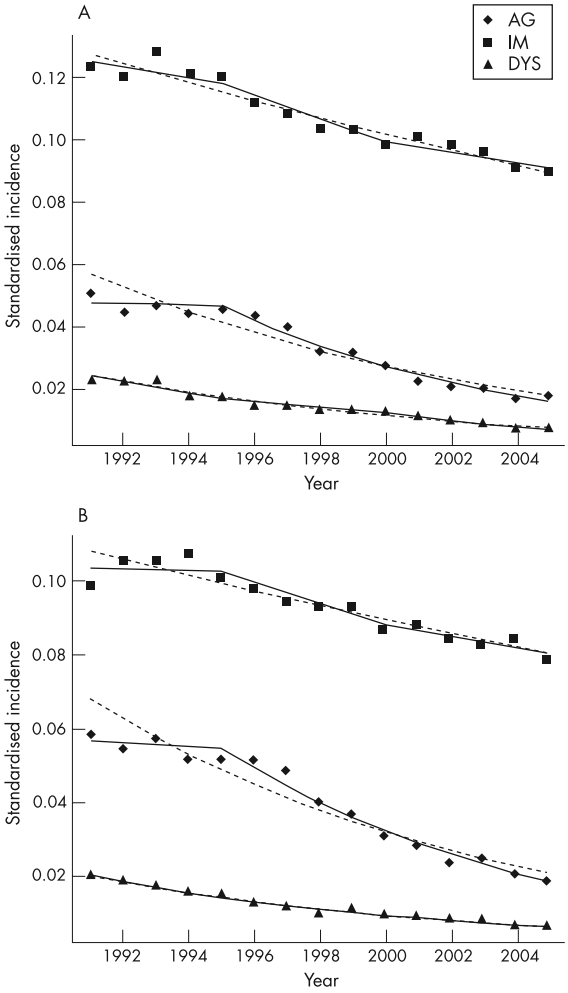
Figure 3. Proportion of patients with pre-malignant gastric lesions relative to total number of patients with a first gastric biopsy within 5-year age groups for total cohort and complete study period.



Legend: AG: atrophic gastritis; IM: intestinal metaplasia; DYS: dysplasia

The incidence of atrophic gastritis declined over the study period by 8.2% per year [95% CI 7.9% to 8.6%], and the incidence of gastric dysplasia declined by 8.1% per year [95% CI 7.5% to 8.6%]. These trends were similar for men and women (p values for differences were respectively 0.32 and 0.73). The decline in the number of diagnoses of intestinal metaplasia was 2.4% per year [95% CI 2.2% to 2.6%] for women and 2.9% per year [95% CI 2.7% to 3.1%] for men (p value for difference 0.02). Age–period–cohort analysis was used to further investigate these drift values, that is, to differentiate between a period and a cohort effect. Significant period effects were demonstrated for atrophic gastritis (p values for men and women <0.001) and intestinal metaplasia (p=0.03 for men, p<0.001 for women), but not for dysplasia (p=0.07 for men, p=0.93 for women). The period pattern showed an accelerating decline after 1996 for both atrophic gastritis and intestinal metaplasia (Figure 4). There were no apparent differences between men and women. In addition, the non-linear cohort effects for atrophic gastritis were significant for men (p<0.001), but not for women (p=0.22) (Figure 5). For men, the proportional decline increased over the whole period, except in the cohort born after 1965. However, the decline for women was almost linear. For intestinal metaplasia, the cohort effect for men was similar to the effect in men with atrophic gastritis, although less clear: the proportional annual change varied from –2% to almost –4% over the cohorts (p<0.001). In

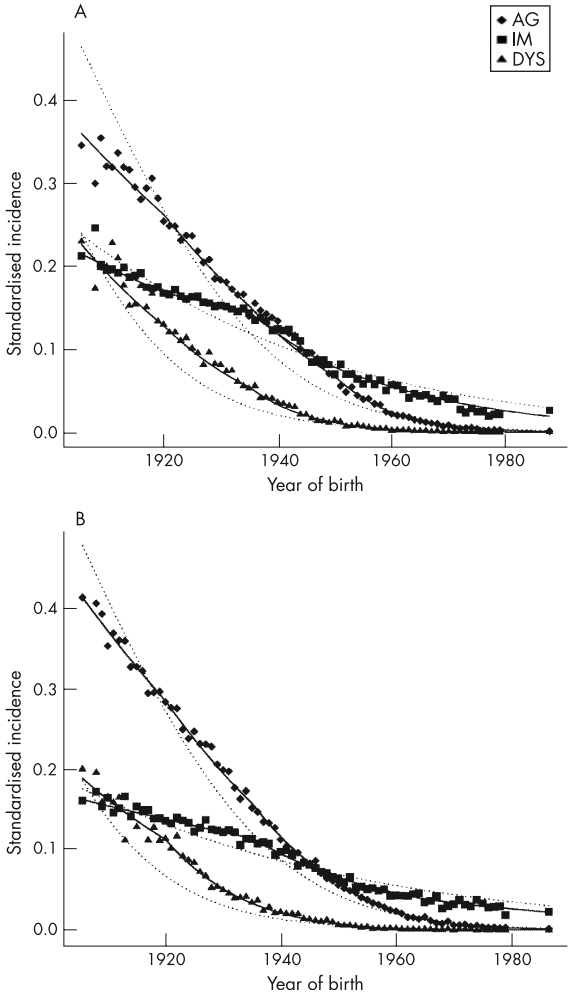
Figure 4. Period effects for pre-malignant gastric lesions for (A) male patients and (B) female patients. Symbols refer to age standardised prevalences, using the study population as standard. Lines are the linear splines from the age–period model; dotted lines show the results of the drift model, that is, the situation where there is a constant PAC over the whole range of years.



Legend: AG: atrophic gastritis; IM: intestinal metaplasia; DYS: dysplasia

women, the decline became less in the younger cohorts and was almost 0 in cohorts born after 1950 ($p<0.001$ for non-linear cohort effect). For dysplasia, men and women showed the same significant pattern again ($p<0.001$; $p=0.004$): a sharper decline for younger cohorts except the cohort born after 1965, possibly because the occurrence rates are low.

Figure 5. Cohort effects for pre-malignant gastric lesions for (A) male patients and (B) female patients. Symbols refer to age standardised prevalences, using the study population as standard. Lines are the linear splines from the age–cohort model; dotted lines show the results of the drift model, that is, the situation where there is a constant PAC over the whole range of birth years.



Legend: AG: atrophic gastritis; IM: intestinal metaplasia; DYS: dysplasia

DISCUSSION

This study shows that pre-malignant gastric lesions are frequently encountered in routine biopsies obtained during upper GI endoscopies in a Western population, especially in older people. Atrophic gastritis is the most common pre-malignant gastric condition, as it can be assumed that all subsequent stages have underlying atrophic changes of the gastric mucosa.

However, the incidence of these lesions has declined significantly over the past 15 years. The PAC increase in incidence in male patients was found to become stronger for men born after 1920. This matches the declining gastric cancer incidence in the Netherlands in the past 20 years and is thought first of all to be related to a decrease in the prevalence of *H. pylori* infection in younger cohorts. (16–18) In the Netherlands, the prevalence of *H. pylori* has declined from approximately 40% to 32% during the investigated period based on serological analyses of 918 and 1600 subjects in 1989 and 2006, respectively, in the age groups of 18 to 70 years. (19, 20)

Similar observations have been made in a Finnish study, which showed a parallel decrease in the age-related prevalence of atrophic gastritis, intestinal metaplasia and gastric cancer in the period from 1977 to 1992. (21) The decline in the incidence of all pre-malignant gastric lesions in our study is larger than the current decline of gastric cancer in the Netherlands, which was 2.13% [95% CI 1.83% to 2.43%] annually over the period 1991–2003. (3) Therefore, a more rapid decline of gastric cancer incidence may be anticipated within the next decades. Based on our findings, a decline of approximately 24% may be expected within the coming 10 years, which corresponds to a decreasing incidence from 6.9 to 5.2/100 000/year (WSR): this incidence is lower than the current incidence in any Western country. (1)

A cohort phenomenon for the prevalence of *H. pylori* has previously been demonstrated by analysing individual longitudinal data, which showed that the prevalence of chronic *H. pylori*-induced gastritis is much lower in younger birth cohorts and that *H. pylori* infection is rarely acquired after childhood. (9, 22) The presence of a similar cohort phenomenon in the incidence of pre-malignant gastric lesions confirms the central role of *H. pylori* in gastric carcinogenesis and gastric cancer cascade described by Correa. (7) Although gastric carcinogenesis is a complex and multifactorial process, *H. pylori* infection rates in childhood can presumably predict the occurrence rates of pre-malignant lesions later in life and possibly even gastric cancer in different birth cohorts.

A cohort effect was clearly demonstrated in this study for male patients. For female patients, a nearly linear decline was demonstrated for the diagnosis of atrophic gastritis, whereas for intestinal metaplasia a decline was almost absent in younger birth cohorts. These findings can probably not be explained by a difference in *H. pylori* prevalence differences between the sexes. Conversely, lifestyle factors, predominantly smoking, are the most probable explanation for these findings, as smoking seems an important factor in gastric carcinogenesis. (23–25) Gender differences in smoking habits in consecutive cohorts were previously observed in an observational Dutch study. This study demonstrated that the relative risk of lung cancer, as an indicator of smoking, is declining for men born after 1914. In contrast, the risk of lung cancer and smoking has steadily increased in women. (26)

In addition, we observed that pre-malignant gastric lesions were diagnosed at a significantly older age in female patients (Figure 3). These findings are in accordance with the male predominance in gastric cancer incidence and imply that female patients enter the

carcinogenic cascade at an older age. Similar observations have previously been made in patients with Barrett's oesophagus. (27) The most probable explanations for our findings are greater use of non-steroidal anti-inflammatory drugs and less smoking in absolute numbers in female patients, although an influence of other factors, such as sex hormones, cannot be excluded. (26)

Atrophic gastritis and intestinal metaplasia have traditionally been evaluated as one entity, in which intestinal metaplasia was considered evidence of atrophic gastritis since specialized glands had been replaced by intestinal crypts. (28–30) As the multistep cascade of gastric carcinogenesis has increasingly been recognised, intestinal metaplasia is now mostly evaluated as a separate entity in accordance with the updated Sydney system. In this study, we also assessed atrophic gastritis and intestinal metaplasia separately. This approach seems valid, as significant differences existed between both groups. For instance, patients with an initial diagnosis of intestinal metaplasia were significantly older than patients with atrophic gastritis ($p<0.001$). Nevertheless, as only the most severe diagnosis at baseline is evaluated in this study, the incidence of atrophic gastritis has probably been underestimated. For a true calculation of the incidence of atrophic gastritis, the numbers of atrophic gastritis, intestinal metaplasia and dysplasia may be added, as it can be assumed that all patients with intestinal metaplasia suffer from atrophic gastritis and similarly, dysplasia in intestinal metaplasia-negative patients can be considered an exception. These calculations result in a decline of 4.4% per year [95% CI 4.2% to 4.6%] for men and women with atrophic changes of the gastric mucosa, and a decline of 3.4% per year [95% CI 3.1% to 3.6%] for men and 2.9% per year [95% CI 2.7% to 3.2%] for women with intestinal metaplasia.

Potential weaknesses of our study are first that this study has been based on the number of histological diagnoses of pre-malignant lesions after upper GI endoscopy. Our findings could be influenced by altered indications for upper GI endoscopy over the past 15 years or by an altered attitude towards obtaining biopsies from macroscopic normal gastric mucosa, for example, increasing interest in diagnosing *H. pylori* for which biopsies from both antrum and corpus are at present commonly obtained. In case the total number of patients with a first gastric biopsy increases, a merely relative decline in the number of diagnoses of pre-malignant lesions could have been misinterpreted as a declining incidence of pre-malignant diagnoses in our study. However, the number of patients with a first gastric biopsy increased sharply before 1998, and thereafter a decline was followed by a slower incline until 2005 (Figure 1). This trend has previously been observed, and is most likely explained by the introduction of Dutch general practitioner guidelines on dyspepsia in 1993, with a revision in 1996, in which restrictions in referrals for upper GI endoscopy were advised. (31) This non-linear pattern was not observed in our period analysis of pre-malignant gastric lesions. Therefore, a true decline in the incidence of pre-malignant gastric lesions has been demonstrated in this study.

Second, changing trends in the assessment of gastric biopsies by pathologists could have attributed to the declining incidence of pre-neoplastic conditions of the stomach. The histo-

logical diagnosis and grading of pre-malignant gastric lesions have been subject of debate for years. At present, the updated Sydney system is most commonly used to grade gastritis. (32) In this classification system several features of inflammation, atrophy and intestinal metaplasia are being assessed individually. Grading of gastric dysplasia is now in particular performed by means of the (updated) Vienna classification. (33, 34) At present, dysplasia is commonly defined as intraepithelial or noninvasive neoplasia. We preferred to maintain the term dysplasia in this study, as this was the original diagnosis in our cases and was used as a search term, but it should be recognised that currently pathologists refer to these lesions as intraepithelial or non-invasive neoplasia. Although it has been shown that considerable differences between pathologists on diagnosing pre-malignant gastric lesions still exist, it can be speculated that the use of these specific grading classifications led to an increase in inter-observer agreement in more recent years. (35–38) Stricter criteria for assessment of dysplasia have been proposed recently, which in theory may have contributed to a decline in the number of new cases in recent years. (34, 39) Yet, it is unclear whether this truly had any effect on the observed declining incidence of dysplasia, as a clear period effect has not been demonstrated in this study. Furthermore, the fact that over the complete period of observation less than 10% of all patients diagnosed with pre-malignant abnormalities of their gastric mucosa were classified as having dysplasia supports the restrictive use of this diagnosis over the whole time period.

On the other hand, the declining incidence of atrophic gastritis and intestinal metaplasia partly results from a period effect. This study showed an accelerating decline after 1996 for these diagnoses. This finding can in part be related to changing histological definitions, in particular with respect to atrophic gastritis in relation to the introduction of the updated Sydney system around 1996. (32) However, as such an effect is less likely for intestinal metaplasia as a relatively straightforward diagnosis not affected by changing histological definitions, other effects must also have played a role. This can in part have been due to the widespread introduction of *H. pylori* diagnosis and treatment starting in the early 1990s.

Moreover, it is plausible that indications for upper GI endoscopy, for example, symptoms, led to a specific selection of the general population in this study. Therefore, these data are only suited to studying prevalence trends within patients with an indication for upper GI endoscopy. However, as differences in prevalence between our population and the general population are presumably small, it can be assumed that trend, period and cohort patterns observed here do reflect incidence patterns in general. To evaluate prevalence in the general Dutch population a prospective endoscopic population based study would be necessary. However, this study design would evidently be time-consuming and costly. Possibly, serological markers can serve as an alternative for this purpose when evaluating atrophic gastritis, however, its value in diagnosing intestinal metaplasia and dysplasia is still unclear. (40)

Unfortunately, we could not evaluate the number of biopsies and intragastric distribution of pre-malignant lesions in this study. For instance, it would be interesting to evaluate whether

extension has decreased in subsequent periods and whether this extension progresses with age. At present, the Sydney system recommends two biopsies from the corpus, two from the antrum and one from the incisura angularis during gastroscopy to classify and grade gastritis. However, for the purpose of evaluation of pre-malignant lesions a more extensive biopsy scheme may be required. As knowledge of the exact intragastric distribution of pre-malignant lesions should guide biopsy sampling during surveillance endoscopy, future research should be focused on clarification of the extension and distribution of pre-malignant gastric lesions.

In conclusion, the incidence of pre-malignant gastric lesions is declining in countries with a low gastric cancer incidence within subsequent birth cohorts, probably caused by a declining incidence of *H. pylori* infections. Therefore, a considerable further decline in gastric cancer incidence of at least 24% in the coming decade may be anticipated in these countries and this will occur without any specific intervention.

APPENDIX

SNOMED-like codes used in the analysis:

Atrophic gastritis: M58000, M58001, M58010.

Intestinal metaplasia: M73000, M73200, M73320, M73321, M73300.

Dysplasia: M74000, M74006, M74007, M74008, M74009.

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CHAPTER 4

Migrant communities constitute a possible target population for primary prevention of *Helicobacter pylori*-related complications in low incidence countries

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ABSTRACT

Objective: Pre-selection of individuals with epidemiological risk factors for *Helicobacter pylori* infection and atrophic gastritis could increase the efficiency of serologic screening to prevent peptic ulcer disease and gastric cancer in Western countries. The aim of this study was to determine the prevalence of and risk factors for *H. pylori* infection and atrophic gastritis in a migrant community in The Netherlands.

Material and methods: Inhabitants from an urban district in Rotterdam, The Netherlands with a large proportion of immigrants were randomly selected. Information was collected on demographic factors, socioeconomic status, lifestyle, history of dyspeptic symptoms and medication use. In addition, serologic *H. pylori* and CagA status and the presence of atrophic gastritis were evaluated

Results: In total, 288 subjects were included. Surinamese or Antillean, Turkish, Cape Verdian and Moroccan subjects were *H. pylori*-infected in 65%, 82%, 86% and 96% of cases, respectively, whereas the infection rate in Dutch subjects was 46% (all $p<0.05$). Within multivariate logistic regression analysis, ethnicity and number of persons in a household were identified as independent risk factors for *H. pylori* infection. In addition, mean pepsinogen I level and pepsinogen I/II ratio were significantly lower in subjects of non-Dutch origin as compared to Dutch subjects (both $p<0.001$). No Dutch subjects suffered from atrophic gastritis, as compared with 12 subjects of non-Dutch origin ($p=0.13$).

Conclusions: The prevalence of *H. pylori* is high in migrant populations in The Netherlands. Furthermore, markers of atrophic gastritis are increased in subjects of foreign origin. Therefore, these migrant communities may constitute a target group for serologic screening to prevent *H. pylori*-related complications in Western countries.

INTRODUCTION

Helicobacter pylori infection is an important risk factor for the development of peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer. The findings of recent studies suggest that *H. pylori* may even be a strong prerequisite for the development of gastric cancer (1). Moreover, *H. pylori* eradication seems to prevent gastric cancer in subjects with chronic *H. pylori*-induced gastritis who have not yet developed the precancerous conditions of atrophic gastritis and intestinal metaplasia (2). Therefore, early *H. pylori* detection and eradication are considered to be important targets for the prevention of associated diseases (3-5).

Yet, the prevalence of *H. pylori* is decreasing in most Western countries, especially in younger birth cohorts (6,7). In parallel, the incidence of *H. pylori*-associated diseases is also decreasing. For instance, an incidence shift from mostly *H. pylori*-associated duodenal ulcers towards predominantly non-steroidal anti-inflammatory drugs (NSAIDs)-associated gastric ulcers has been observed (8,9). In addition, a decrease in the incidence of premalignant gastric lesions in the past 15 years indicates that gastric cancer incidence will most likely decline further in the next few decades (10). The need for prevention of *H. pylori*-associated diseases in Western countries on a population basis thus becomes less significant and treatment on an individual basis is the current widespread approach. Nevertheless, morbidity and mortality of these *H. pylori*-associated diseases still remain considerable and therefore a primary preventive strategy may be valuable, even in low incidence countries (8,9,11). In these countries, stepwise identification of individuals at increased risk of *H. pylori*-associated diseases seems essential to detect gastric cancer at an early and curable stage and to prevent the development of peptic ulcer disease (3). Some small subpopulations have been identified in the past, for instance, a high prevalence of *H. pylori* among inhabitants and long-term employees of institutes for the intellectually disabled has been reported, but other subgroups are less clear (12).

The combination of serum pepsinogen levels and *H. pylori* antibodies is used in population-based serologic screening for *H. pylori* infection and atrophic gastritis in countries with a high gastric cancer incidence, such as Japan (13,14). However, a screening strategy of this kind would be costly and inefficient in most Western countries with currently low prevalences of *H. pylori* (15). Therefore, identification of individuals at high risk of *H. pylori* infection and atrophic changes of the gastric mucosa based on epidemiological criteria may be an adequate pre-selection strategy for serologic screening programs.

As the prevalence of *H. pylori* infection varies among different countries, and infection seems to be mainly acquired in early childhood, immigrants from countries with a high prevalence of *H. pylori* may constitute a high-risk population for *H. pylori* infection in developed countries (6,16,17). However, there is a scarcity of prevalence data on *H. pylori* infection and atrophic gastritis from population-based studies in this potential risk group.

The aim of the present epidemiological study was to determine the actual prevalence and risk factors of *H. pylori* infection and atrophic gastritis in a migrant community in The Netherlands, i.e. ethnicity, environmental setting and socio-demographic factors, in order to identify a possible target group for preventive strategies in Western countries.

MATERIAL AND METHODS

Study population

A balanced sample of 1787 subjects was drawn from the civil registration system in a district with a large proportion of immigrants in Rotterdam, The Netherlands (Oud-Charlois). The district is in an old part of the city, with predominantly 19th- and early 20th-century housing and around 13,000 inhabitants. This sample was drawn in order to gain insight into the prevalence and feasibility of screening for several infectious diseases in the general population such as hepatitis A, B and C and *H. pylori* infection. Subjects of Dutch, Surinamese, Turkish, Moroccan, Antillean or Cape Verdian origin and aged from 18 to 65 years were included in the sample. To obtain groups of comparable size, non-Dutch subjects were oversampled in anticipation of a lower response in these groups. Subjects were recruited from April 2004 to December 2005 by letter and invited to take part in an interview and subsequently a blood sample was obtained. All subjects provided written informed consent and the study was approved by the Institutional Review Board of the Erasmus MC Rotterdam.

Interview

Subjects were interviewed in their native language by trained interviewers. Information was collected on demographic factors (age, gender and ethnicity), socio-economic status (educational level, occupational status), lifestyle (smoking habits, alcohol consumption), history of dyspeptic symptoms and peptic ulcer and medication use (e.g. anti-dyspeptic agents).

Serologic data

To determine *H. pylori* and CagA status, and pepsinogen levels, a blood sample was obtained from all subjects. Serologic testing for *H. pylori* and CagA status and pepsinogen I and II levels was performed using commercial ELISA tests (Orion Diagnostica, Ravo Diagnostica, and Bio-Hit). Based on the manufacturer's recommendation, an IgG antibody index of ≥20 U/ml was considered to be *H. pylori* positive. Atrophic gastritis was defined as either pepsinogen I <70 µg/L in combination with a pepsinogen I/II ratio <3.0, or pepsinogen I <28 µg/L (18,19).

Statistical analysis

To generalize *H. pylori* and atrophic gastritis prevalence numbers within this study sample to the district population, reverse probability weighting was used, based on gender and ethnicity distribution in the district population. X^2 tests and t-tests were used to compare categorical and continuous characteristics, respectively. Comparisons between more than two groups were corrected with the Bonferroni test. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated by logistic regression. A two-sided p-value of less than 0.05 was considered statistically significant.

RESULTS

In total, 1787 persons were identified and invited by letter to participate; 288 (16%) subjects responded to the letter and were included in the study (Table I). Non-response was significantly more common in men than in women (p=0.006) and in subjects younger than 45 years (p<0.001).

In total, 55 (19%) subjects of Dutch origin were included, 107 (37%) of Surinamese or Antillean origin, 62 (22%) of Turkish origin, 50 (17%) of Moroccan and 14 (5%) of Cape Verdian origin (Table I). The mean age of the study population was 39.4 years (range 19-65 years), subjects of Dutch origin were significantly older (mean age 43.6 years) in comparison to subjects of Surinamese or Antillean origin (36.8 years) (p=0.008).

Table I. Baseline characteristics and *H. pylori* status.

	Total study population n=288	*H. pylori* positive n=206	*H. pylori* negative n=82	p-value
Mean age (years) (range)	39.4 (19-65)	40.0 (19-65)	38.3 (20-65)	0.30
Sex				
- Male	123	89 (72%)	34 (28%)	0.90
- Female	165	117 (71%)	48 (29%)	
Ethnicity				
- Dutch	55	25 (46%)	30 (55%)	<0.001
- non-Dutch:	233	181 (78%)	52 (22%)	
o Surinamese, Antillean/Aruba	107	70 (65%)	37 (35%)	
o Turkish	62	51 (82%)	11 (18%)	
o Moroccan	50	48 (96%)	2 (4%)	
o Cape Verdian	14	12 (86%)	2 (14%)	

H. pylori infection

Two hundred and six (72%) subjects tested *H. pylori* positive; the infection rate was not significantly different between men and women (p=0.90). The weighted overall prevalence of *H. pylori* in this migrant community was 57% (95% CI, 51-63%). Subjects of Surinamese or Antillean, Turkish, Moroccan and Cape Verdian origin were infected in, respectively, 65%,

Table II. Evaluation of risk factors for *H. pylori* infection.

	H. pylori positive n/N	%	OR univariate	95% CI	OR multivariate	95% CI
Gender						
- Male	89/123	72%	1.0		-	-
- Female	117/165	71%	0.93	0.55-1.56		
Age						
- <30 years	51/75	68%	1.0		-	-
- 31-40 years	59/87	68%	0.99	0.51-1.92		
- 41-50 years	50/67	75%	1.38	0.67-2.88		
- 51-65 years	46/59	78%	1.67	0.76-3.65		
Ethnicity						
- Dutch	25/55	45%	1.0		1.0	
- Surinamese, Antillean/ Aruba	70/107	65%	2.27	1.17-4.41	2.08	1.05-4.11
- Moroccan	48/50	96%	28.80	6.36-130.47	21.85	4.69-101.86
- Turkish	51/62	82%	5.56	2.40-12.89	4.35	1.80-10.53
- Cape Verdian	12/14	86%	7.20	1.47-35.25	7.39	1.47-37.10
Residence childhood (main residence during first 10 years)						
- The Netherlands	44/81	54%	1.0		-	-
- Other	119/154	77%	2.86	1.61-5.09		
Educational level						
- Low (primary school)	112/144	78%	1.0		-	-
- Middle (high school)	76/110	69%	0.64	0.36-1.12		
- High (college/ university)	12/26	46%	0.25	0.10-0.58		
Number of persons in household						
- 1-2	85/134	63%	1.0		1.0	
- 3-4	68/97	70%	1.35	0.77-2.36	0.90	0.49-1.67
- ≥5	52/56	93%	7.49	2.56-21.98	4.01	1.30-12.39
Number of siblings						
- ≤1	28/49	57%	1.0		-	-
- 2-3	51/72	71%	1.82	0.85-3.90		
- 4-6	63/88	72%	1.89	0.91-3.93		
- ≥7	61/76	80%	3.05	1.37-6.78		

OR= odds ratio; CI= confidence interval

82%, 96% and 86% of cases, whereas the infection rate in subjects of Dutch origin was 46% (all p<0.05) (Table I). In total, 120 (44%) patients tested CagA positive. Overall, infection with a CagA-positive *H. pylori* strain was more common in Surinamese or Antillean (48%), Turkish (52%), Moroccan (42%) and Cape Verdian subjects (54%) as compared to Dutch subjects (25%) (p=0.009, resp. p=0.004, p=0.09 and p=0.09). However, within the subgroup of *H. pylori*-infected subjects, no significant differences in CagA status were observed either between native Dutch subjects and immigrants, or between specific ethnic groups (p=0.38, resp. p=0.24).

Within univariate logistic regression analysis, non-Dutch ethnicity (OR 4.18, 95% CI 2.26-7.72), foreign residence in childhood (OR 2.86, 95% CI, 1.61-5.09), educational level (high educational level OR 0.25, 95% CI, 0.10-0.58) and crowding reflected by the number of persons in the household (≥5 persons, OR 7.49, 95% CI, 2.56-21.98) were significantly associated with *H. pylori* status (Table II). Within multivariate analysis, non-Dutch ethnicity and high number of persons in the household were identified as independent risk factors for *H. pylori* infection (Table II).

Atrophic gastritis

Mean pepsinogen I level was 118.4 µg/L (SD 55.9) in subjects of Dutch origin as compared to 91.1 µg/L (SD 42.3) in subjects of non-Dutch origin (p<0.001), specifically 90.3 µg/L (SD 41.7) in Surinamese or Antillean subjects, 97.0 µg/L (SD 48.3) in Turkish subjects, 85.5 µg/L (SD 38.0) in Moroccan subjects and 91.9 µg/L (SD 34.0) in Cape Verdian subjects (p=0.002, resp. p=0.12, p=0.003 and p=0.52) (Table III). Mean pepsinogen I/II ratio was 11.7 (SD 4.7) in Dutch subjects as compared to 9.1 (SD 4.5) in subjects of non-Dutch origin (p<0.001), i.e. 10.3 (SD 5.1) in Surinamese or Antillean subjects, 8.0 (SD 3.4) in Turkish subjects, 8.2 (SD 3.9) in Moroccan subjects and 8.6 (SD 3.2) in Cape Verdian subjects (p=0.60, resp. p<0.001, p=0.001 and p=0.21).

Table III. Pepsinogen levels.

	Pepsinogen I (mean)	Pepsinogen I/ II ratio (mean)	Atrophic gastritis* (n)
Ethnicity			
- Dutch	118.4 µg/L	11.7	0/54 (0%)
- non-Dutch	91.1 µg/L	9.1	12/233 (5.2%)
o Surinamese, Antillean/ Aruba	90.3 µg/L	10.3	5/107 (4.7%)
o Moroccan	85.5 µg/L	8.2	4/50 (8.0%)
o Turkish	97.0 µg/L	8.0	3/62 (4.8%)
o Cape Verdian	91.9 µg/L	8.6	0/14 (0%)
Age			
- <40 years	90.6 µg/L	9.8	6/162 (3.7%)
- >40 years	103.6 µg/L	11.3	6/125 (4.8%)

* Atrophic gastritis: pepsinogen I< 70 µg/L and pepsinogen I/II ratio<3.0, or pepsinogen I <28 µg/L.

Overall, serologic evidence of atrophic gastritis was present in 12 subjects (4.2%). The weighted prevalence of atrophic gastritis in the total study population was 2.0% (95% CI, 0.3-3.6%). The prevalence of atrophic gastritis was 3.7% in subjects younger than 40 years as compared to 4.8% in subjects older than 40 years (p=0.77). No subjects of Dutch origin suffered from atrophic gastritis, as compared to 12 (5.2%) of the immigrant population (p=0.13) (mean age 38.9; SD 11.0), specifically 5 (4.7%) subjects of Surinamese or Antillean origin, 3 (4.8%) subjects of Turkish origin and 4 (8.0%) subjects of Moroccan origin (p=0.17, resp. p=0.25 and p=0.05) (Table III).

Dyspeptic complaints

One or more dyspeptic symptoms were present in 131 (46%) of the subjects, but no significant differences existed between *H. pylori*-positive and *H. pylori*-negative subjects with respect to the prevalence of these symptoms (p=0.36) and the nature of these complaints (all p>0.05) (Table IV). The overall prevalence of dyspeptic complaints was not significantly different between ethnic groups (p= 0.24). However, Turkish and Moroccan subjects reported significantly more upper abdominal pain as compared with Dutch subjects (p=0.03, resp. p=0.03).

Seventy (24%) of the interviewed subjects used anti-dyspeptic agents on prescription during the 12 months prior to the interview, but there were no significant differences between different ethnic groups (p=0.11). Thirty-eight (13%) subjects had a previous history of peptic ulcer disease, 79% of whom tested positive for *H. pylori* infection.

Table IV. Dyspeptic symptoms.

	Total study population n=283*	*H. pylori* positive n=202	*H. pylori* negative n=81	p-value
Abdominal discomfort (one or more symptoms)	131 (46%)	90 (45%)	41 (51%)	0.36
- Upper abdominal pain	82 (29%)	54 (27%)	28 (35%)	0.25
- Heartburn	87 (31%)	63 (31%)	24 (30%)	0.89
- Nausea	63 (22%)	45 (22%)	18 (22%)	1.00
- Vomiting after meal	23 (8%)	16 (8%)	7 (9%)	0.81

* missing data from 5 patients

DISCUSSION

This study clearly shows a high *H. pylori* infection rate in a migrant community in a population-based sample in The Netherlands. Strikingly even among autochthonous inhabitants of this multiethnic district, the *H. pylori* infection rate is high, especially in case of crowding.

Moreover, significantly more infections with CagA-positive *H. pylori* strains and serological evidence of atrophic gastritis were observed in subjects of foreign origin.

Although a relatively small number of subjects were included in this study, it adds to the existing knowledge as these epidemiological findings resemble the actual prevalence of *H. pylori* in a Western multiethnic population. The response rate in this study was only 16%, therefore there may have been a selection bias. Given the general aim of this study to evaluate the prevalence and feasibility of screening for several infectious diseases, it is unlikely that (non-) participation in the study was directly associated with the exposure to *H. pylori* or dyspeptic symptoms and therefore this is probably not a systematic error. However, selection of particularly patients with concerns about their health for various reasons cannot be excluded, as well as selection of subjects who were not receiving medical care elsewhere. As the response rate in subjects younger than 45 years was low, our results are mainly representative of *H. pylori* status and prevalence of atrophic gastritis in first-generation immigrants. Multiethnic populations are common; cities like Rotterdam and many others in Western countries have a 40-60% immigrant population. A high *H. pylori* infection rate in immigrants in Western countries has previously been described and this observation has been confirmed in this unselected population (20-22). The vast majority of immigrants included in our study were born abroad and migrated to The Netherlands at varying ages, yet mostly after the age of 10 years (Table II). Studies evaluating second-generation migrants showed lower *H. pylori* infection rates (23). This suggests that migration after childhood does not strongly affect infection rate and confirms the common idea that *H. pylori* infection is mainly acquired during childhood.

To the best of our knowledge, a significant lower level of pepsinogens in immigrants has not been described previously. Although our study population is too small and too young for significant differences to be detected in the actual prevalence of atrophic gastritis, we can assume that a significant lower level of pepsinogens at a relatively young age indicates a higher risk of development of atrophic gastritis in later life (24).

The *H. pylori* prevalence in autochthonous subjects in our study is higher than that previously demonstrated in other Dutch epidemiological studies, in which a prevalence of approximately 30% was observed in healthy blood donors (20,25). The most likely explanation for this dissimilar observation is the clustering of inhabitants of lower socio-economic class in multiethnic districts, as reflected in this study by the large number of persons per household. Low socio-economic status and crowded living conditions during childhood have previously been described as important risk factors for *H. pylori* infection (22,26-28). This finding confirms that not only immigration from a country with a high prevalence of *H. pylori* infection, but also socio-economic class can be used as epidemiological risk factors for the identification of high-risk individuals in the development of screening strategies.

To confirm the importance of prevention of *H. pylori*-related complications in migrant communities in Western countries, an increased risk of gastric cancer and peptic ulcer dis-

ease in this subpopulation needs to be established prior to the development of screening strategies. In fact, a significantly increased risk of gastric cancer has been demonstrated for immigrants from the Antilles, Aruba, Japan and Turkey to Western countries (29-33). Gastric cancer risk is highest in persons born abroad, where especially the first two decades of life seem to determine cancer risk, and seem principally to concern distal gastric cancer (29,33). The difference in risk of gastric cancer between first- and second-generation immigrants suggests an important aetiologic role of environmental factors, i.e. *H. pylori* infection, smoking and dietary habits. Yet, an increased risk of gastric cancer in autochthonous inhabitants of multiethnic districts has not been established.

We did not observe any correlation between dyspeptic symptoms and *H. pylori* infection; this observation is in accordance with previous findings (34-36). Selection for *H. pylori* screening on the basis of symptoms therefore seems inappropriate, which underlines the need for the identification of a high-risk population for *H. pylori*-associated diseases. In addition, nearly 80% of subjects who reported a history of peptic ulcer disease tested positive for *H. pylori* infection. This finding emphasizes the need for monitoring *H. pylori* status in this population.

Where serologic screening for *H. pylori* and CagA antibodies and pepsinogens is used, subsequent endoscopic follow-up of patients with serologic proof of atrophic gastritis should be carried out. In this way, a stepwise screening approach can be developed in which the use of increasingly invasive procedures is proportional to gastric cancer risk. Still, the cost-effectiveness of this approach in the prevention of *H. pylori*-related diseases requires further investigation.

In conclusion, migrant communities constitute a possible target group for serologic screening to prevent *H. pylori*-related complications in countries with an overall low incidence of these diseases. More research is needed to specify the most suitable epidemiological selection criteria and screening strategy to prevent *H. pylori*-associated diseases.

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CHAPTER 5

Increased risk of squamous cell carcinoma of the esophagus in patients with gastric atrophy: independent of the severity of atrophic changes

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ABSTRACT

An association between gastric atrophy and esophageal squamous cell carcinomas (ESCC) has been described. However, the mechanism of this association is unknown. In this study, we aimed to examine this relation in a cohort of patients with varying grades of gastric atrophy to increase the understanding about the causality of the association. Patients diagnosed with gastric atrophy between 1991 and 2005 were identified in the Dutch nationwide histopathology registry (PALGA). The incidence of ESCC and, presumably unrelated, small cell lung carcinomas (SCLC) observed in these patients was compared with that in the general Dutch population. Relative risks and 95% confidence intervals were calculated by a Poisson model. At baseline histological examination, 97 728 patients were diagnosed with gastric atrophy, of whom 23 278 with atrophic gastritis, 65 934 with intestinal metaplasia, and 8516 with dysplasia. During follow-up, 126 patients were diagnosed with ESCC and 263 with SCLC (overall rates 0.19, respectively 0.39/ 1000 person years at risk). Compared with the general Dutch population, patients with gastric atrophy ran a relative risk of developing ESCC of 2.2 [95% CI 1.8-2.6], and of SCLC of 1.8 [95% CI 1.6-2.1]. The risk of ESCC did not increase with increasing severity of gastric atrophy (p=0.90). In conclusion, this study found an association between gastric atrophy and both ESCC and SCLC, but the risk of ESCC did not increase with the severity of gastric atrophy. Therefore, a causal relationship seems unlikely. Confounding factors, such as smoking, may explain both associations.

INTRODUCTION

Chronic *Helicobacter pylori* infection has been widely accepted as predisposing condition for a number of gastric and duodenal disorders, such as peptic ulcer disease, MALT lymphoma, and gastric cancer. (1) However, over the past years, interest has been directed towards the potential role of *H. pylori* infection in the etiology of esophageal diseases. (2) This new focus has emerged from epidemiological studies demonstrating a negative association between *H. pylori* infection and gastro-esophageal reflux disease (GERD), and its related complications, in particular Barrett's esophagus and esophageal adenocarcinoma. (3-6)

In addition, recent studies have demonstrated an elevated risk of esophageal squamous cell carcinomas (ESCC) in patients with atrophic changes of the gastric mucosa. (3;7-10) A hypothesis explaining this unexpected association is, however, lacking. (11) Confounding by joint risk factors such as lifestyle, was not observed in case-control studies, thus suggesting a direct causal relationship between both conditions. (3;9) A causal relation would strengthen the importance of *H. pylori* eradication in the prevention of upper gastro-intestinal malignancies. In case causality exists, the magnitude of the association would be expected to increase with the severity of gastric atrophy. On the other hand, were the association between gastric atrophy and ESCC based on confounding by shared risk factors, similar associations would be expected between gastric atrophy and other carcinomas with the same risk factors. An obvious candidate shared risk factor for the development of both gastric atrophy and ESCC is smoking. (12-14)

In order to examine the existence of a causal relationship between ESCC and gastric atrophy, we investigated the correlation between the severity of gastric atrophy and risk of ESCC within a large cohort of patients with varying histological stages of gastric atrophy, i.e. atrophic gastritis, intestinal metaplasia and dysplasia. The cascade from chronic *H. pylori* gastritis via atrophic gastritis, intestinal metaplasia, dysplasia towards gastric cancer has been widely accepted. (15) In line with this cascade, patients with intestinal metaplasia or dysplasia have been demonstrated to suffer from more extensive atrophic changes of the gastric epithelium as compared to patients with only atrophic gastritis. (16) In addition, we also investigated the risk of small cell lung carcinoma (SCLC) in the same study cohort, as this tumor is anatomically unrelated to the gastric and esophageal conditions and is known to be strongly associated with smoking. (17)

MATERIAL AND METHODS

Histopathology database

All histo- and cyto-pathology reports in the Netherlands are collected in a national archive (PALGA database), which since 1991 has had nationwide coverage. (18) Patients in this database are identified by date of birth, gender and the first four characters of their family name. Every record in the database contains a summary of a pathology report and diagnostic codes similar to the Systematized Nomenclature of Medicine (SNOMED) classification of the College of American Pathologists. (19) The diagnostic code contains a term indicating the anatomical location, type of sample, and a morphological term describing the finding, e.g. 'stomach*biopsy*intestinal metaplasia'. Details with regard to the number and intragastric location of biopsies and presence of *H. pylori* are not uniformly registered. After a report has been coded, it is submitted online to the central database. The present study was based on data recorded in the PALGA database between 1991 and 2006. The following items were made available for each report: gender, date of birth, date of pathology review, summary text and diagnostic code.

Patient selection

All patients with a first histologically confirmed diagnosis of gastric atrophy, i.e. atrophic gastritis, intestinal metaplasia and dysplasia, between 1991 and 2005 were identified in the database which had complete nationwide coverage since 1991. The most severe stage of gastric atrophy at baseline was evaluated as initial diagnosis. This meant that patients with atrophic gastritis without a diagnosis of concomitant intestinal metaplasia were classified as having atrophic gastritis, patients with atrophic gastritis and intestinal metaplasia as intestinal metaplasia, and patients with gastric dysplasia as dysplasia.

As far as could be determined from the database, all patients who had undergone gastric or esophageal surgery, or had been diagnosed with an esophageal or gastric malignancy prior to, or simultaneously with the first diagnosis of a pre-malignant gastric lesion, were excluded from analysis.

Statistical analysis

The incidences of ESCC and SCLC in the cohort of patients with gastric atrophy were calculated on the basis of the total number of ESCC and SCLC registered in the PALGA database within the cohort in relation to the number of person-years at risk. The relative risk of ESCC and SCLC in patients with pre-malignant lesions of the gastric mucosa was then calculated by comparing these incidences with those for ESCC and SCLC within the general Dutch

population from 1991 until 2006. Unless an autopsy had been performed, the date of death of patients registered in the PALGA database is not recorded. Therefore, censoring because of death was imputed to evaluate the number of person-years at risk for all patients that did not develop esophageal or gastric cancer during follow-up, using survival data from the general Dutch population. (Dutch Cancer Registry, personal communication, October 2007) The incidence of ESCC and SCLC in the general Dutch population were calculated on the basis of the total number of ESCC and SCLC registered in the PALGA database and the midyear Dutch population. (20) As less than 1% of all ESCC within the general Dutch population occur in patients aged below 40 years, relative risks were only calculated for patients aged over 40 years. (21) The size of and incidence within the general Dutch population was corrected for the number of and incidence of ESCC and SCLC within patients with gastric atrophy. To explore the presence of selection bias, ESCC risk was calculated for the first year of follow-up, between one year to four years follow-up and after more than four years follow-up after the initial diagnosis of gastric atrophy. The relative risks and 95% confidence intervals (CIs) were calculated by a Poisson model, corrected for age categories, gender and calendar year. Comparisons of relative risks between different groups were also calculated with the Poisson model.

RESULTS

The study cohort consisted of 97 728 patients (49 739 men/ 47 989 women) with a first histological diagnosis of gastric atrophy registered between 1991 and 2005. It comprised atrophic gastritis in 23 278 (24%) patients, intestinal metaplasia in 65 934 (67%) patients, and dysplasia in 8516 (9%) patients (Table 1). Overall, mean age at diagnosis was 63.5 years (SD 15.6). Data on the incidence of gastric atrophy over the study period have been published previously. (22)

Table 1. Baseline characteristics of our study cohort with gastric atrophy.

	Total cohort	Atrophic gastritis	Intestinal metaplasia	Dysplasia
Number of patients (n) (%)	97 728	23 278 (24%)	65 934 (67%)	8 516 (9%)
Male/ Female (%)	49 739/ 47 989 (51%/ 49%)	10 527/ 12 751 (45%/ 55%)	34 573/ 31 361 (52%/ 48%)	4 639/ 3 877 (54%/ 46%)
Age (years) (mean) 25^{th}-75^{th} percentile	63.5 53.2- 75.5	59.2 46.6- 73.4	64.7 55.0- 75.9	66.7 57.3- 77.6

Esophageal squamous cell carcinomas

Between 1991 and 2006, ESCC was diagnosed in 126 patients (77 men/ 49 women) from the cohort at a mean age of 68.7 years (SD 11.3). The rate of developing ESCC was 0.19/ 1000 person years at risk in patients older than 40 years.

For all patients with gastric atrophy, the long-term relative risk (RR) of ESCC was 1.98 [95% CI 1.58-2.48] in male patients and 2.52 [95% CI 1.90-3.34] in female patients as compared to the general Dutch population aged over 40 years (Table 2). The overall relative risk of ESCC within the first year of follow-up after the diagnosis of gastric atrophy was significantly higher as compared to one to four years or more than four years follow-up (RR 5.99 [95% CI 4.48-8.01], respectively RR 1.57 [95% CI 1.11-1.21] and RR 1.53 [95% CI 1.16-2.03]) ($p<0.001$). In patients with atrophic gastritis as the most severe diagnosis at baseline, the relative risk was 1.90 [95% CI 1.15- 3.16] for men and 2.84 [95% CI 1.71- 4.72] for women. In patients with intestinal metaplasia and dysplasia the relative risks were respectively 2.06 [95% CI 1.60-2.68] in men and 2.16 [95% CI 1.49- 3.14] in women, and 1.53 [95% CI 0.69- 3.40] in men and 4.10 [95% CI 1.96- 8.56] in women. Therefore, for both men and women, the risk of ESCC did not increase with the severity of pre-malignant gastric lesions at baseline ($p=0.82$, respectively $p=0.83$). Similarly, no significant difference was demonstrated for the risk of ESCC between different histological diagnoses at baseline within the first year of follow-up, one to four years follow-up, or more than four years follow-up ($p=0.69$, respectively $p=0.14$ and $p=0.11$).

Table 2. Relative risk of esophageal squamous cell carcinomas and small cell lung carcinomas in patients with gastric atrophy (n=97 728) in comparison to the general Dutch population. The relative risks and 95% confidence intervals (CIs) were calculated by a Poisson model, corrected for age categories, gender and calendar year.

	Number of cases ESCC	Relative risk ESCC	95% CI	Number of cases SCLC	Relative risk SCLC	95% CI
Overall	126	2.16	[1.81-2.57]	263	1.84	[1.63-2.07]
Sex						
- Male	77	1.98	[1.58-2.48]	182	1.64	[1.41-1.90]
- Female	49	2.52	[1.90-3.34]	81	2.55	[2.05-3.17]
Age at baseline						
- 40-54 years	19	3.56	[2.27-5.59]	17	2.97	[1.85-4.77]
- 55-69 years	40	1.77	[1.30-2.42]	119	2.32	[1.93-2.78]
- ≥ 70 years	67	2.19	[1.72-2.80]	127	1.47	[1.23-1.75]
Most severe grade of gastric atrophy at baseline						
- Atrophic gastritis	30	2.28	[1.59-3.26]	36	1.19	[0.87-1.63]
- Intestinal metaplasia	83	2.09	[1.69-2.59]	200	2.02	[1.76-2.32]
- Dysplasia	13	2.31	[1.35-3.97]	27	1.88	[1.29-2.74]

Legend: ESCC: esophageal squamous cell carcinoma; SCLC: small cell lung carcinoma

Small cell lung carcinomas

In total, 263 patients (182 men/ 81 women) from the cohort were diagnosed with SCLC at a mean age of 69.0 years (SD 8.5). The rate of developing SCLC was 0.39/ 1000 person years at risk in patients older than 40 years. For all patients with gastric atrophy, the relative risk of SCLC was 1.64 [95% CI 1.41-1.90] in male patients and 2.55 [95% CI 2.05-3.17] in female patients as compared to the general Dutch population. Here, again there was no relation between the severity of gastric atrophy and the risk of development of SCLC (Table 2).

DISCUSSION

This large, nationwide study confirms a positive association between gastric atrophy and the risk of ESCC. Our findings showed an overall relative risk of 2.2 for the development of ESCC in patients with gastric atrophy. However, the risk of ESCC in our population did not increase with the severity of gastric atrophy, with relative risks of 2.3 for atrophic gastritis, 2.1 for intestinal metaplasia and 2.3 for dysplasia being observed.

There were considerable variations in the magnitude of the association between gastric atrophy and ESCC observed in previous studies from Sweden and Japan and in our study. (3;7-9) These differences may have resulted from the fact that all studies used different study populations and detection methods of gastric atrophy. In the Swedish studies the diagnosis of gastric atrophy was based on surrogate markers, i.e. either clinically diagnosed pernicious anemia, gastric ulcer disease, or pepsinogen I serology, resulting in elevated risks of respectively 3.3, 1.8 and 4.3 times for the development of ESCC as compared to the general population. In the Japanese study the diagnosis of gastric atrophy was based on both pepsinogen I serology and histology, resulting in elevated risks of 8.2 and 4.2 respectively. In contrast, instead of employing such surrogate markers, our study was able to estimate the ESCC risk within a population with histologically confirmed gastric atrophy. The selection of patients aged above 40 years has not influenced the generalisability of our observations to the whole population, as the incidence of ESCC is extremely low under this age both in our cohort (none of the cases) and in the general Dutch population (considerably less than one percent of all ESCC cases). In addition, our study shows that the risk of developing ESCC is especially high within the first year of follow-up. The high number of ESCC diagnoses shortly after the diagnosis of gastric atrophy suggests the presence of selection bias, as this could for instance have resulted from overlooking an incipient cancer or sampling error during the first endoscopy. The presence of selection bias has probably overestimated the overall relative risk of ESCC in this and previous studies.

Although this risk of developing ESCC was significantly higher in patients with gastric atrophy than in the general Dutch population, this association lacks clinical relevance, as the

magnitude of the association was far too small to direct surveillance practices. Nevertheless, this association could provide important insights into the pathogenesis of both conditions.

The positive association between ESCC and gastric atrophy is not easily explained, it could either be causal or the result of confounding risk factors involving both conditions. Previous case-control studies from Sweden and Japan reported gastric atrophy to increase the risk of ESCC independently of patently obvious confounding risk factors, such as smoking. (3;9;12) In addition, the Japanese investigators observed the ESCC risk to correlate positively to the severity of gastric atrophy. (9) Possible mechanisms for a causal relation were suggested, for instance that achlorhydria in patients with gastric atrophy may constitute an intragastric environment favoring bacterial overgrowth and bacterial n-nitrosation resulting in an increased exposure of the esophageal mucosa to carcinogenic endogenous nitrosamines. (11) Since patients with intestinal metaplasia have more extensive and generally longer existing atrophic changes of the gastric mucosa as compared to patients with merely atrophic gastritis, an increased formation of carcinogenic mediators and thus a higher incidence of ESCC may be expected in patients with intestinal metaplasia.

Our findings in this large cohort study of patients with histologically confirmed cases of gastric atrophy, however, contradict these observations. The absence of any association between the severity of gastric atrophy and the risk of ESCC undermines the presence of a causal relation between both conditions. The absence of a causal relation is further supported by the finding that within different intervals of follow-up no significant difference in ESCC risk was demonstrated between patients with atrophic gastritis, intestinal metaplasia or dysplasia. As no causal relation was demonstrated, *H. pylori* eradication is unlikely to prevent the development of ESCC. Moreover, the demonstration of a similar association between gastric atrophy and SCLC in this study not only demonstrates the spuriousness of the previously assumed relationship but also points to joint causal risk factors for all three conditions, the most prominent of which is obviously smoking. The discrepancy between our data and those of previous studies is probably explained by the relatively small number of patients included in previous studies. For example, in the study from Japan only 29 patients with intestinal metaplasia were included.

Nevertheless, other explanations for the positive association between gastric atrophy and ESCC are worth exploring. It may well be that both conditions do share genetically determined pathogenetic mechanisms facilitating a similar destructive process, which damages both the gastric and esophageal epithelium, for instance via inflammatory response or defective DNA repair. (23-25) Prospective studies into these mechanisms may elucidate such an association. In addition, the observed association between gastric atrophy and SCLC may result from an unidentified interaction between the upper gastrointestinal tract and the lung. Such an association has been described, as for instance an increased prevalence of asthma in subjects with gastro-esophageal reflux. (26) Moreover, the production of carcinogenic nitrosamines in

the atrophic stomach may theoretically cause lung cancer via a haematogenous route. (27) These hypotheses are also worth exploring in future research.

Strengths of our study are the nationwide selection of individuals and the large number of patients with histologically confirmed diagnoses included in this study. Nevertheless, in spite of its large size, the selection of our study population will not have been complete, as not all subjects with gastric atrophy in the general population have undergone endoscopy with biopsy sampling and thus been diagnosed. Therefore, the general population that was used as control-group in this study would certainly include patients with undetected gastric atrophy, which could have resulted in underestimating the true relative risks of the association between both conditions. Secondly, it was impossible to calculate ESCC risk for different intragastric locations of gastric atrophy, as the intragastric location of biopsies is not uniformly registered in the PALGA database. However, it has been recognized for long that pre-malignant gastric lesions occur most commonly in the antrum and incisura angularis. Subsequently, these lesions spread along the lesser curvature to the proximal stomach and at the same time increase in severity. Biopsies from the antrum are commonly obtained during routine upper gastrointestinal endoscopy. Therefore, the diagnoses in this study most likely reflect the most severe gastric lesions at baseline. As patients with intestinal metaplasia or dysplasia have generally more extensive and longer existing atrophic changes of the gastric mucosa, they also demonstrate a higher prevalence of fundic atrophy. Therefore, no difference in the risk of ESCC and gastric atrophy between patients with distal gastric atrophy and patients with fundic atrophy was demonstrated in this study. Thirdly, as patients were treated in all hospitals throughout the country, differences in histological assessment cannot be excluded. However, the large number of patients in this study most likely compensates for these variations. Fourthly, we lack information on possible confounding risk factors. However, as we demonstrated an association between gastric atrophy and SCLC, we can presume that these confounders are present. Finally, we used imputation of survival estimates to calculate the relative risks. The imputation of survival estimates was based on the assumption that patients with gastric atrophy had a life expectancy similar to the general population. However, as they may well suffer from increased co-morbidity and mortality, this assumption could have led to an overestimation of the cohort at risk and consequently, an underestimation of its relative risk of developing ESCC and SCLC. (28) Nevertheless, we think that these co-morbidities have only slightly influenced the reported relative risks, as the large size of this study presumably compensated these inaccuracies and their limited effect on overall mortality.

In conclusion, although this study confirms a positive association between gastric atrophy and ESCC, the risk of ESCC does not increase in parallel with the increasing severity of gastric atrophy. Therefore, a causal relationship between gastric atrophy and ESCC seems unlikely. Moreover, as a similar association was demonstrated between gastric atrophy and the anatomically unrelated SCLC, these associations are best explained by confounding factors, such as smoking.

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CHAPTER 6

Gastric MALT lymphoma: epidemiology and high adenocarcinoma risk in a nationwide study

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ABSTRACT

Background: Gastric marginal zone non-Hodgkin lymphomas MALT type (gMALT) and gastric adenocarcinomas (GC) are long-term complications of chronic *Helicobacter pylori* gastritis, however, the incidence of gMALT and the GC risk in these patients is unclear.

Objective: To evaluate epidemiological time trends of gMALT in the Netherlands and to estimate GC risk.

Methods: Patients with a first diagnosis of gMALT between 1991 and 2006 were identified in the Dutch nationwide histopathology registry (PALGA). Age-standardised incidence rates were calculated. The incidences of GC in patients with gMALT and in the Dutch population were compared. Relative risks were calculated by a Poisson Model.

Results: In total, 1419 patients were newly diagnosed with gMALT, compatible with an incidence of 0.41/100,000/year. GC was diagnosed in 34 (2.4%) patients of the cohort. Patients with gMALT had a sixfold increased risk for GC in comparison to the general population ($p < 0.001$). This risk was 16.6 times higher in gMALT patients aged between 45 and 59 years than in the Dutch population ($p < 0.001$).

Conclusions: GC risk in patients with gMALT is six times higher than in the Dutch population and warrants accurate re-evaluation after diagnosis and treatment for gMALT.

INTRODUCTION

Helicobacter pylori causes chronic inflammation of the gastric mucosa in virtually all infected subjects. This inflammatory process can progress through the pre-malignant stages of atrophic gastritis, intestinal metaplasia and dysplasia to gastric adenocarcinomas. (1,2) As such, *H. pylori* infection is the most important risk factor for the development of gastric adenocarcinomas. Although, the incidence of gastric cancer is declining in the Western world, gastric cancer remains the 4th most common cancer and second leading cause of cancer-related death worldwide. (3,4) The declining incidence of gastric cancer in Western countries is similar to the declining incidence of peptic ulcer disease, attributed to the declining *H. pylori* prevalence. (5,6)

In addition, *H. pylori* infection has increasingly been recognised in the pathogenesis of gastric mucosa-associated lymphoid tissue lymphomas (gMALT). (7,8) Although gMALTs are also strongly associated with *H. pylori* infection, the incidence of this condition has, in contrast to the gastric cancer incidence, been reported to increase. (8–12) It is controversial whether this is a true increase with a shift in outcomes of *H. pylori* infection. Alternatively, changes in the number of endoscopic procedures, biopsy sampling protocols and histological criteria could have influenced the number of diagnoses. (12) Progression of low-grade gMALT is slow, and *H. pylori* eradication alone leads to partial or complete remission in 60–80% of patients, in particular those without a specific API2-MALT1 t(11;18) chromosomal translocation. (2,13) On the contrary, gastric cancer is usually diagnosed at an advanced stage with only limited curative options and consequently a low 5-year survival rate. Although both conditions are long-term complications of chronic *H. pylori* infection, the potential interrelation is unclear and it is controversial whether gastric cancer risk is increased in patients with gMALT. Previous case series and small cohort studies described the occurrence of adenocarcinomas simultaneously or during follow-up of gMALT, (14–18) however, other studies could not confirm these observations. (11,19–21) In addition, a recent study observed increased progression of pre-malignant gastric lesions in patients with gMALT as compared to patients with non-complicated gastritis. (13) On the basis of these contrasting data and in the absence of long-term data in larger cohorts, the risk for gastric cancer in patients with gMALT remains unclear.

Therefore, the aim of this study was to evaluate epidemiological time trends of gMALT in the Netherlands and to evaluate gastric cancer risk in patients with a diagnosis of gMALT.

METHODS

Histopathology database

In the Netherlands, all histopathology and cytopathology reports are collected in a national archive (PALGA database), which has nationwide coverage since 1991. (22) Patients in this database are identified by date of birth, gender and the first four characters of their family name. Though sometimes identities of two patients are falsely matched, this identification string enables the linkage of different tests belonging to the same patient, and therefore also to follow individual testing histories (dates and diagnoses) irrespective of the facility of treatment. (23)

All specimens receive a diagnostic code, similar to the Systematised Nomenclature of Medicine (SNOMED) classification of the College of American Pathologists. (24) This code consists of a term indicating the anatomical location, type of sample and a morphological term describing the finding. The records in the database contain these codes and the summary of the pathology report. In this study, data recorded in the PALGA database between 1991 and 2006 were included. For each report, gender, date of birth, date of pathology report, summary text and diagnostic codes were made available.

Patient selection

All patients with a histologically confirmed diagnosis of gMALT were identified in the database. The diagnostic codes that were used to identify the patients with gMALT are described in Appendix. To evaluate the incidence of gMALT in different age classes, incidence numbers in different periods were calculated within the 5-year age groups. The ratio of the number of new patients with a positive biopsy for gMALT to the number of new patients with a first time gastric biopsy was calculated, in order to correct for possible changes in frequency of upper gastro-intestinal endoscopies with biopsy sampling.

Within the cohort of patients with a gMALT, all patients with a histologically confirmed diagnosis of gastric cancer were identified. Timing of gastric cancer diagnosis was evaluated with regard to diagnosis of gMALT. In this evaluation, patients with a gastric cancer diagnosis simultaneously with, or within one year prior to or after diagnosis of gMALT were considered concomitant diagnoses.

In addition, all patients with a diagnosis of atrophic gastritis, intestinal metaplasia or dysplasia prior to, simultaneous with, or after the diagnosis of gMALT were identified.

Statistical analysis

Age-standardised incidence rates (World standardised rate, WSR) of histologically confirmed gMALT were evaluated for the study period. To compare categorical and continuous variables between patients with low, intermediate to high and undefined grade gMALT, $\chi 2$-tests, t-tests and one way ANOVA tests were used, considering a two-sided p-value <0.05 as statistically significant.

To calculate the relative risk of gastric cancer in patients with gMALT, the incidence of gastric cancer observed in patients with gMALT was compared to the incidence of gastric cancers in the general Dutch population from 1991 to 2006 and aggregated over age and sex. As the PALGA registry does not contain date of death of patients, unless an autopsy had been performed, the person-years at risk would be overestimated. Therefore, we imputed death to get a correct estimate of the number of person-years at risk for all patients that did not develop gastric cancer during follow-up. Starting from the calendar year, age and gender of the persons, we collected the survival data from the general Dutch population for ever open-ended follow-up. Drawing from a binomial distribution for every year then yielded a dataset with an approximately unbiased number of years at-risk. The number of patients is large, but we tried multiple imputation, that did not change the results, as was to be expected. The incidence of gastric cancer in the Dutch population was calculated on the basis of the total number of gastric cancers registered in the PALGA database and the midyear Dutch population. (25) A Poisson Model, corrected for age categories, gender and calendar year, was used for calculating the relative risks and 95% confidence intervals (CIs).

RESULTS

Between 1991 and 2006, 1419 patients were newly diagnosed with gMALT, 972 patients were initially diagnosed with a low-grade lymphoma, 357 patients with an intermediate to high-grade lymphoma and in 90 patients the grade of the lymphoma was undefined (Table

Table 1. Baseline characteristics.

	Total	Low grade	Intermediate to high grade	Undefined grade
Number of patients with gastric MALT lymphoma	1419	972 (68.5%)	357 (25.2%)	90 (6.3%)
Male/Female (%)	51.9/48.1	51.3/48.7	53.5/46.5	52.2/47.8
Age				
Median (yrs)	68.0	67.0	70.6	68.7
Percentile 25th and 75th	57.6/76.7	57.1/75.4	58.9/78.7	57.1/76.2

1). Within the group of patients with a low-grade lymphoma, 32 (3.3%) patients developed a high-grade lymphoma within 1 to 8 years.

Epidemiology

Overall, the mean age of patients at diagnosis of gMALT was 66.1 (SD 14.1) years (range 13.7–98.2 years), and the peak incidence of gMALT both in men and women was between 70 and 74 years (Figure 1). The proportion of male to female patients in the cohort was 51.9 to 48.1% (Table 1). No significant differences in male to female ratios were observed between patients with low-grade, intermediate to high-grade or undefined grade gMALT (p = 0.78). Patients with an initial diagnosis of low-grade gMALT (median age 67.0 years) were significantly younger compared to patients with intermediate to high-grade gMALT (median age 70.6 years) (p = 0.002). Age at diagnosis was significantly higher in females as compared to males, both in patients with low-grade gMALT (p = 0.03) and intermediate to high-grade gMALT (p = 0.001).

Figure 1. Age at gastric MALT lymphoma diagnosis.

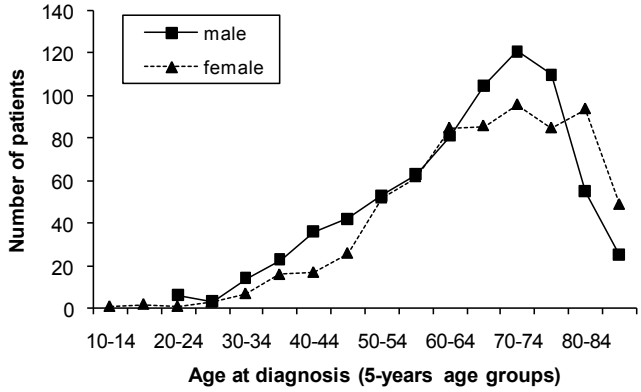
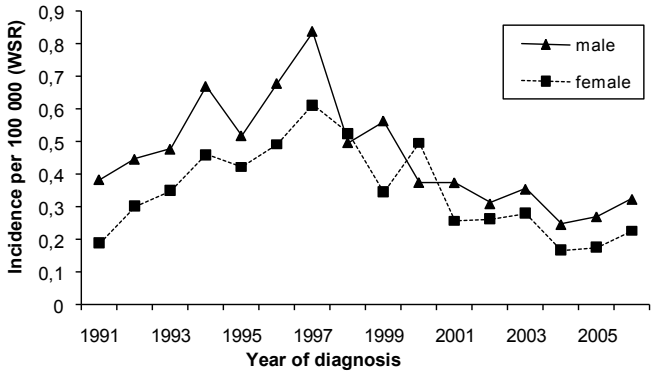


Figure 2. The incidence of gastric MALT lymphoma (WSR, World standardised rate) in the Netherlands.



Over the whole study period, the average number of new diagnoses of gMALT was 88.7 cases per year, and the age standardized incidence rate was 0.41 per 100,000 per year (WSR) (Figure 2). This incidence was not stable over the total study period. At first, the incidence of gMALT increased with 5.8% (95% CI 1.9–9.9%) per year in the period from 1991 to 1997. This was followed by an annual 8.8% (95% CI 6.2–11.4%) decline until 2006 (Figure 2). Altogether, this corresponded with an annual WSR of 0.28 per 100,000 in 1991, increasing to a maximum of 0.72 in 1997, followed by a decrease to 0.27 in 2006. Gastric MALT lymphoma was diagnosed significantly more often in the period from 1991 to 2000 as compared to the period from 2001 to 2006 ($p < 0.001$).

Gastric cancer risk

In total, 34 (2.4%) gMALT patients (18 males, 16 females) were diagnosed with gastric cancer at a median age of 72.0 years (SD 9.6). This comprised 2.7% of 1244 patients in whom no gastrectomy was performed after diagnosis of gMALT. Gastric cancer was diagnosed prior to the diagnosis of gMALT in 3 (8.8%) patients, in 18 (52.9%) patients both malignancies were diagnosed simultaneously (i.e. within a time frame of one year), and in 13 (38.2%) patients gastric cancer was diagnosed more than one year after the gMALT diagnosis (Table 2). The median interval between gastric cancer and gMALT in patients with gastric cancer development after diagnosis of gMALT was 6.0 (range 1.1–7.4) years.

Table 2. Gastric MALT lymphoma and gastric cancer diagnosis.

	Total	Low grade	Intermediate to high grade	Undefined grade
Timing of gastric cancer diagnosis				
Prior to MALT lymphoma (%)	3(8.8)	3(10.7)	0	0
Concomitant with MALT lymphoma (%)	18(52.9)	16(57.1)	1(20.0)	1(100)
After MALT lymphoma (%)	13(38.2)	9(32.1)	4(80.0)	0
Male/Female (%)	52.9/47.1	60.7/39.3	20.0/80.0	0/100
Age				
Median (yrs)	72.0	73.2	70.2	72.2
Percentile 25th and 75th	65.5/78.7	64.2/78.2	61.0/86.9	

Details on stage of gastric cancer were provided in 15 (44%) patients. Five (15%) patients were diagnosed at a stage of early gastric cancer, however, in 10 (29.4%) patients the tumour was already invading the lamina propria, submucosa or beyond. In addition, lymph nodes were involved in 4 (11.8%) patients, as demonstrated by histological evaluation after gastric resection.

Overall, the study population contained 440 (31%) patients with a diagnosis of a pre-malignant gastric lesion prior to, simultaneously with, or after the diagnosis of gMALT, of which 65 (4.6%) patients were diagnosed with atrophic gastritis, 302 (21.3%) patients with intestinal metaplasia and 73 (5.1%) patients with dysplasia. In 21% of these patients a diagnosis of atrophic gastritis, intestinal metaplasia or dysplasia preceded the diagnosis of gastric cancer.

Gastric cancer risk was not significantly different between patients with low, intermediate to high or undefined grade gMALT ($p = 0.21$). In addition, no significant differences in gastric cancer risk were demonstrated between male and female patients ($p = 0.91$).

Overall, patients with a diagnosis of gMALT were at a six times higher risk of developing gastric cancer as compared to the general Dutch population (Table 3). Males with gMALT had a 4.4 times higher risk as compared to the general population ($p < 0.001$), whereas females had a 10.0 times higher risk ($p < 0.001$). The relative risk of gastric cancer was significantly higher in female patients with a gMALT as compared to male patients ($p = 0.02$). However, the absolute risk of gastric cancer for males and females older than 45 years was not significantly different (respectively, 4.0/1000 person-years and 4.3/1000 person-years; $p = 0.81$). Gastric cancer risk was 16.6 times increased in patients aged between 45 and 59 years as compared to the general Dutch population ($p < 0.001$), 10-fold increased in patients aged between 60 years and 74 years and threefold increased in those above 74 years (Table 3). These differences in relative risk for the age groups were significant ($p = 0.004$). However, the absolute gastric cancer risk in patients with gMALT did not differ between those aged 45 to 59 years and those above 59 years ($p = 0.07$).

Table 3. The relative risk of gastric cancer (GC) in patients with gastric MALT lymphoma (gMALT) as compared to the general Dutch population.

		GC in Dutch population	GC in gMALT patients	Relative risk	95% CI	P value for difference
Overall		36,577	30	6.11	[4.28-8.72]	
Sex	Male	22,778	15	4.39	[2.65-7.28]	0.02
	Female	13,799	15	10.04	[6.07-16.60]	
Age at baseline	45-59 yrs	6,229	5	16.64	[5.45-50.80]	0.004
	60-74 yrs	15,253	17	10.64	[6.52-17.4]	
	≥ 75 yrs	13,666	8	3.43	[1.91-6.13]	

DISCUSSION

First of all this study provides long-term nationwide data on the incidence of gMALT in a Western population. It shows an overall incidence of gMALT of approximately 0.4/100,000/year. Secondly, our data show that this incidence has considerably changed over the past 18 years, initially increasing between 1991 and 1997, which was followed by a rapid decline.

Thirdly, we provide long-term data that confirm the suggestion from previous case reports that gMALT patients have a considerably higher gastric cancer risk than the general population. In most cases, gastric cancer is diagnosed within one year prior to or after the diagnosis of gMALT. Therefore, on the basis of our data, accurate evaluation of gMALT seems to be warranted for a diagnosis of gastric cancer concomitantly or after the diagnosis of gMALT.

Our data demonstrate that gMALT is a relatively rare disease in a Western population. Previous studies in Western countries have demonstrated incidences varying between 0.21/100,000 (England) and 13/100,000 (Italy). (2,26,27) These differences are probably explained by differences in the prevalence of *H. pylori* between the studied populations, study power based on the magnitude of the study population, the period of follow-up and the timing of the study. (2,26,28) In our population, a diagnosis of gMALT was not extremely rare as approximately 0.2% of the total number of patients with a first gastric biopsy over the study period were diagnosed with a gMALT.

Previous studies described an increasing incidence of gastric lymphomas in contrast to the declining incidences of *H. pylori* infection, peptic ulcer disease, atrophic gastritis, intestinal metaplasia and gastric adenocarcinomas. (5,6,12) Our data similarly demonstrate that the incidence of gMALT increased from 1991 to 1997, but decreased rather rapidly thereafter. The initial increase is probably related to the increasing interest in this diagnosis after the discovery of an association between *H. pylori* infection and gMALT in 1991. (8) The importance of *H. pylori* as risk factor for MALT lymphoma was confirmed by the regression of low-grade MALT lymphoma after *H. pylori* eradication. (19,29) Thereby, gMALT became an infection-associated malignant disease. (2) This led in a change of primary treatment strategy from chemoradiotherapy and surgery to *H. pylori* eradication therapy. This major change may have contributed to an increase in the number of new cases diagnosed with gMALT during those years. Furthermore, improved endoscopic and histological diagnostic procedures may also have contributed to the increasing incidence of gMALTs. (30–32) For several years, all non-Hodgkin lymphomas (NHLs) were classified following the Working Formulation (WF) in low-grade and high-grade lymphomas. This working formulation did not include several morphologic and clinical distinct entities, including gMALT. Consensus for a more multifaceted approach to NHLs was reached in a revised European–American lymphoma (REAL) classification in 1993, which recognised the mucosa-associated lymphomas. (33) Thereafter, gMALTs were considered a specific entity. (2) Currently their incidence is rapidly declining. This decline is likely in part related to the current decline in the prevalence of *H. pylori* in Western countries. However, the decline of incidence of gMALT is much more rapid than the declining *H. pylori* prevalence. (5,34,35) Therefore, other factors must additionally play a role and need to be further investigated.

Although several case series were published on synchronous and metachronous occurrence of both gastric cancer and gMALT, it remained unclear whether gastric cancer risk was increased in gMALT patients compared to the general population. (11,14,16,19,36–38) Our

study demonstrates this risk is indeed about six times increased (Table 3). The absolute risk was equal in male and female gMALT patients, which contrasts with the general population, where the risk for gastric cancer is considerably higher in men. Thus, the relative risk of gastric cancer in MALT patients is higher in women than in men. Similarly, the gastric cancer risk was the same in younger and elderly gMALT patients, and thus the relative risk for gastric cancer was significantly higher in younger MALT lymphoma patients (Table 3). The relative risks of gastric cancer after a diagnosis of gMALT described in our study could even be higher since gastrectomy was performed in 175 patients after diagnosis of a gMALT, in particular in the early years when *H. pylori* eradication was not yet an accepted treatment method.

As patients with gastric MALT lymphoma are already at an increased risk of developing gastric cancer by being *H. pylori* positive, a further comparison between *H. pylori*-positive subgroups is essential. Previous studies demonstrated that *H. pylori* infection increased gastric cancer risk at least twofold resulting for *H. pylori*-positives in an estimated lifetime risk for gastric cancer of approximately 1%. (39,40) In addition, we recently published a study describing the risk of gastric cancer in a large cohort of patients with atrophic gastritis and intestinal metaplasia, which occurs like MALT lymphoma against a background of *H. pylori* infection. This study demonstrated that within ten years of follow-up the gastric cancer risk in these subjects with a pre-neoplastic condition varied between the two and three percent. (41) This background supports the conclusion that patients with gMALT are at increased risk for gastric cancer compared to *H. pylori*-positive subjects, and that this risk is in fact very similar to patients with atrophic gastritis and intestinal metaplasia. (41)

In 38% of patients with diagnosis of gastric cancer, gastric cancer was diagnosed after gMALT with a median interval of 6.0 years (range 1–7). This interval is similar to the interval observed in a review of previous cases on metachronous occurrence of gMALT which reported 6 months to 5 years. (16) However, the exact period between diagnosis of a gMALT and cancer or remission is difficult to interpret, since different histological scoring systems have been used to evaluate lymphoma response to therapy over the past decade. (29,42) As these grading systems demonstrated low interobserver reproducibility, a new grading system based on evaluation of diagnostic features of lymphoepithelial changes was put forward. (43) According to this grading system, a recent study described a favourable disease course of patients treated with *H. pylori* eradication, after 42.2 months of follow-up, in which one-third of the patients went into complete remission. (21,43) However, the findings in our study emphasise the need of accurate endoscopic and histological re-evaluation of the gastric mucosa after diagnosis of a gMALT, since the majority who developed gastric cancer was diagnosed with adenocarcinoma concomitantly (52.9%) with their gMALT or during later surveillance (38.2%).

Although this study describes a large nationwide cohort of patients with gMALT with long-term follow-up, potential limitations of this study warrant consideration. Firstly, for most of the period under study, MALT lymphomas were classified as either low- or high-grade, and

it is therefore that our report included cases under these search terms. At present, gMALTs are considered as a specific disease entity of marginal zone lymphoma (mucosa-associated lymphoid tissue lymphoma (MALT) type), which led to the formalized WHO classification, according to which these lesions are now referred to as gastric marginal zone lymphomas MALT type. (44) Also, the term high-grade MALT lymphoma was replaced by Diffuse Large B-Cell Lymphoma (DLBCL) in this new classification, as it was discovered that low-grade and high-grade gMALTs have a different histogenesis. (44) These DLBCLs may contain a low-grade MALT lymphoma component. However, it remains unclear to which extent they transformed from low-grade MALT lymphomas versus de novo DLBCLs. (45) For these reasons, it is likely that a small proportion of the high-grade gastric MALT lymphomas in our cohort included DLBCLs unrelated to MALT. However, these changes of nomenclature have not led to a major change in diagnoses and therefore unlikely affected the main outcome parameters of our study, i.e. the incidence of gMALTs and the risk for gastric cancer in these patients.

Secondly, we could not evaluate the extension of pre-malignant gastric lesions in the mucosa surrounding the MALT lymphomas, as the relatively low percentage of patients with gastric atrophy, intestinal metaplasia and dysplasia prior to or simultaneous with gMALT diagnosis made this impossible. In addition, details on location and invasion of the MALT lymphomas were not provided. Lymphomas tend to occur proximally in the stomach, whereas gastric adenocarcinomas occur more distal. (36) For these reasons, details on extension of pre-malignant gastric lesion, and size and depth of MALT lymphoma might identify patients at higher risk and consequently lead to more accurate surveillance. Similarly, evaluating the gastric cancer risk in the cohort after stratification by *H. pylori* and translocation status may also result in more accurate surveillance and prognosis. Previous studies observed the specific API2-MALT1 t(11;18) chromosomal translocation in approximately 30% (range 18–40%) of gMALT patients. (2,46,47) Most patients with this specific translocation do not respond to *H. pylori* eradication and demonstrate dissemination to regional lymph nodes or distal sites than the stomach more frequently. Development of gastric cancer was reported to occur in translocation-positive patients. However, these case series were very small and the exact risk of developing gastric cancer remained unclear. (48,49) For these reasons, a large prospective study of patients with gMALT and determination of their translocation status is essential to evaluate patients at high risk of developing gastric cancer, however, the rare appearance of gMALTs will make this study hardly feasible.

Thirdly, as limited numbers of biopsies can provide insufficient information for subtyping, and determination of horizontal extension and multifocality of gMALTs, previous studies described the need for a standardised protocol taking 20–30 biopsies from involved and uninvolved mucosa both at baseline and during follow-up. (32,50) However, we could not evaluate the number and distribution of biopsies obtained within each individual case and at every time point. Therefore, the number of patients with in particular pre-malignant gastric lesions after a diagnosis of gMALT may have been overdiagnosed. (51)

Finally, a previous study proposed that gMALT patients treated with chemo- and/or radiotherapy were particularly at increased risk for gastric cancer (52), but we were unable to assess this in our study population as we lack details with respect to chemoradiotherapy that without doubt has been given to patients during the first years of our study period.

In conclusion, the overall incidence of gMALT is low and currently declining, which is likely related to the current decline in the prevalence of *H. pylori* infections, but also has to be due to other unidentified factors as the decline is considerably more rapid than the decline of *H. pylori* prevalence. After a diagnosis of gMALT, an accurate endoscopic and histological re-evaluation of the gastric mucosa seem to be warranted as gastric cancer risk in patients with gMALT is substantial and the majority who develop gastric cancer are diagnosed concomitantly or after their gMALT. Future research is needed to clarify the clinical course of these patients in order to improve treatment and prognosis of patients with gMALT.

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APPENDIX

The following SNOMED-like codes were used:
Stomach: T63000.
Atrophic gastritis: M58000, M58001, M58010.
Intestinal metaplasia: M73000, M73200, M73320, M73321, M73300.
Dysplasia: M74000, M74006, M74007, M74008, M74009.
Gastric cancer: M81403, M80103, M84803, M81443, M81453, M84903, M82113, M80503, M82603, M69360, M81404, M80104, M80105, M80123, M80193, M80213, M80203.
MALT lymphoma: M97153, M97183, M97163, M96993, M97183.
Malignant lymphoma/malignant non-Hodgkin lymfoma: M95903, F40640.

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CHAPTER 7

The detection, surveillance and treatment of premalignant gastric lesions related to *Helicobacter pylori* infection

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ABSTRACT

Gastric cancer is an important worldwide health problem and causes considerable morbidity and mortality. It represents the second leading cause of cancer-related death worldwide. A cascade of recognizable precursor lesions precedes most distal gastric carcinomas. In this multistep model of gastric carcinogenesis, *Helicobacter pylori* causes chronic active inflammation of the gastric mucosa, which slowly progresses through the premalignant stages of atrophic gastritis, intestinal metaplasia and dysplasia to gastric carcinoma. Detection and treatment of premalignant lesions may thus provide a basis for gastric cancer prevention. However, at present, premalignant changes of the gastric mucosa are frequently disregarded in clinical practice or result in widely varying follow-up frequency or treatment. This review provides an overview of current knowledge on detection, surveillance and treatment of patients with premalignant gastric lesions, and identifies the uncertainties that require further research.

INTRODUCTION

Gastric cancer is the fourth most common cancer and second leading cause of cancer-related death worldwide. Although the incidence of gastric cancer is declining, in particular in the Western world, the absolute annual number of new cases increases, due to aging of the world population and expansion of the population in developing countries with a high gastric cancer incidence. The estimated current incidence of gastric cancer is approximately 16.2/100,000 persons per year (world standardized rate), with highest incidences in Eastern Asia, Eastern Europe, and South America (1).

As symptoms are often absent or nonspecific in patients with an early stage of disease, gastric cancer is usually diagnosed in an advanced stage, when curative options are limited. Consequently, gastric cancer carries a poor prognosis, with an overall 5-year survival rate of less than 20% (2).

The vast majority of gastric malignancies are adenocarcinomas, which can be divided into two types: intestinal type and diffuse (undifferentiated) type (3). Most gastric carcinomas are of the intestinal type. *Helicobacter pylori* infection increases the risk of developing gastric cancer more than sixfold and is therefore considered an important carcinogenic trigger (4). In contrast to diffuse-type carcinomas, intestinal-type carcinomas are generally thought to be preceded by a sequence of precursor lesions. In this multistep model of gastric carcinogenesis, *H. pylori* causes chronic inflammation of the gastric mucosa, which slowly progresses through the premalignant stages of atrophic gastritis, intestinal metaplasia and dysplasia to gastric adenocarcinomas (5). Some authors have suggested that the presence of corpus-predominant gastritis by itself predisposes to gastric cancer rather than the progression through different premalignant stages; however, the presence of corpus-predominant gastritis correlates highly with the presence of atrophic gastritis (6-8). Although several other gastric conditions with an increased cancer risk have been described, e.g. adenomatous polyps, previous distal gastric resection, Ménétrier's disease, fundic gland polyps in subjects with the familial adenomatous polyposis syndrome, and hamartomas in patients with Peutz-Jeghers syndrome, this review will focus on atrophic gastritis, intestinal metaplasia and dysplasia.

Premalignant changes of the gastric mucosa are commonly observed in routine biopsies obtained during gastroscopy. Nevertheless, clear guidelines for follow-up and treatment of these patients are lacking, which means that in clinical practice follow-up frequency and treatment of individual patients vary widely. An overview of current knowledge on detection, surveillance and treatment of patients with premalignant gastric lesions will be provided in this review. Furthermore, uncertainties that hinder clinical decision-making and require further research prior to development of guidelines, will be identified.

HISTOLOGIC CLASSIFICATION

Atrophic Gastritis

Atrophic gastritis (AG) is defined as loss of glandular structures of the gastric mucosa. This is associated with a loss of specialized cells and thus a reduction of gastric secretory function (9). Various classifications of AG have been proposed over the years, with definitions such as A/B/AB/C types, "superficial" versus "diffuse", "diffuse antral-predominant" versus "multifocal atrophic gastritis", and "nonulcer pangastritis" versus "progressive intestinalized pangastritis". However, these classifications are difficult to use in clinical practice and suffer from considerable interobserver variation (10–14). At present, the updated Sydney System is generally used both in clinical practice and in research (Table 1) (9). In this classification system, which has proven its value over the past decade, several features of inflammation, atrophy and intestinal metaplasia need to be assessed individually. A visual analogue scale was added to facilitate grading of the individual features. The evaluation of most features displays good reproducibility, but agreement on the recognition and grading of gastric atrophy remains inadequate (15–17). New methods to classify AG objectively, in particular by quantification of the loss of glandular structures, have been developed (18–20). However, these have not yet been implemented in routine assessment, since clinical consequences of grading AG are commonly absent.

Table 1. Sydney System: Classification of chronic gastritis (9).

Type of gastritis	Etiologic factors
Non atrophic	*Helicobacter pylori*
Atrophic	
Autoimmune	Autoimmunity
Multifocal atrophic	*Helicobacter pylori*, Dietary, Environmental factors
Special forms	
Chemical	Chemical irritation: Bile, NSAID's, Other agents
Radiation	Radiation injury
Lymphocytic	Idiopathic? Immune mechanisms, Gluten, Drug, *Helicobacter pylori*
Noninfectious	
Granulomatous	M. Crohn, M. Wegener, Sarcoidosis, Foreign substances, Idiopathic
Eosinophilic	Food sensitivity, Other allergies
Other infectious gastritides	Bacteria (other than *H. pylori*), Viruses, Fungi, Parasites

Intestinal Metaplasia

Intestinal metaplasia (IM) is defined as replacement of gastric columnar epithelial cells by cells of intestinal morphology. IM probably results from diverted differentiation of gastric stem cells towards cells of small intestine or colonic phenotype. IM is characterized by the presence of intestinal-type, mucin-containing goblet cells, Paneth cells and absorptive cells (Figure 1). Several classifications of IM have been described; the most widely used is that of Filipe and Jass (Table 2) (21). The interobserver agreement of this classification system is satisfactory. However, a disadvantage is the labour-intensiveness, since additional staining is required to differentiate between types. Furthermore, differentiation between subtypes of IM has no proven relevance for clinical practice and is therefore usually omitted.

Figure 1. Intestinal metaplasia in gastric antrum (H&E staining).

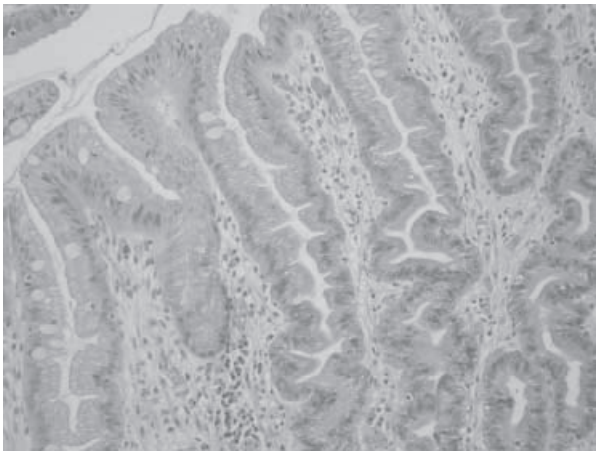


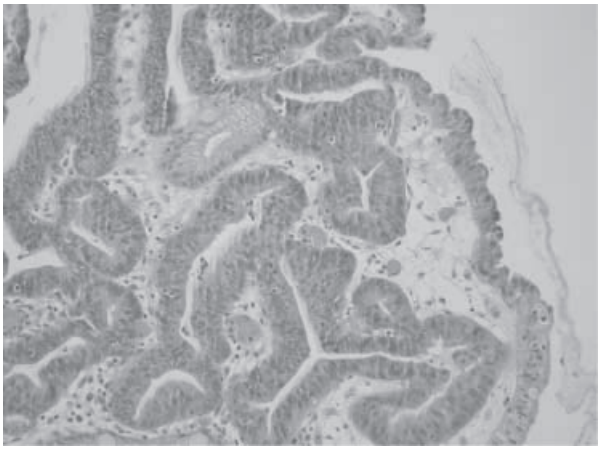
Table 2. Types of gastric intestinal metaplasia (21).

Types of gastric intestinal metaplasia	
Type I, Complete, small intestinal type	absorptive cells with brush borders goblet cells secreting sialomucin Paneth cells
Type II, Incomplete, enterocolic type	few absorptive cells goblet cells secreting sialomucin, but also sulphomucin columnar cells secreting sialomucin few Paneth cells
Type III, Incomplete, colonic type	no absorptive cells goblet cells secreting sialomucin or sulphomucin columnar cells secreting mainly sulphomucin rare Paneth cells

Dysplasia

Gastric dysplasia is characterized by variation in size, shape and orientation of epithelial cells, enlargement and atypia of nuclei, and distortion of normal glandular arrangement (Figure 2). Assessment of dysplasia is often difficult and interobserver agreement in grading dysplasia is poor. In addition, differences exist between Japanese and Western gastrointestinal pathologists in classification of gastric dysplasia and cancer. Japanese pathologists diagnose cancer based on cellular and structural abnormalities, whereas Western pathologists focus on the presence of tissue invasion as a prerequisite for a diagnosis of cancer (22). In 2000, the unified Padova classification was proposed, which divided dysplasia and adenocarcinoma into five categories. The Vienna classification further subdivided the categories of low-grade dysplasia and high-grade dysplasia and was revised to improve the correlation with clinical management (Table 3) (23–25).

Figure 2. Gastric dysplasia (H&E Staining).



LOCALIZATION

Premalignant gastric lesions are most frequently localized in the antrum up onto the transitional zone between antrum and corpus, with exception of AG related to pernicious anemia, which tends to be corpus-predominant. More detailed intragastric distribution of the lesions is unclear. It has long been assumed that AG has a largely multifocal distribution, with individual foci of AG initially arising at the incisura angularis. These foci may subsequently spread and interconnect along the lesser curvature and anterior and posterior wall (9). However, a recent study showed that the majority of intestinal gastric carcinomas arise within a continuous sheet of AG with small, scattered islands of IM, according to an "advancing atrophic front pattern". In this pattern the continuous sheet of AG seems to progress proximally and

Table 3. The revised Vienna classification of gastrointestinal neoplasia (24).

Category	Diagnosis	Clinical management
1.	Negative for neoplasia	Optional follow-up
2.	Indefinite for neoplasia	Follow-up
3.	Mucosal low grade dysplasia Low grade adenoma Low grade dysplasia	Endoscopic resection/ Follow-up
4.	Mucosal high grade dysplasia	Endoscopic or surgical local resection
4.1	High grade adenoma/ dysplasia	
4.2	Non-invasive carcinoma (carcinoma in situ)	
4.3	Suspicious for invasive carcinoma	
4.4	Intramucosal carcinoma	
5.	Submucosal invasion by carcinoma	Surgical resection

towards the greater curvature with advancing disease (26). A minority of carcinomas arise in an "atrophic antrum", in which the antrum is almost completely replaced with IM, whereas the corpus is non-atrophic. Multifocal dysplasia was detected both in areas with and without IM. At present, the Sydney System recommends two biopsies from the corpus, two from the antrum and one from the incisura angularis during gastroscopy to classify and grade gastritis. As knowledge of the exact intragastric distribution of premalignant lesions should guide biopsy sampling during surveillance endoscopy, clarification of distribution by further research is essential.

PREVALENCE

In parallel to the prevalence of *H. pylori* infection and the incidence of intestinal type gastric cancer, the incidence of AG and IM is declining in Western countries (27). However, premalignant gastric lesions are still commonly encountered conditions in routine biopsies after endoscopy.

The prevalence of premalignant gastric lesions is influenced by a number of factors. First, the prevalence of these lesions shows considerable geographic differences. As their development is strongly linked to *H. pylori* infection (28), the prevalence is elevated in countries with a higher prevalence of *H. pylori* infection. Nonetheless, some reports describe regions with a low prevalence of gastric cancer and premalignant gastric lesions, despite a high *H. pylori* infection rate (29). Therefore, other factors, including diet, *H. pylori* strain characteristics and host immune response probably also play a role in geographic variation. Second, longitudinal analyses showed that the total prevalence of chronic gastritis is stable over time within specific birth cohorts; however, with increasing age a larger proportion of individuals becomes affected with AG compared to nonatrophic gastritis (28,30,31). Finally, as discussed

previously, the variation in prevalence of dysplasia may in part be a reflection of differences in applied classification criteria.

In the West European population *H. pylori* infection prevalence is approximately 40%. AG occurs in up to 60% and IM in 40–50% of *H. pylori* -infected individuals during their lifetime, whereas 5–10% of uninfected individuals are affected with these lesions (28,32,33). In Japan, the overall prevalence of *H. pylori* infection prevalence is approximately 60%. AG is present in about 80% of *H. pylori* infected and 10% of uninfected individuals, whereas IM is present in, respectively, 40% and 5% of individuals (34). Overall, AG and IM are present in approximately one third and one quarter of individuals in Western Europe, and in, respectively, more than half and one third of individuals in Japan. Prevalences of dysplasia vary from 0.5% to 4% in a Western population and between 9% and 20% in high-risk areas for gastric carcinomas. However, these percentages could be influenced by differences in classification criteria (35).

NATURAL HISTORY

After recognition of the neoplastic cascade of premalignant gastric lesions, various studies in subsequent decades further investigated the progression rate of AG, IM, and dysplasia to gastric cancer (Table 4) (36–75).

The reported progression rates of AG, both related and unrelated to pernicious anemia, to gastric cancer are remarkably stable despite diverse geographic setting of the studies, and vary roughly between 0% and 1.8% per year. In contrast, the reported progression rates of IM and dysplasia to cancer vary greatly, from 0% to 10% per year for IM, and from 0% to 73% per year for dysplasia.These variations can probably be explained by a variety of factors such as differences in study design and included populations, and variations in definitions of IM and dysplasia. For instance, the number and sites of biopsies have not been standardized in most studies. Therefore, sampling errors due to multifocal distribution of IM and dysplasia could have led to inaccurate estimates of progression rates, even more so when smaller cohorts are followed for shorter periods of time. Second, some studies excluded cases from analysis when gastric cancer was detected within 1 year after the diagnosis of dysplasia based on the argument that dysplasia and cancer in these cases might already have coexisted at baseline (39,47,62,63). Other studies did not use this approach, which is a further explanation for the discrepant results between studies. Third, some studies defined preneoplastic lesions only vaguely and grouped IM and dysplasia as one entity (41,58,72), and/or considered in particular type III metaplasia as synonymous to low-grade dysplasia.

For each of the categorized premalignant lesions, the gastric cancer risk is related to the extent of the lesion (71,76–78). For atrophic gastritis, gastric cancer risk particularly increases with extensive atrophic gastritis of the corpus. It seems plausible that the risk of cancer also increases with severity of lesions within these categories. This assumption has been proven

Table 4. Overview of studies evaluating progression of atrophic gastritis, intestinal metaplasia and dysplasia to gastric cancer.

Atrophic gastritis	Country of origin	Study design	Study population			Follow-up after endoscopy	Outcome	
			Patients (n)	*H. pylori* positive (%)	Mean age at diagnosis		Progression to gastric cancer n (%)	Annual incidence of gastric cancer n/ 100,000 / year
Findley (52) 1950	USA	Retrospective	100	NS	47 years	8.5 years (mean)	0 (0%)	0
Siurala (68;69) 1966, 1974	Finland	Prospective	116	NS	NS	15 years (maximum)	9 (7.8%)	≥ 517
						23 years (maximum)	10 (8.6%)	≥ 375
Irie (53) 1970	Japan	Unknown	100	NS	NS	4 years (maximum)	5 (5%)	≥ 1250
Walker (73) 1971	Australia	Retrospective	40	NS	NS	15 years (mean)	4 (10%)	≈ 666
Cheli (41) 1973	Italy	Retrospective	105	NS	NS	18 years (maximum)	9 (8.6%)	≥ 476
Ectors (45) 1986	United Kingdom	Retrospective	59	NS	58 years	9 years (maximum)	1 (1.7%)	≥ 188
Borch (40) 1986	Sweden	Prospective	61 PA*	NS	NS	2.7 years (mean)	0 (0%)	0
Sjöblom (70;56) 1993, 1998	Finland	Prospective	48 PA*	NS	57 years	3 years	2 (4.2%)	1388
			63 PA*	NS	59 years	12 years (maximum)	2 (3.2%)	≥ 265
Armbrecht (38) 1990	United Kingdom	Prospective	16 PA*	NS	NS	7 years (maximum)	0 (0%)	0
Tatsuta (71) 1993	Japan	Retrospective	471	NS	NS	19 years (maximum)	moderate AG: 8 (3.3%) severe AG: 11 (7.6%)	≥ 171 ≥ 399

Atrophic gastritis	Country of origin	Study design	Study population			Follow-up after endoscopy	Outcome	
			Patients (n)	*H. pylori* positive (%)	Mean age at diagnosis		Progression to gastric cancer n (%)	Annual incidence of gastric cancer n/ 100,000 / year
Sakaki (64) 1997	Japan	Retrospective	22	64%	55 years	13.4 years (mean)	0 (0%)	0
You (75) 1999	China	Prospective	1240	NS	NS	5 years (maximum)	mild AG: 1 (0.1%) severe AG: 0 (0%)	≥ 16 ≥ 0
Lahner (57) 2001	Italy	Prospective	42	19%	57 years (median)	4 years (maximum)	0 (0%)	0
Sakaki (65) 2002	Japan	Prospective	35	100%	58 years	10 years	0 (0%)	0
Whiting (74) 2002	United Kingdom	Prospective	11	NS	NS	10 years (maximum)	2 (18.2%)	≥ 1818
Dinis-Ribeiro (44) 2004	Portugal	Retrospective	58	53%	55 years (median)	3 years (maximum)	0 (0%)	0
Lahner (58) 2005	Italy	Prospective	106	74%	NS	7 years (median)	1 (0.9%)	≈ 135

Intestinal metaplasia	Country of origin	Study design	Study population			Follow-up after endoscopy	Outcome	
			Patients (n)	*H. pylori* positive (%)	Mean age at diagnosis		Progression to gastric cancer n (%)	Annual incidence of gastric cancer n/ 100,000 / year
Ectors (45) 1986	United Kingdom	Retrospective	171	NS	60 years	9 years (maximum)	2 (1.2%)	≥ 130
Testoni (72) 1987	Italy	Prospective	261	NS	54 years	9 years (mean)	12 (4.6%)	≈ 511
Silva (67) 1990	Portugal	Prospective	124	NS	NS	6 years (maximum)	Type I: 0 (0%) Type II: 0 (0%) Type III: 0 (0%)	0
Rokkas (60) 1991	United Kingdom	Prospective	26	NS	NS	7 years (maximum)	Type III: 11 (42%)	≥ 6044
Filipe (51) 1994	Slovenia	Retrospective	1281	NS	NS	19 years (maximum)	Type I: 6 (1.3%) Type II: 5 (3.5%) Type III: 15 (9.8%)	≥ 68 ≥ 184 ≥ 516
You (75) 1999	China	Prospective	842	NS	NS	5 years (maximum)	superficial IM: 2 (0.8%) deep IM: 16 (2.7%)	≥ 156 ≥ 546
El-Zimaity (46) 2001	USA	Prospective	79	100%	60 years (median)	9 years (maximum)	0 (0%)	0
Whiting (74) 2002	United Kingdom	Prospective	93	NS	NS	10 years (maximum)	10 (11%)	≥ 1075
Dinis- Ribeiro (44) 2004	Portugal	Retrospective	120	53%	55 years (median)	3 years (maximum)	Type I: 0 (0%) Type II: 1 (2.1%) Type III: 3 (30%)	0 ≥ 694 ≥ 10000

Dysplasia	Setting	Study design	Study population			Follow-up after endoscopy	Outcome	
			Patients (n)	*H. pylori* positive (%)	Mean age at diagnosis		Progression to gastric cancer n (%)	Annual incidence of gastric cancer n/ 100,000 / year
Farini (48) 1982	Italy	Prospective	25	NS	NS	6.2 years (maximum)	0 (0%)	0
Farini (49) 1983	Italy	Prospective	20	NS	NS	4.6 years (maximum)	0 (0%)	0
Andersson (37) 1987	Denmark	Prospective	14	NS	NS	3.3 years (median)	0 (0%)	0
Saraga (66) 1987	Switzerland	Retrospective	85	NS	NS	3.5 years (mean)	mild DYS: 0 (0%) moderate DYS: 1 (2.4%) severe DYS: 17 (81.0%)	0 ≈ 697 ≈ 23129
Lansdown (59) 1990	United Kingdom	Prospective	20	NS	72 years (median)	2 years (maximum)	low grade DYS: 0 (0%) high grade: 11 (85%)	0 ≈ 42308
Coma del Corral (42) 1990	Spain	Retrospective	67	NS	50 years	10 years (maximum)	moderate DYS: 2 (4.9%) severe DYS: 8 (30.7%)	≥ 488 ≥ 3077
Koch (54) 1990	Germany	Retrospective	689	NS	67 years	NS	grade II DYS: 1% grade III DYS: 31%	Unknown
Rugge (47;61-63) 1991, 1993, 1994, 2003	Italy	Prospective	134	NS	62 years	1.6 years (mean)	mild DYS: 5 (6.1%) moderate DYS: 7 (22.6%) severe DYS: 6 (46.2%)	≥ 3811 ≥ 14113 ≥ 28846
			49	NS	64 years	1.6 years (mean)	moderate DYS: 8 (23.5%) severe DYS: 8 (53.3%)	≈ 14706 ≈ 33333
			93	84%	61 years	2 years 2.6 years 1.6 years (median)	mild DYS: 2 (3.8%) moderate DYS: 8 (23.5%) severe DYS: 4 (22.2)%	≈ 1887 ≈ 9050 ≈ 13889
			118	93%	56 years	4.3 years (mean)	low grade DYS: 8 (8.8%) high grade DYS: 11 (68.8%)	≈ 2067 ≈ 15988

Dysplasia	Setting	Study design	Study population			Follow-up after endoscopy	Outcome	
			Patients (n)	*H. pylori* positive (%)	Mean age at diagnosis		Progression to gastric cancer n (%)	Annual incidence of gastric cancer n/ 100,000 / year
Fertitta (50) 1993	Italy	Prospective	52	NS	NS	1.1 years (mean)	moderate DYS: 7 (33.3%) severe DYS: 25 (80.6%)	≈ 30303 ≈ 73314
Di Gregorio (43) 1993	Italy	Prospective	99	NS	56 years	1.7 years (mean)	mild DYS: 4 (5.5)% moderate DYS: 2 (12.5%) severe DYS: 6 (60%)	≈ 3223 ≈ 7353 ≈ 35294
Bearzi (37) 1994	Italy	Prospective	125	NS	NS	10 years (maximum)	low grade DYS: 22 (27.2%) high grade DYS: 36 (81.8%)	≥ 2716 ≥ 8182
Kokkola (55) 1996	Finland	Prospective	88	NS	63 years	4 years (mean)	mild DYS: 0 (0%) moderate DYS: 0 (0%) severe DYS: 2 (66.7%)	0 0 ≈ 16667
You (75) 1999	China	Prospective	546	NS	NS	5 years (maximum)	mild DYS: 14 (2.8%) moderate/ severe DYS: 3 (7.0%)	≥ 560 ≥ 1400
Whiting (74) 2002	United Kingdom	Prospective	7	NS	NS	10 years (maximum)	0 (0%)	0
Dinis- Ribeiro (44) 2004	Portugal	Retrospective	62	53%	55 years (median)	3 years (maximum)	low grade DYS: 7 (11% high grade DYS/ GC)	≥ 3763
Yamada (36) 2004	Japan	Retrospective	43	NS	59 years	6 years (mean)	low grade DYS: 1 (3.0%) high grade DYS: 1 (10%)	≈ 505 ≈ 1667

Legend:
NS= not specified; PA= pernicious anaemia; DYS= dysplasia;
* = pernicious anaemia patients with dysplasia or gastric cancer at the first endoscopy were excluded from analysis

for AG, but is still controversial for IM as there is still considerable debate on whether intestinal metaplasia type III represents a more pro-carcinogenic phenotype (45,46,51,71). One retrospective study claimed that patients with type III IM had a more than twofold increased risk for gastric cancer compared to subjects with atrophic gastritis without IM or with type I or II IM (51). However, upon re-analysis of the archival histology samples, this claim was refuted as a diagnosis of type III IM could not be confirmed in many patients. A cohort study from the UK did also not observe that the risk of gastric cancer was related to IM subtypes (45). This could also explain why the vast majority of patients with gastric cancer do not have any evidence of type III IM.

SURVEILLANCE

The necessity of re-evaluation or surveillance of patients with premalignant gastric lesions is controversial (35,39,43,44,47,50,57,63,74,79,80). As a consequence, clear guidelines are still not available and recommended follow-up frequencies vary widely. This is remarkable, since guidelines for surveillance of other gastrointestinal premalignant conditions have been widely developed, as for instance for Barrett's esophagus or colonic adenomas.

As only a small minority of patients with premalignant lesions will eventually develop gastric cancer, surveillance of all patients with premalignant gastric lesions is probably not indicated. Some authors have tried to identify patients with premalignant gastric lesions at increased risk of gastric cancer. In a study from Japan, investigators observed an increased gastric cancer risk in patients with extensive atrophic gastritis, as measured by low serum pepsinogen levels (81). Cancer risk was increased in those with and without serologic evidence of *H. pylori* infection. Extent and severity of the lesion, persistent *H. pylori* infection, age, male sex, alcohol use, and drinking water from a well were identified as risk factors for progression of premalignant lesions (81–83). Nevertheless, selection of individuals for surveillance in clinical practice is still difficult.

At this moment, regular surveillance of at least patients with mild or moderate dysplasia of the gastric mucosa seems indicated after initial diagnosis, given their high risk for a diagnosis of gastric cancer within the first two years. When repeated endoscopy with surveillance biopsy sampling confirms the presence of dysplasia, continued surveillance is warranted. When dysplasia cannot be confirmed during reevaluation endoscopy, it is unclear for how long surveillance has to be continued. For patients with severe dysplasia surgical or endoscopic resection is indicated, although some authors recommend close endoscopic surveillance (24,43,47,50,84).

In Japan, a country with a high incidence of gastric cancer, repeated endoscopic population screening for gastric neoplasia is routine practice. However, also in low-incidence countries, surveillance of patients with premalignant gastric may lead to early detection of gastric

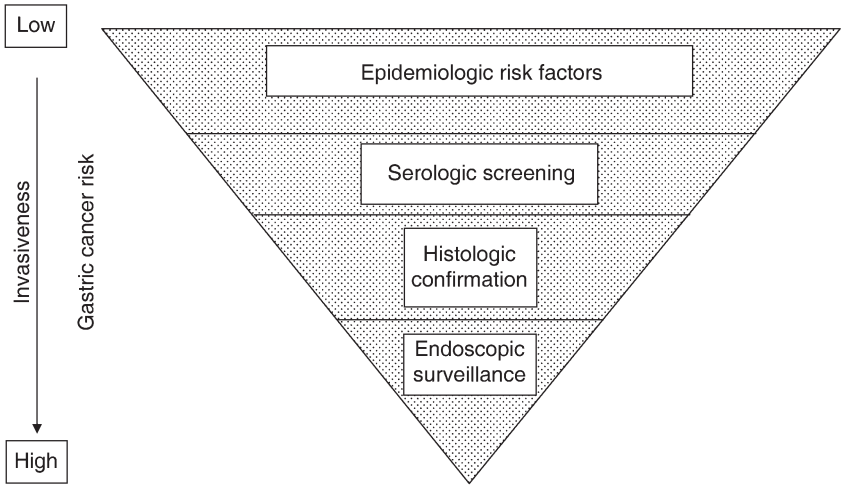
cancer and thereby reduced mortality. To evaluate the exact value of surveillance in patients with premalignant gastric lesions and establish follow-up frequencies, more precise data on progression are needed. These data should preferably be obtained in large prospective studies with adequate follow-up of patients with premalignant gastric lesions and these should be performed in different geographic areas.

DETECTION

The implementation of nationwide mass screening programs in Japan has resulted in detection of more gastric carcinomas at an early stage. Several uncontrolled trials have suggested that cancer mortality has thereby been reduced (85–88). However, an invasive mass-screening program in countries with a relatively low incidence of gastric cancer is less appropriate, considering for instance the burden for patients, ethical objections, and costs. In these countries a more targeted approach is required to detect gastric cancer at an early and curable stage. Case finding, i.e. screening of patients who have sought health care for disorders that may be unrelated to the chief complaint, on the initiative of individual physicians will inevitably lead to disorganized screening. An approach with several screening stages with stepwise increasing invasiveness in proportion to gastric cancer risk seems therefore more suitable (Figure 3).

In this approach, the first step should be to select a population sample of the general population that should be offered noninvasive screening. This selection should probably be based on epidemiologic risk factors, as symptoms cannot predict the presence of pre-

Figure 3. Flow chart gastric cancer screening in low-incidence countries.



malignant lesions or early gastric cancer (i.e. gastric carcinomas confined to the mucosa or submucosa). A risk profile could be defined based on known epidemiologic risk factors, as for instance low socioeconomic class, blood group A, and familial occurrence of gastric cancer (5,89,90). The next step, noninvasive, serologic screening is attractive to identify a population at high risk of gastric cancer in low-incidence countries, since costs and burden for patients are acceptable and thereby a large population sample can be screened. The aim of serologic screening would be to identify patients with premalignant gastric lesions that require histologic confirmation after endoscopy. Finally, endoscopic surveillance should be offered to individuals with premalignant lesions at high risk of progression. Yet, this proposal may obviously also be debated and requires testing in appropriately designed trials.

Non-Invasive Screening

Since *H. pylori* is probably the most important and most prevalent risk factor of gastric cancer, screening for *H. pylori* antibodies is an appropriate first approach to identify subjects at risk for (pre)malignant lesions of the gastric mucosa. However, the specificity of this test for the detection of (pre)malignant lesions is low, since the presence of *H. pylori* antibodies does not differentiate between chronic, nonatrophic gastritis, and (pre)malignant lesions. In addition, with longstanding, widespread AG or the presence of IM, *H. pylori* colonization can disappear and serology then becomes negative. Specific strains of *H. pylori* contain determinants, e.g. *cagA* , *vacA* and *babA* , which are associated with increased gastric cancer risk. Testing for these markers adds to the sensitivity of *H. pylori* tests to detect (pre)malignant lesions, however, the specificity of these tests remains low (91). As a result, these tests are not useful as single screening tests.

Other potential tests are pepsinogens I and II, and gastrin, which provide valuable information on the status of gastric mucosa. Pepsinogen I is produced by chief cells in the gastric fundus and corpus, whereas pepsinogen II is produced throughout the whole stomach. Gastric inflammation causes increased production of both pepsinogens, with a larger increase in pepsinogen II production in comparison to pepsinogen I. AG causes a decreased production of both pepsinogens, with a more pronounced decrease of the production of pepsinogen I in comparison with pepsinogen II. As a result of these changes, chronic gastritis is associated with a reduced pepsinogen I/II ratio, and this ratio further decreases when AG occurs (92) IM and dysplasia are probably associated with even greater decreases in pepsinogen I/II ratios (93). In addition, gastrin is synthesized and secreted almost solely from antral G-cells. *H. pylori* gastritis tends to raise the serum levels of gastrin, probably due to hyperplasia of the antral G-cells. Increased production of gastrin also occurs in patients with AG in the corpus in response to reduced acid secretion, whereas in patients with antral-predominant AG, the level of gastrin decreases (94).

By combining pepsinogens and gastrin levels with *H. pylori* serology in a decision algorithm, it is possible to establish the presence of gastritis, distinguish AG, and locate atrophic changes with high sensitivity and specificity (95). However, the value of these tests to discern a population at risk of IM and dysplasia is still unclear. Thus, serologic screening is suited for clinical use in countries with a relatively low incidence of gastric cancer when further endoscopic follow-up is given to cases with an abnormal serologic profile suggestive of AG.

Endoscopy

In Western countries, premalignant gastric lesions and early gastric cancer are generally diagnosed on histologic examination of random biopsies, whereas in Asian countries, especially in Japan, the presence and extension of these lesions are frequently established at endoscopy (96,97). These remarkable differences are explained by training and a different attitude towards inspection of the stomach. In Japan, endoscopists spend considerably more time on a thorough inspection of the stomach and are trained in endoscopic recognition of discrete mucosal alterations compatible with atrophy and early cancer.

Although the image quality of standard endoscopes has improved dramatically over the last decades, findings at conventional endoscopy often still correlate poorly with histologic diagnoses of AG, IM, and dysplasia (98–102). This results from unsatisfactory visualization of structure, color, and vascularity by conventional techniques, as all these features seem to play a role in adequate distinction of premalignant and early gastric cancer lesions. As a consequence, several alternative and supplementary strategies have been developed to overcome the limitations of standard endoscopic imaging.

Several studies have been performed to evaluate magnification endoscopy in patients with premalignant gastric lesions or early gastric cancer. An excellent correlation with histologic diagnoses was shown (103–108). The detailed visualization of the superficial gastric mucosa has resulted in classifications of pit and sulci patterns. In addition, the superficial capillary networks can be viewed in detail (109). Specific surface and microvascular patterns can identify *H. pylori*-induced chronic gastritis and the entities of premalignant gastric lesions. In *H. pylori* gastritis, collecting venules lose their regular starfish pattern and can even become completely invisible. In AG, changes in the subepithelial capillary network and collecting venules correlate with the degree of atrophy. Areas with IM are suspected in case of depression with large and long epithelial crests by deep sulci (103).

Several in vivo staining techniques can be used as an adjunctive to plain visualization of gastric mucosal lesions at conventional or magnifying endoscopy. Methylene blue utilizes the absorptive capability of cells to stain IM, whereas indigo carmine can be useful to enhance minute architectural changes in neoplastic lesions. The use of chromoendoscopy in detection of premalignant gastric lesions has long been based on expert opinion rather than scientific evidence. However, a recent study confirmed the validity of chromoendoscopy in

a surveillance setting for hereditary gastric cancer (110). This study showed that the use of chromoendoscopy facilitated detection of small foci of early gastric carcinoma not visible with white light gastroscopy.

A number of techniques that use specific spectral and absorptive features of light have been developed; these include narrow-band imaging, autofluorescence, and hemoglobin enhancement. Narrow-band imaging has been evaluated in combination with magnification endoscopy. This technique uses narrow filtered bands in the excitation light to thereby improve imaging of the superficial capillary network and surface contrast within the mucosa. Seemingly, this technique is also suited to visualize in-depth invasion and could thereby assist the excision of lesions by endoscopic techniques (111,112). However, data are still preliminary. Autofluorescence endoscopy is characterized by exposure of tissue to light of shorter wavelength, typically blue light, and emission of the light by endogenous fluorophores. The results of studies into the role of autofluorescence in patients with gastric cancer have been highly conflicting and its value in gastric cancer surveillance is therefore probably small (113–116). Super-addition of a pseudocolor image based on the hemoglobin content in the mucosa (hemoglobin enhancement) can be used to facilitate the delineation of lesions (117).

In spite of promising results of these new techniques, the added value in detection of premalignant gastric lesions still awaits confirmation in controlled trials and development of validated, uniform classification criteria. Thereafter, evaluation in a surveillance setting is indicated. Nonetheless, the reliance on visual subjective judgement is a drawback of these techniques. Therefore, in vivo measurement of tissue characteristics by spectroscopy techniques could add to existent techniques, as for instance fluorescence spectroscopy, elastic scattering spectroscopy, and Raman spectroscopy (118–120). Yet, as many of these advanced techniques will remain in the hands of a few experts, the most effective approach to improve the initial detection of (pre)malignant lesions would probably be to train endoscopists in scrutinizing areas of mucosa at risk and recognizing the subtle visible changes using standard equipment (121).

TREATMENT

The importance of premalignant gastric lesions in the neoplastic cascade of gastric cancer is increasingly recognized. This leads to an augmenting interest in therapeutic options for these conditions. These therapeutic options can be divided into chemopreventive and endoscopic strategies.

Chemoprevention

Chemoprevention is defined as the use of pharmacologic agents to reverse or halt carcinogenesis. Chemoprevention by means of *H. pylori* eradication therapy is frequently prescribed in patients with premalignant gastric lesions. However, controversy remains whether eradication halts the progression or can even cause regression of premalignant lesions, since the evidence from several clinical prospective trials is conflicting. Nevertheless, trials with a randomized controlled design have suggested that *H. pylori* eradication can lead to a regression of atrophic gastritis (83,122–135). Whether this is also true for intestinal metaplasia is less clear. From five prospective studies that have evaluated the effect of *H. pylori* eradication in patients with premalignant lesions to the endpoint of gastric cancer (83,122,129,136,137), only one nonrandomized prospective study demonstrated a significant reduction of gastric cancer development after *H. pylori* eradication in comparison with persistent *H. pylori*-positives (136). Almost all gastric carcinomas (37 of 43 cases, 86%) in these prospective studies occurred in patients who already had intestinal metaplasia or dysplasia at baseline. Unfortunately, the total number of patients with premalignant lesions at baseline included in these studies was relatively low in some studies and not specified in others. Therefore, data of more intervention studies with adequate follow-up after *H. pylori* eradication of large populations of patients with premalignant gastric lesions, especially with intestinal metaplasia and dysplasia, are still eagerly awaited.

So far, the conclusion from the available prospective studies can only be that *H. pylori* eradication does not reverse or halt progression of premalignant lesions in all infected patients. This finding suggests that premalignant lesions can either pass a point of no return, or that other pathogenetic mechanisms besides infection play a role in the progression from preneoplasia to invasive cancer of the stomach. Factors that may be involved include bile reflux, dietary deficiencies, and autoimmunity. Therefore, alternative chemopreventive agents may have an additional effect to *H. pylori* eradication. In addition, *H. pylori*-negative patients with premalignant lesions, possibly through loss of colonization of *H. pylori*, may benefit from alternative chemoprevention too.

Potential alternative chemoprevention agents are dietary supplementation and COX-2 inhibitors (138). Adequate consumption of fruit and vegetables seems to reduce the risk of cancer and the declining incidence of gastric cancer in Western countries appears partly caused by diet changes. Although some studies have shown promising results of folic acid, vitamin C, and beta-carotene supplementation, these results were not confirmed in a large meta-analysis (123,139–142). It is therefore doubtful that feeding supplements will favorably affect premalignant gastric lesions in individuals with an adequate nutritional status. In addition, as the expression of COX-2 is upregulated early in gastric carcinogenesis, COX-2 inhibition may inhibit carcinogenesis. Several experimental and animal studies have focused on the chemopreventive effect of COX-2 inhibitors and have demonstrated reduced progression

of premalignant gastric lesions (143–149). Moreover, epidemiologic and meta-analysis have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce gastric cancer risk (150). Nevertheless, a recently published randomized controlled trial failed to demonstrate significant regression of IM by rofecoxib after 2 years' follow-up (151). Unfortunately, the risk of gastrointestinal, renal, and cardiovascular side-effects will probably preclude future clinical trials with COX-2 inhibitors in patients with premalignant gastric lesions (152).

Endoscopic Treatment

Over the past decades endoscopic alternatives to gastrectomy have been developed to treat severe dysplasia and early invasive cancers with limited risk for lymph node metastasis. Endoscopic mucosal resection (EMR) is designed to remove mucosal lesions by dissection through the submucosa. This technique is an accepted alternative to surgical resection in patients with intestinal type well-differentiated malignant lesions that are confined to the mucosa. According to the Japanese gastric cancer guidelines, lesions should be smaller than 2 cm in size (153).

A wide variety of EMR techniques and instruments have been described, for instance lift-and-cut, band-and-cut and capped EMR. A new development is endoscopic submucosal dissection (ESD) of gastric lesions larger than 2 cm without lymph node metastasis. In contrast to standard EMR in which a snare is used to dissect the lesion, this technique uses a needle-knife to separate the lesion from the surrounding mucosa and basal layer underneath. Basically, all EMR techniques may be of equal quality when performed by experienced endoscopists, however, comparative studies are not yet available.

From an oncological point of view, en-bloc resection is obviously preferable to piecemeal resection, since lateral margins can be assessed and recurrence rates are significantly lower (154). Local recurrence rates are 2% after en-bloc resections and 15% for piecemeal resections (Table 5). Compared to conventional EMR techniques, ESD results in higher en-bloc resection rates, especially in lesions larger than 2 cm (155). Since experience with a large number of cases is necessary to select eligible lesions and perform this procedure safely and effectively,

Table 5. Curability and local recurrence rate after endoscopic mucosal resection (155).

	Curative	Non-curative	Not evaluable
En-bloc resections (N=1115)	911 (82%)	16 (1.4%)	44 (4%)
Local recurrence	0	16	8
Piecemeal resections (N=326)	146 (45%)	80 (25%)	100 (30%)
Local recurrence	7	26	17

EMR and especially ESD should only be performed in specialized centers by experienced interventional endoscopists (156–159).

A Japanese study showed that after EMR allowed complete free-margin resection of 69% of intramucosal lesions (160). No gastric cancer-related deaths occurred after a median follow-up of 38 months and major complications, bleeding and perforation, occurred in 5% of interventions. Based on these excellent treatment results, EMR has been implemented in the routine management for early gastric cancer in several countries. However, a recently published Cochrane review retrieved no randomized controlled trials to substantiate this policy and concluded that there is still a need for randomized controlled trials to determine the effects of EMR compared to gastrectomy (161). As EMR is nowadays used as a first approach allowing extensive histology in many expert centers, it is very doubtful whether such randomized trials will be performed. Another debatable issue is the necessity and the timing of endoscopic follow-up after EMR to detect recurrence of the index lesion or development of metachronous tumors. A recently published retrospective study suggests annual endoscopic examinations after successful EMR; however, more data are needed (162).

CONCLUSIONS

The understanding of gastric carcinogenesis has advanced considerably over the past decades. Especially the insights into the role of *H. pylori* infection and the progression of chronic gastritis through premalignant stages to gastric cancer have shifted the focus of gastric cancer research from merely palliative strategies to the development of preventive strategies. *H. pylori* eradication may provide an important basis for gastric cancer prevention; however, controversy still remains whether eradication halts progression or can even cause regression of premalignant gastric lesions. To improve survival of patients with gastric cancer, detection and treatment in an early stage of disease are essential, and both require further research. Moreover, the development of an approachable population-screening program is likely to become mandatory, although in countries with relatively low incidence rates of gastric cancer cost-benefit evaluation will be required.

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CHAPTER 8

Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands

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ABSTRACT

Background & Aims: A cascade of precursor lesions (eg, atrophic gastritis, intestinal metaplasia, and dysplasia) precedes most gastric adenocarcinomas. Quantification of gastric cancer risk in patients with premalignant gastric lesions is unclear, however. Consequently, endoscopic surveillance is controversial, especially in Western populations.

Methods: To analyze current surveillance practice and gastric cancer risk in patients with premalignant gastric lesions, all patients with a first diagnosis between 1991 and 2004 were identified in the Dutch nationwide histopathology registry (PALGA); follow-up data were evaluated until December 2005.

Results: In total, 22,365 (24%) patients were diagnosed with atrophic gastritis, 61,707 (67%) with intestinal metaplasia, 7616 (8%) with mild-to-moderate dysplasia, and 562 (0.6%) with severe dysplasia. Patients with a diagnosis of atrophic gastritis, intestinal metaplasia, or mild-to-moderate dysplasia received re-evaluation in 26%, 28%, and 38% of cases, respectively, compared with 61% after a diagnosis of severe dysplasia ($P < .001$). The annual incidence of gastric cancer was 0.1% for patients with atrophic gastritis, 0.25% for intestinal metaplasia, 0.6% for mild-to-moderate dysplasia, and 6% for severe dysplasia within 5 years after diagnosis. Risk factors for gastric cancer development were increasing severity of premalignant gastric lesions at initial diagnosis (eg, severe dysplasia, hazard ratio 40.14, 95% confidence interval 32.2– 50.1), increased age (eg, 75– 84 years, hazard ratio 3.75, 95% confidence interval 2.8 –5.1), and male gender (hazard ratio 1.50, 95% CI 1.3–1.7).

Conclusions: Patients with premalignant gastric lesions are at considerable risk of gastric cancer. As current surveillance of these patients is inconsistent with their cancer risk, development of guidelines is indicated.

INTRODUCTION

Gastric cancer represents the fourth most common cancer and second leading cause of cancer-related death worldwide. (1) Although the incidence of gastric cancer has declined over the past decades, especially in Western countries, the mortality rate due to this disease remains high. As symptoms are frequently absent or only vague until the disease reaches an advanced stage, curative therapeutic options are usually limited at the time of diagnosis. (2)

Detection of gastric cancer at a curable stage substantially improves morbidity and survival. For instance, nationwide mass screening programs for gastric neoplasia in Japan have resulted in a higher detection rate of early gastric cancer. It has been suggested that cancer mortality has thereby been reduced. (3) However, population screening is presumably less appropriate in regions with low incidences of gastric cancer, such as Western Europe and North America. Therefore, a more targeted approach seems necessary to reduce mortality in these regions. Identification and surveillance of individuals at high risk for gastric cancer may provide the basis for such a strategy.

An important risk factor for gastric cancer development is the presence of premalignant changes of the gastric mucosa. (4) These lesions are involved in a widely accepted model leading to intestinal-type gastric carcinomas. In this multistep model of gastric carcinogenesis, *Helicobacter pylori* causes chronic inflammation of the gastric mucosa, which over years progresses through the premalignant stages of atrophic gastritis, intestinal metaplasia, and dysplasia to eventually gastric adenocarcinomas. (4,5)

The detection and surveillance of patients with these premalignant lesions could potentially lead to early detection and treatment of advanced precursors and gastric carcinomas. Quantification of gastric cancer risk in patients with premalignant gastric lesions is unclear, however, as studies evaluating the progression of premalignant lesions to gastric cancer have shown conflicting results. Reported progression rates to gastric cancer varied between 0% and 2% per year for atrophic gastritis. (6) However, for intestinal metaplasia and dysplasia, progression rates to gastric cancer varied widely from 0% to 10% per year and from 0% to 73% per year, respectively. (6) As a result, the efficacy of re-evaluation or surveillance of patients with premalignant gastric lesions remains highly controversial. (7–10) In particular, in Western countries, only very limited recent data are available on this issue. Even for patients with gastric dysplasia, a condition carrying a presumed high cancer risk, clear guidelines on clinical management are lacking, and recommendations on timing and frequency of follow-up investigations vary widely.

In this study, we therefore investigated the progression rates of premalignant gastric conditions to gastric cancer in a Western population, and in addition evaluated whether the surveillance practice of patients with these premalignant gastric lesions matches their cancer risk. The resulting data should provide a basis for decisions on gastric cancer surveillance practice in Western populations.

MATERIALS AND METHODS

Histopathology Database

In the Netherlands, all histopathology and cytopathology reports are collected in a national archive (PALGA database), which has nationwide coverage since 1991. (11) Each report can be tracked to an individual patient with a unique identifier, allowing follow-up on an individual basis regardless of whether treatment is received at the same or different institutes. Every record in the database contains a summary of the original pathology report and diagnostic codes similar to the Systematized Nomenclature of Medicine classification of the College of American Pathologists that are given by the pathologist who made the diagnosis. (12) The diagnostic code contains a term indicating the anatomical location, type of sample, and a morphological term describing the finding (eg, "stomach*biopsy*intestinal metaplasia"). Details regarding the number and intragastric location of biopsies and presence of *H. pylori* are not uniformly registered. The present study was based on data recorded in the PALGA database between 1991 and 2005.

Surveillance and Progression Analysis

Patients with histologically confirmed diagnoses of premalignant gastric lesions, (eg, atrophic gastritis, intestinal metaplasia, or dysplasia) were identified in the database (see Appendix). Only the most severe premalignant lesion at baseline (ie, the first observation of a premalignant lesion) was evaluated as the initial diagnosis.

Patients with either gastric or esophageal surgery or malignancy registered before or simultaneously with the first diagnosis of a premalignant gastric lesion were excluded from the cohort. In addition, a period of at least 1-year follow-up to receive a re-evaluation upper-gastrointestinal (GI) endoscopy was taken into consideration; consequently, patients with a first diagnosis in 2005 were excluded from analysis. For each patient, all summary texts and diagnostic codes concerning gastric biopsies from the first diagnosis of a premalignant gastric lesion to the end of the study period (December 2005) were retrieved.

In order to analyze surveillance, patients with a diagnosis of Barrett's esophagus prior to or simultaneously with the diagnosis of a premalignant gastric lesion were excluded from analysis, as most of them participated in an endoscopic surveillance program for this indication.

For diagnoses of esophageal and cardia adenocarcinomas, the pathology report of the surgical resection specimen was reviewed; only carcinomas of which the bulk was macroscopically located below the esophagogastric junction were evaluated as primary gastric cancer.

Statistical Analysis

As the PALGA registry does not contain the patients' date of death, unless an autopsy had been performed, censoring because of death was imputed to evaluate the length of follow-up, using survival data from the general Dutch population (Dutch Cancer Registry personal communication, October 2007). Within each category of premalignant gastric lesions, intervals between initial and repeated upper GI endoscopies with biopsies and between initial premalignant and gastric cancer diagnosis were evaluated by Kaplan–Meier survival analysis; equality between the categories of premalignant gastric lesions was tested with the log-rank test. Univariate and multivariate Cox-regression analysis was performed to identify independent risk factors for progression of premalignant gastric lesions to more advanced gastric lesions in general or gastric cancer.

RESULTS

A cohort of 92,250 patients with a first diagnosis of a premalignant gastric lesion was identified, with a 1:1 male-to-female ratio (Table 1). Median age at initial diagnosis was significantly higher with increasing severity of the categories of premalignant gastric lesions ($P < .001$) (Table 1). Women were significantly older than men at the initial diagnosis of atrophic gastritis (median age 63.2 years vs 57.8 years), intestinal metaplasia (68.7 vs 64.6), mild-to-moderate dysplasia (70.9 vs 66.9), and severe dysplasia (77.6 vs 72.1) (all $P < .001$). The mean age difference between men and women did not increase significantly with increasing severity of the categories of premalignant lesions ($P = .35$ univariate analysis of variance).

Table 1. Baseline characteristics of our study population.

	Total	Atrophic gastritis	Intestinal metaplasia	Mild to moderate dysplasia	Severe dysplasia
Number of patients (n) (%)	92,250	22,365 (24%)	61,707 (67%)	7,616 (8.3%)	562 (0.6%)
Male/ Female	46,985/ 45,265	10,110/ 12,255	32,415/ 29,292	4,153/ 3,463	307/ 255
Age					
Median	65.7	60.7	66.5	68.7	75.3
25th-75th percentile	53.1-75.5	46.4-73.3	54.9-75.8	56.8- 77.2	64.9- 81.4
Barrett's esophagus (%)	1934 (2.1%)	460 (2.1%)	1219 (2.0%)	244 (3.2%)	11 (2.0%)

Surveillance

After excluding patients with Barrett's esophagus, surveillance was evaluated in 90,316 patients using the unique identifier of each individual patient (Table 1). Patients with a di-

agnosis of gastric atrophy or intestinal metaplasia received at least 1 re-evaluation upper GI endoscopy with histological re-evaluation in 26% and 28% of cases, respectively, compared with 38% after a diagnosis of mild or moderate dysplasia and 61% of patients with severe dysplasia ($P < .001$) (Figure 1). In all categories of premalignant gastric lesions, patients who underwent subsequent histological re-evaluation were significantly younger than patients who did not ($P < .001$) (Figure 2). The mean interval between initial diagnosis and histological re-evaluation was 2.6 years (standard deviation [SD] 2.9) in patients with atrophic gastritis, 2.0 years (SD 2.6) for patients with intestinal metaplasia, 1.6 years (SD 2.4) in patients with mild-to-moderate dysplasia, and 0.4 years (SD 1.0) in patients with severe dysplasia ($P < .001$) (Figure 3). These findings show that the majority of patients with premalignant gastric lesions do not receive endoscopic follow-up, not even those with a diagnosis of dysplasia.

Figure 1. The proportion of patients with atrophic gastritis, intestinal metaplasia, and dysplasia receiving 1 or more follow-up upper-gastrointestinal endoscopies.

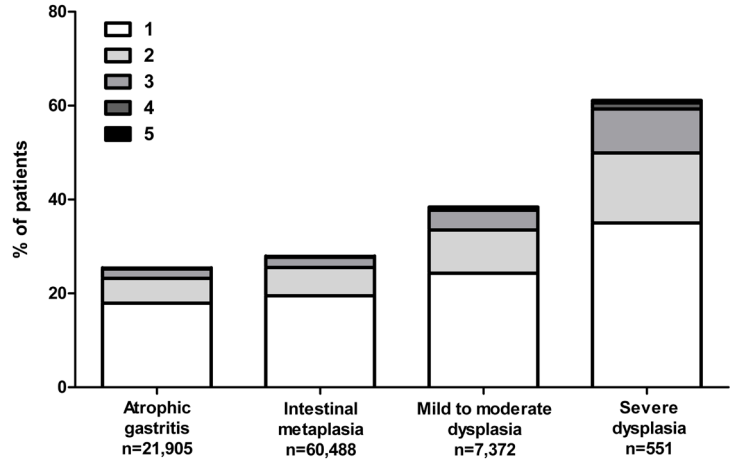


Figure 2. The proportion of patients with atrophic gastritis, intestinal metaplasia, and dysplasia receiving histological follow-up according to 5-year age categories.

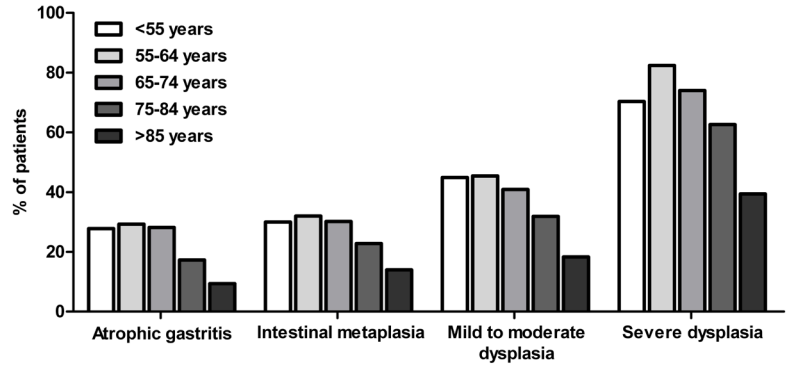
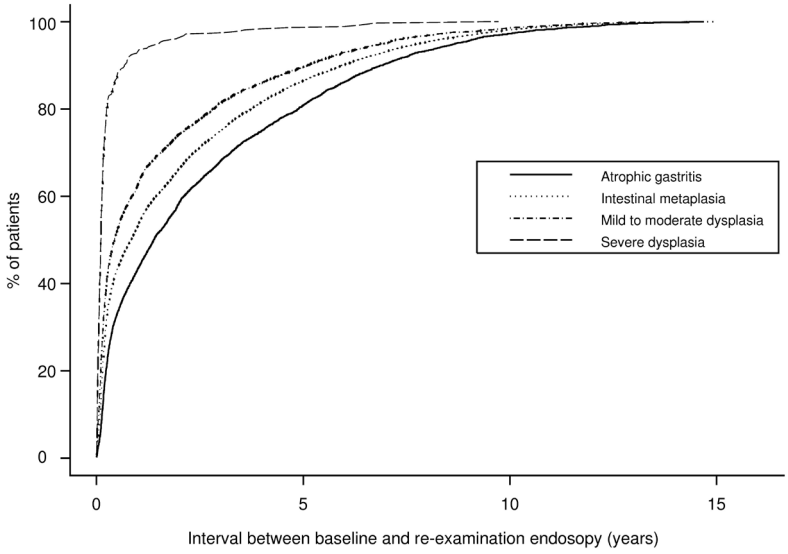


Figure 3. Timing of re-examination in patients who received histological re-evaluation of premalignant gastric lesions.



Progression

Histological follow-up data on the gastric mucosa were available on 26,538 patients (Figure 4). Progression to more advanced lesions overall, was significantly more common in patients with severe dysplasia as compared with patients with atrophic gastritis, intestinal metaplasia, and mild-to-moderate dysplasia ($P < .001$).

Figure 4. Follow-up results in patients in whom histological re-evaluation was performed. The results are presented as most advanced gastric lesion during follow-up for each category of premalignant gastric lesions at baseline. The outcome of patients who developed esophageal or cancer at the esophagogastric junction is not mentioned in this figure. Mean length of follow-up for patients with atrophic gastritis, intestinal metaplasia, mild-to-moderate dysplasia, and severe dysplasia: 3.5, 2.8, 2.5, and 1.0 years, respectively.

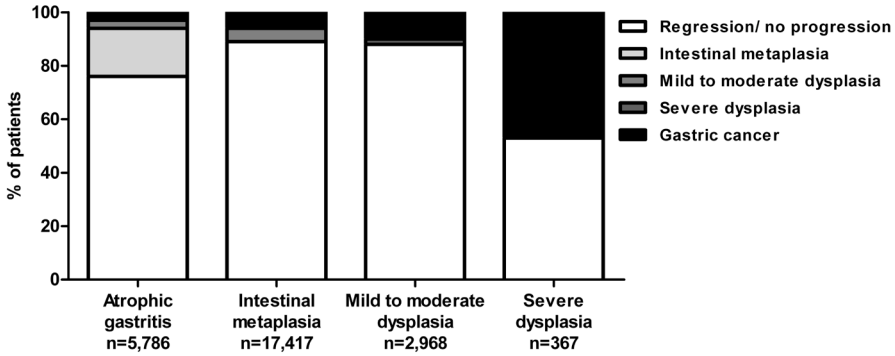
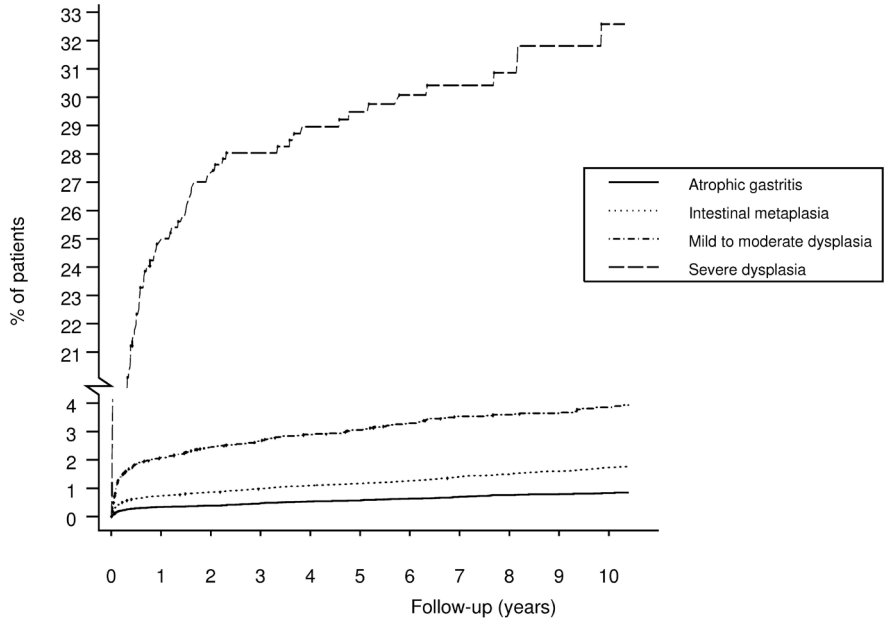


Figure 5. Progression rate of premalignant gastric lesions to gastric cancer in 92,250 patients with premalignant gastric lesions (90,780 censored patients).



Progression to gastric cancer was evaluated for the whole cohort of 92,250 patients (Figure 5). During follow-up, 1470 patients developed gastric cancer at a median age of 73.5 years (SD 11.5) (61% men, 39% women). In total, 161 of these patients had at baseline been diagnosed with atrophic gastritis, 874 patients with intestinal metaplasia, 270 patients with mild-to-moderate dysplasia, and 165 patients with severe dysplasia. The age at diagnosis of gastric cancer was not significantly different between different diagnoses of premalignant gastric lesions at baseline ($P = .34$). Men were significantly younger at diagnosis of gastric cancer (median age, 72.3 years) as compared with women (75.5 years) ($P < .001$). The median interval between initial diagnosis and gastric cancer was 1.6 years (SD 3.2) in patients with atrophic gastritis, 0.90 years (SD 3.4) for patients with intestinal metaplasia, 0.45 years (SD 3.1) in patients with mild-to-moderate dysplasia, and 0.13 years (SD 2.7) in patients with severe dysplasia ($P < .001$). Within 1, 5, and 10 years of follow-up after initial diagnosis, gastric cancer was diagnosed in 0.3%, 0.6%, and 0.8% of patients with atrophic gastritis; 0.7%, 1.2%, and 1.8% of patients with intestinal metaplasia; 2.1%, 3.1%, and 3.9% of patients with mild-to-moderate dysplasia; and 24.9%, 29.5%, and 32.7% of patients with severe dysplasia ($P < .001$) (Figure 5). Men with intestinal metaplasia or mild-to-moderate dysplasia showed faster progression to gastric cancer as compared with women (both $P < .001$), whereas no significant difference was shown for men and women with atrophic gastritis or severe dysplasia ($P = .16$, respectively $P = .45$).

The high number of gastric cancer diagnoses within 1 year of follow-up in patients with severe dysplasia suggests that these patients need to be re-examined shortly after diagnosis. Periodical surveillance seems indicated in all patients with gastric dysplasia; however, in patients with atrophic gastritis or intestinal metaplasia, risk of progression to gastric cancer is too low to recommend surveillance in all patients. Surveillance may be considered, however, at larger intervals in younger patients with more severe or widespread atrophic gastritis and intestinal metaplasia.

Risk Factors for Progression

Within multivariate Cox-regression analysis, male gender was independently associated with an increased risk of progression to more advanced lesions overall (hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.4 –1.7) and with an increased risk of gastric cancer (HR 1.50, 95% CI 1.3–1.7), as compared with female gender (Table 2). In addition, increasing age at initial diagnosis was also independently associated with both progression to more advanced lesions and gastric cancer development. Moreover, gastric cancer risk increased significantly with the severity of premalignant gastric lesions at baseline and was clearly elevated in patients with intestinal metaplasia (HR 1.74, 95% CI 1.5–2.1), mild-to-moderate dysplasia (HR 3.93, 95% CI 3.2– 4.8), and severe dysplasia (HR 40.14, 95% CI 32.2–50.1) as compared with patients

Table 2. Risk factors for progression to advanced precursor lesions and gastric cancer in univariate and multivariate Cox-regression analysis.

Baseline	Overall progression				Gastric cancer			
	HR univariate	95% CI	HR multivariate	95% CI	HR univariate	95% CI	HR multivariate	95% CI
Sex								
- Female	1.0		1.0		1.0		1.0	
- Male	1.29	[1.2-1.4]	1.55	[1.4-1.7]	1.49	[1.3-1.7]	1.50	[1.3-1.7]
Age								
- 35-44 years	1.0		1.0		1.0		1.0	
- 45-54 years	0.97	[0.8-1.2]	1.06	[0.9-1.3]	1.47	[1.0-2.1]	1.39	[1.0-2.0]
- 55-64 years	1.43	[1.2-1.7]	1.62	[1.4-1.9]	2.62	[1.9-3.6]	2.38	[1.7-3.3]
- 65-74 years	2.04	[1.8-2.4]	2.33	[2.0-2.7]	3.93	[2.9-5.3]	3.44	[2.5-4.7]
- 75-84 years	3.46	[3.0-4.1]	3.94	[3.4-4.6]	4.53	[3.3-6.2]	3.75	[2.8-5.1]
- >85 years	5.34	[4.3-6.7]	6.45	[5.1-8.1]	3.27	[2.3-4.7]	2.64	[1.8-3.8]
Histopathology								
- Atrophic gastritis	1.0		1.0		1.0		1.0	
- Intestinal metaplasia	0.52	[0.5-0.6]	0.43	[0.4-0.5]	2.10	[1.8-2.5]	1.74	[1.5-2.1]
- Mild to moderate dysplasia	0.68	[0.6-0.8]	0.53	[0.5-0.6]	5.05	[4.2-6.1]	3.93	[3.2-4.8]
- Severe dysplasia	6.11	[5.2-7.2]	3.57	[3.0-4.2]	55.94	[45.0-69.5]	40.14	[32.2-50.1]
Period of initial diagnosis								
- 1991-1995	1.0		1.0		1.0		1.0	
- 1996-2000	1.32	[1.2-1.4]	1.26	[1.2-1.4]	0.88	[0.8-1.0]	0.92	[0.8-1.0]
- 2001-2004	2.02	[1.8-2.3]	1.83	[1.6-2.1]	0.83	[0.7-1.0]	0.82	[0.7-1.0]

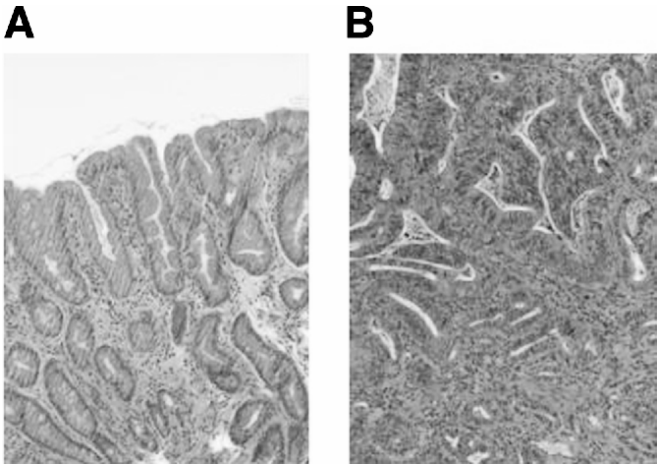
with atrophic gastritis. Time period at initial diagnosis seemed an irrelevant risk factor for neoplastic progression, because a diagnosis in the period from 2001 to 2005 was associated with an increased risk of progression to more advanced lesions as compared with a diagnosis in the period from 1991 to 1995 (HR 1.83, 95% CI 1.6 –2.1); however, gastric cancer risk was lower (HR 0.82, 95% CI 0.7–1.0). These findings show that male patients with premalignant gastric lesions carry a higher risk of gastric cancer development than female patients. Gastric cancer risk is especially elevated at an older age and after a diagnosis of more severe lesions at baseline.

DISCUSSION

This large, nationwide study shows that patients with premalignant gastric lesions carry a significant risk of gastric cancer within 10 years of follow-up (Figure 6). However, in Dutch clinical practice, which is likely to be representative for many Western countries, surveillance of these patients is regularly omitted, even in patients with overt dysplasia.

Within 5 years of follow-up, the annual incidence of gastric cancer in our Western population was 0.1% for patients with atrophic gastritis, 0.25% for intestinal metaplasia, 0.6% for mild-to-moderate dysplasia, and 6% for severe dysplasia. These observations are in line with the multistep cascade described by Correa. (4,13,14) Although this multistep cascade has been accepted for many years, quantification of gastric cancer risk in men and women with different premalignant gastric lesions has remained unclear, in particular in Western populations.

Figure 6. Progression from intestinal metaplasia to gastric adenocarcinoma after 10 years' follow-up within the same patient. (A) Gastric mucosa (corpus) showing mild gastritis with marked intestinal metaplasia, no dysplasia (1993). (B) Gastric mucosa (angulus) showing moderately differentiated gastric adenocarcinoma (2003). H&E staining, original magnification x100.



Previous cohort studies had limited sample sizes, used older histological classifications, in part specifically focused on patients with pernicious anemia, and the first studies used blindly obtained instead of endoscopic gastric biopsy samples. For these reasons, those data are of limited use for current daily practice. As a result, endoscopic surveillance of premalignant gastric lesions is highly controversial. The present data provide important insights in cancer risk and current management of patients with premalignant gastric lesions. They show that surveillance with endoscopy and biopsy sampling is relevant in patients with more advanced premalignant lesions and may lead to early detection of cancer. The improved prognosis after such early detection underlines the importance of development of surveillance guidelines.

As only a small proportion of patients with atrophic gastritis or intestinal metaplasia eventually develops gastric cancer, endoscopic follow-up of all patients with these lesions is not indicated but should be limited to patients at high risk. Previous studies have identified the intragastric location, severity, and distribution of atrophy and intestinal metaplasia, as well as the concomitant presence of associated lesions, especially, mucosa-associated lymphoid tissue (MALT) lymphoma or gastric ulcer, as markers of increased risk. (9,15,16) Furthermore, the risk is influenced by *H. pylori* virulence factors, a family history of gastric cancer, host genetics, and environmental factors (cigarette smoking, in particular). (17–21)

From our data, we can conclude that the cancer risk in patients with mild-to-moderate gastric dysplasia is similar to or even considerably higher than the risk of cancer after removal of colonic adenomas, as well as in patients with Barrett's esophagus or long-standing inflammatory bowel disease. (22–24) It is remarkable that surveillance guidelines have been widely accepted for these conditions, whereas similar guidelines for follow-up of patients with dysplastic gastric lesions are lacking. Such a guideline should include the need for follow-up biopsy, confirming the presence of dysplasia, as well as recommendations on *H. pylori* eradication.

Patients with severe dysplasia, currently classified as noninvasive high-grade neoplasia according to the revised Vienna classification, are at high risk to develop gastric cancer within 2 years of follow-up. (25,26) This finding is in line with the results of previous studies. (27–29) Given this high cancer risk, thorough endoscopic and histological re-evaluation shortly after initial diagnosis is strongly indicated. (26) New endoscopic techniques, such as magnification endoscopy and narrow band imaging may help the identification of neoplastic lesions, enable targeted biopsies, and assist endoscopic resection. (30–32) All patients with identified dysplasia should be kept under strict surveillance with repeated multiple biopsy sampling. Preliminary data show that endoscopic resection of early neoplastic lesions needs to be considered. (33)

This study identifies male gender as an important independent risk factor for progression to more advanced lesions and gastric cancer. Moreover, men showed a significantly faster progression of premalignant lesions to gastric cancer as compared with women ($P < .001$). This observation remained unchanged after stratifying patients by age. In addition, premalignant

gastric lesions were diagnosed at a significantly higher age in women. These findings are in accordance with the male predominance in gastric cancer incidence and imply that women not only enter the carcinogenic cascade at an older age but also progress slower through subsequent stages. The explanations for these differences are unknown; however, plausible explanations are an increased use of non-steroidal anti-inflammatory drugs, less smoking, a lower prevalence of virulent *H. pylori* strains, and a preventive effect of female hormones. (34–36) However, the influence of sex hormones is contradicted by the fact that differences in progression rate to gastric cancer between genders persisted after menopause.

Although this study describes a large nationwide cohort, potential weaknesses warrant consideration. First, it was impossible to evaluate clinicians' motivation to choose for or against surveillance. The majority of subjects never received endoscopic follow-up, not even those with advanced lesions at a young age. This supports the hypothesis that clinicians are insufficiently aware of the cancer risk of these patients and remain uncertain about the clinical management in the absence of guidelines. Second, as patients were treated in all hospitals throughout the country, differences in biopsy sampling protocol and histological assessment cannot be excluded. (37) Nevertheless, for grading of gastritis, it has long been routine to obtain antrum biopsies. It is at this same location that premalignant lesions predominate, with spread along the lesser curvature. (38) As we have categorized patients according to the most severe lesion, this is likely to reflect the true status of their gastric mucosa. The finding that this categorization correlates strongly with gastric cancer risk supports this assumption. In addition, the large number of patients in this study generously compensates for biopsy sampling and observer variation. Third, to evaluate progression rates to gastric cancer, a virtual life expectancy was calculated for all patients without follow-up until December 2005 based on the life expectancy of the general population. This assumption may have led to a slight underestimation of gastric cancer risk, however, as a population undergoing endoscopy tends to have increased comorbidity and mortality rates. In particular, risk factors for the development of premalignant gastric lesions may have caused a higher overall mortality rate. (15,21,39) Fourth, it was impossible to evaluate the influence of *H. pylori* eradication on the reported progression rates of premalignant gastric lesions in our study population. During most of our study period, however, the presence of premalignant gastric lesions was not an indication for *H. pylori* eradication. Also, previous studies have suggested that *H pylori* eradication may only have a very limited effect on subsequent gastric cancer incidence in patients with pre-existent premalignant gastric lesions, such as our population. (40–43) For these reasons, it is unlikely that the observed annual cancer incidences were strongly influenced by *H. pylori* eradication treatments in our population. Finally, an important problem in studies evaluating progression of premalignant lesions is the occurrence of sampling errors (ie, the inability to biopsy the exact same intragastric location twice), which is even more relevant when the preneoplastic lesion has a patchy distribution. (44) In patients with dysplasia, lesions are more likely to be visible endoscopically, thus allowing for targeted biopsy

sampling. In contrast, atrophic gastritis and intestinal metaplasia are mostly diagnosed in random biopsies, reflecting the background status of the gastric mucosa in these patients. Our results show that this background status allows differentiation into risk categories for gastric cancer.

Judgment on the efficacy of surveillance of patients with premalignant gastric lesions requires consideration of burden for patients, costs, and capacity of hospital care. Detailed research into these aspects is required to identify individuals who should be offered surveillance. In case surveillance is performed, more research is needed on the exact design of strategies, including the most optimal endoscopic surveillance frequency, techniques, and biopsy sampling protocols.

In conclusion, gastric cancer risk in patients with atrophic gastritis, intestinal metaplasia, and dysplasia of the stomach increases significantly with progressive severity of the lesions. The occurrence and progression of these lesions are more pronounced in men than in women. Most importantly, the risk of cancer is comparable or even higher in patients with premalignant gastric lesions than in patients with other premalignant gastrointestinal conditions, which are routinely monitored. Therefore, follow-up should also be seriously considered in patients with premalignant gastric lesions. As current surveillance of premalignant gastric lesions is discrepant with the substantial gastric cancer risk of these lesions, development of clinical guidelines on endoscopic surveillance or treatment of premalignant gastric lesions is strongly indicated. Our data show that routine endoscopic surveillance at short intervals is warranted in patients with gastric dysplasia, whereas surveillance at longer intervals should be considered for patients with atrophic gastritis and intestinal metaplasia. Knowledge of detailed individual risk of progression to gastric cancer is important and requires further investigation.

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APPENDIX

PALGA diagnosis codes used in the analysis:
Atrophic gastritis: M58000, M58001, M58010
Intestinal metaplasia: M73000, M73200, M73320, M73321, M73300
Dysplasia: M74000, M74006, M74007, M74008, M74009

Gastric adenocarcinomas: M80011, M80101, M80102, M81403, M80103, M84803, M81443, M81453, M84903, M82113, M80503, M82603, M69360, M80104, M80105, M80123, M80193, M80203, M81404, M80213

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CHAPTER 9

The use of clinical, histological and serological parameters to predict the intragastric extent of intestinal metaplasia: a recommendation for routine practice

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ABSTRACT

Background: Surveillance of intestinal metaplasia (IM) of the gastric mucosa should be limited to patients at high risk of gastric cancer. Patients with extensive IM are at increased cancer risk; however, the intragastric extent of IM is usually unknown at the time of initial diagnosis.

Objective: To assess the predictive value of clinical, histological and serological parameters for the intragastric extent of IM.

Design and Setting: Prospective, multi-center study.

Patients: 88 patients with a previous diagnosis of IM of the gastric mucosa.

Intervention: Surveillance gastroscopy with extensive random biopsy sampling.

Main outcome measurements: Biopsies were evaluated according to the Sydney classification system. In addition, serological testing of *Helicobacter pylori* and CagA status, pepsinogens I and II, gastrin, and intrinsic factor antibodies was performed. The association between available parameters and extensive IM was evaluated with logistic regression analysis.

Results: In 51 patients (58%) IM was present in the biopsies from at least two intragastric locations. The most important predictors of extensive IM were a family history of gastric cancer, alcohol use ≥ 1 unit/ day, moderate or marked IM at the index biopsy, and a pepsinogen I to II ratio <3.0. A simple risk score based on these factors could identify extensive IM in 24/25 (96% sensitivity) patients.

Limitation: A prospective cohort study should confirm the proposed risk stratification.

Conclusions: A risk score of clinical, histological and serological parameters can predict extensive intragastric IM and may serve as a practical tool to select patients for surveillance endoscopy in routine clinical practice.

INTRODUCTION

In the model of gastric carcinogenesis, *Helicobacter pylori* plays a pivotal role in causing chronic active gastritis. Chronic *H. pylori*-induced gastritis progresses over years through the sequential stages of atrophic gastritis, intestinal metaplasia and dysplasia to gastric adenocarcinomas. (1;2) The identification and surveillance of these pre-malignant lesions could potentially lead to early detection and treatment of advanced precursors and gastric carcinomas. (3-5)

To date, pre-malignant gastric lesions are often accidentally diagnosed in random biopsy samples obtained during routine upper gastrointestinal endoscopy. As the management of patients with pre-malignant gastric lesions is controversial, the performance of endoscopic surveillance largely depends on the personal experience of clinicians and is frequently omitted in current clinical practice. (3;6)

Surveillance of patients with pre-malignant gastric lesions should preferably be limited to patients at high risk of gastric cancer. The substantial cancer risk in patients with gastric dysplasia demands periodical surveillance or endoscopic intervention. Since atrophic gastritis and intestinal metaplasia eventually progress to gastric cancer in only a small proportion of patients, surveillance in these individuals should preferentially be offered to those at highest risk. (3)

Previous studies have shown that the intragastric extent of intestinal metaplasia is an important indicator of this cancer risk. (7-9) However, the degree of intestinal metaplasia can only be judged accurately after repeated endoscopy with multiple biopsy samples. This has significant disadvantages, such as burden for patients, high work load and high costs. Therefore, other methods to estimate the extent of intestinal metaplasia at the time of diagnosis are highly relevant to select patients for endoscopic surveillance.

In this study, we aimed to determine the value of clinical characteristics, histological assessment of routine gastric biopsies, and serological markers as predictors for the intragastric extent of intestinal metaplasia.

METHODS

Patient selection

Consecutive outpatients with a previous histological confirmed diagnosis of intestinal metaplasia of the gastric mucosa (index diagnosis) were invited to undergo a surveillance endoscopy between March 2006 and June 2007. The surveillance endoscopy was performed within six years after the initial diagnosis of intestinal metaplasia. Patients with a previous diagnosis of upper gastrointestinal malignancy or a history of esophageal or gastric surgery

were excluded. The institutional review boards of the participating hospitals approved this study and written informed consent was obtained from all patients prior to surveillance endoscopy.

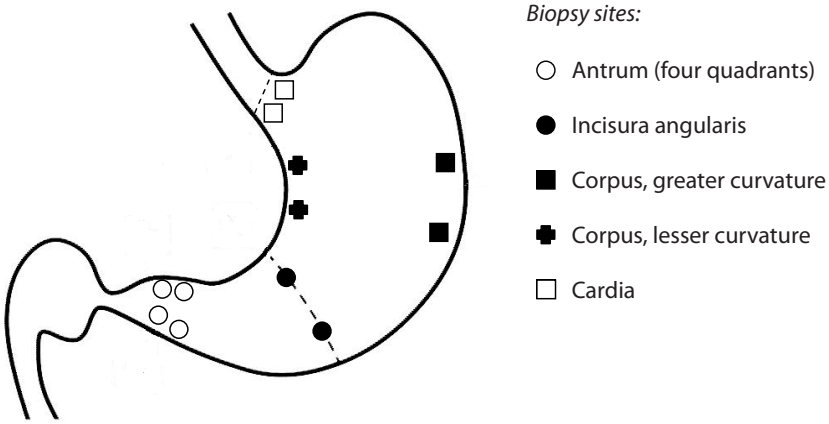
Clinical characteristics

A structured questionnaire was used, which comprised information on lifestyle factors, medication use, medical history, and family history of gastric cancer. In addition, information with regard to macroscopic lesions detected at the baseline endoscopy was retrieved from endoscopy reports.

Endoscopy

All patients underwent a conventional upper gastrointestinal endoscopy using a standard forward-viewing video gastroscope (Olympus GIF-Q160, Olympus Optical Co., Tokyo, Japan). Biopsies for histological assessment were taken from five standardized intragastric locations: 4 quadrant biopsies from the antrum (2-3 cm proximal to the pylorus), 2 from the angulus, 4 from the mid corpus (2 from the lesser curvature, 2 from the greater curvature) and 2 from the cardia (Figure 1). In case of endoscopically visible lesions or suspicion of Barrett's esophagus, additional targeted biopsy samples were obtained. These additional biopsies were not part of this study.

Figure 1. Random biopsy scheme: biopsies were obtained from five standardized intragastric locations. (Adapted from Dixon *et al.* (10))



Histological assessment

Gastric biopsy specimens were fixed in buffered formalin and embedded in paraffin. The slide sections were stained with haematoxylin and eosin (H&E). An expert gastro-intestinal pathologist (HVD) assessed all histological sections from the baseline and surveillance endoscopy. The pathologist was blinded to the patient data, index diagnosis, and endoscopic findings. All histological sections were assessed according to the updated Sydney classification system. The following items were evaluated separately: *H. pylori* density, acute inflammation (neutrophil infiltration), chronic inflammation (mononuclear infiltration), gastric atrophy, and intestinal metaplasia. (10) All these items were scored from 0 (absent), to 1 (mild), 2 (moderate), or 3 (marked). In addition, gastritis was evaluated with the OLGA staging system and classified into four stages (I-IV), provided that at least two antrum and two corpus biopsies were available for histological assessment. (11) Dysplasia was assessed according to the revised Vienna classification. (12;13)

Serological markers

Fasting blood samples were obtained from all included patients. Separated serum samples were stored at -80°C until analysis. Serological testing of *H. pylori* and CagA status, pepsinogens I and II, gastrin, and intrinsic factor antibodies was performed using commercial ELISA tests (Orion Diagnostica, Ravo diagnostica, Biohit, Euroimmun). The tests were performed according to the instructions of the manufacturers.

Statistical analysis

Two definitions were used for the identification of extensive intragastric intestinal metaplasia at surveillance endoscopy: 1) intestinal metaplasia in the random biopsies from at least two different intragastric locations (multifocal intestinal metaplasia); 2) moderate or marked intestinal metaplasia in at least two random biopsies (severe grades of intestinal metaplasia). Chi-square tests and t-tests were used to evaluate clinical, histological and serological parameters in patients with extensive intestinal metaplasia as compared to patients with no or only limited intestinal metaplasia at surveillance endoscopy. Associations with the presence of extensive intestinal metaplasia were estimated with univariate and multivariable logistic regression analysis. The most important predictors were selected using Akaike's Information Criterion (AIC) (14). The use of AIC corresponds roughly to a p-value < 0.15 for selection of predictors. Multivariable logistic regression analysis was initially performed within the different categories of parameters, i.e. clinical, histological and serological parameters. Thereafter, the most important parameters were combined in a simple clinical score, based on the regression coefficients. The odds ratio (OR) with 95% confidence intervals (CIs) was used as

measure of association. A two-sided p-value < 0.05 was considered statistically significant. Discriminative ability of the clinical score was quantified by the area under the receiver operating characteristic curve (AUC). The internal validity of the regression model was assessed by "bootstrapping" techniques. Random bootstrap samples were drawn with replacement from the full sample. The discriminative ability of the regression model was determined on the bootstrap samples and on the full sample, in which predictions were based on the regression models fitted on the bootstrap samples. This technique gives an impression of how "over-optimistic" the model is, i.e. how much the performance of the model may deteriorate when applied to a new group of similar patients. (15-17) Analyses were performed with SPSS software (v 11.5, SPSS Inc, Chicago, Ill) and R software (v 2.5.1, R: A Language and Environment for Statistical Computing, Vienna, Austria, http://www.R-project.org).

RESULTS

In total, 88 patients (43 men, 45 women) with a mean age of 60.4 years (range 24.0-75.9) underwent a surveillance endoscopy at a mean follow-up interval of 1.7 years (SD 1.5) after initial diagnosis. Seventy-one patients (81%) were from native Dutch and 17 (19%) from non-Dutch origin. Previous peptic ulcer disease was reported in the medical records of 25 patients (28%), and *H. pylori* eradication therapy in the records of 36 patients (41%).

Baseline endoscopy

At the initial baseline endoscopy, a gastric ulcer was present in one patient (1%), gastric erosions in nine patients (10%), and a gastric polyp in five patients (6%) (histology of polyps showed intestinal metaplasia in four patients and hyperplasia in one patient). The gastritis stage according to the OLGA system was assessed in 68 patients (77%), and showed stage 0 gastritis in 22 patients, stage I in one patient, stage II in 27 patients, stage III in 14 patients and stage IV in four patients.

Surveillance endoscopy

At surveillance endoscopy, the presence of intestinal metaplasia was confirmed histologically in 63/88 patients (72%), whereas in 25/88 patients (28%) no intestinal metaplasia was detected in the random biopsies. Of these latter patients, atrophic gastritis was diagnosed as most severe histological finding in only one patient, and moderate or marked chronic gastritis in three patients. The remainder had only mild chronic gastritis or no histological abnormalities. In total, 7/25 (28%) patients in whom the presence of intestinal metaplasia

Table 1. Evaluation of risk factors for extensive intestinal metaplasia at surveillance endoscopy with stepwise logistic regression analysis; associations are presented as odds ratios with 95% confidence intervals (CI) corrected for age and sex.

		Total	At least two locations with IM[1]	Univariate analysis [95% CI]	Multivariable analysis [95% CI]	Moderate/ marked IM in two or more biopsies[2]	Univariate analysis [95% CI]	Multivariable analysis [95% CI]
		n=88 (%*)	n=51 (%*)			n=42 (%*)		
Clinical parameters	Sex							
	- Male	43 (49%)	21 (41%)	1.0	1.0	19 (45%)	1.0	1.0
	- Female	45 (51%)	30 (59%)	2.1 [0.9-5.0]	3.5 [0.9-14.1]	23 (55%)	1.3 [0.6-3.1]	1.5 [0.3-6.6]
	Age							
	- <50 yrs	14 (16%)	6 (12%)	1.0	1.0	6 (14%)	1.0	1.0
	- 50- 65 yrs	39 (44%)	23 (45%)	1.9 [0.6-6.6]	0.9 [0.15-6.0]	20 (48%)	1.4 [0.4-4.8]	0.5 [0.04-5.3]
	- >65 yrs	35 (40%)	22 (43%)	2.3 [0.6-8.0]	1.1 [0.2-6.8]	16 (38%)	1.1 [0.3-3.9]	0.2 [0.01-2.4]
	Smoking							
	- Non-smoker	41 (47%)	26 (51%)	1.0		21 (50%)	1.0	
	- Current smoker	15 (17%)	9 (18%)	0.9 [0.3-2.9]		6 (14%)	0.6 [0.2-2.1]	
	- Former smoker	30 (34%)	14 (27%)	0.5 [0.2-1.3]		13 (31%)	0.7 [0.3-1.9]	
	Alcohol use***							
	- < 1 unit/ day	54 (61%)	24 (47%)	1.0	1.0	20 (48%)	1.0	1.0
	- ≥ 1 unit/ day	32 (36%)	25 (49%)	4.5 [1.7-12.1]	4.0 [0.9-16.9]	20 (48%)	2.8 [1.1-7.0]	3.4 [0.8-13.6]
	PPI use							
	- No PPI	44 (50%)	25 (49%)	1.0		21 (50%)	1.0	
	- PPI	44 (50%)	26 (51%)	1.1 [0.5-2.6]		21 (50%)	1.0 [0.4-2.3]	
	NSAIDs/ Aspirin use							
	- no NSAIDs	73 (83%)	41 (80%)	1.0		32 (76%)	1.0	
	- NSAIDs	14 (16%)	9 (18%)	1.4 [0.4-4.6]		9 (21%)	2.3 [0.7-7.6]	
	Family history of gastric cancer**							
	- Negative	70 (80%)	39 (76%)	1.0	1.0	33 (79%)	1.0	
	- Positive	9 (10%)	8 (16%)	6.4 [0.8-53.6]	8.3 [0.8-87.1]	7 (17%)	3.9 [0.8-20.2]	

		Total	At least two locations with IM[1]	Univariate analysis [95% CI]	Multivariable analysis [95% CI]	Moderate/ marked IM in two or more biopsies[2]	Univariate analysis [95% CI]	Multivariable analysis [95% CI]
		n=88 (%*)	n=51 (%*)			n=42 (%*)		
Histological parameters (index endoscopy)	Chronic gastritis corpus							
	- None/ mild	80 (91%)	45 (88%)	1.0		36 (86%)	1.0	1.0
	- Marked/ moderate	8 (9%)	6 (12%)	2.3 [0.4-12.3]		6 (14%)	3.7 [0.7-19.3]	37.7 [1.7-843]
	Localisation IM							
	- Antrum	64 (72%)	33 (65%)	1.0		26 (62%)	1.0	
	- Corpus	12 (14%)	8 (16%)	1.9 [0.5-6.9]		7 (17%)	2.0 [0.6-7.2]	
	- Antrum and corpus	12 (14%)	10 (20%)	4.7 [0.9-23.2]		9 (21%)	4.4 [1.1-17.8]	
	Grade IM							
	- Mild	34 (39%)	13 (25%)	1.0	1.0	7 (17%)	1.0	1.0
	- Moderate	29 (33%)	18 (35%)	2.6 [1.0-7.3]	3.8 [0.9-16.0]	16 (38%)	4.7 [1.6-14.4]	20.2 [2.1-193]
	- Marked	25 (28%)	20 (39%)	6.5 [1.9-21.4]	11.6 [2.2-60.2]	19 (45%)	12.2 [3.5-42.1]	134 [10.8-1663]
Serological parameters	Pepsinogen I							
	- <28 µg/L	16 (18%)	14 (27%)	1.0		12 (29%)	1.0	
	- ≥28 µg/L	68 (77%)	36 (71%)	0.2 [0.0-0.8]		29 (69%)	0.2 [0.07-0.8]	
	Pepsinogen I/ II							
	- <3.0	16 (18%)	15 (29%)	1.0	1.0	14 (33%)	1.0	1.0
	- ≥3.0	68 (77%)	35 (69%)	0.1 [0.0-0.6]	0.07 [0.01-0.7]	27 (64%)	0.09 [0.02-0.4]	0.01 [0.001-0.2]
	Gastrin							
	- <5 pmol/L	27 (31%)	11 (22%)	1.0		9 (21%)	1.0	
	- 5-<10 pmol/L	9 (10%)	5 (10%)	1.8 [0.4-8.3]		2 (5%)	0.6 [0.1-3.3]	
	- ≥10 pmol/L	50 (57%)	34 (67%)	3.1 [1.2-8.2]		30 (71%)	3.0 [1.1-8.0]	
	Intrinsic factors antibodies							
	- Negative	79 (90%)	44 (86%)	1.0		36 (86%)	1.0	
	- Positive	7 (8%)	6 (12%)	4.8 [0.5-41.5]		5 (12%)	3.0 [0.5-16.3]	
	Helicobacter pylori							
	- Negative	59 (67%)	35 (69%)	1.0		27 (64%)	1.0	
	- Positive	27 (31%)	16 (31%)	1.1 [0.4-2.7]		14 (33%)	1.3 [0.5-3.2]	
	CagA status							
	- Negative	60 (68%)	31 (61%)	1.0		26 (62%)	1.0	
	- Positive	26 (30%)	19 (37%)	0.8 [0.3-1.8]		15 (36%)	0.7 [0.3-1.7]	

Legend: IM: intestinal metaplasia; [1]multifocal intestinal metaplasia; [2]severe grades of intestinal metaplasia; *the percentages may not add up to 100% as a result of missing data; ** at least one first-degree relative with gastric cancer; *** 1 unit of alcohol= 1 glass ~ 10ml /8 grams ethanol.

was not confirmed, had received *H. pylori* eradication between baseline and surveillance endoscopy.

In patients with intestinal metaplasia at surveillance endoscopy, the most severe grade of intestinal metaplasia was mild in 12/63 patients (14%), moderate in 19/63 patients (22%), and marked in 32/63 patients (36%) (Table 1). Dysplasia was detected in 7/32 patients (22%) with marked intestinal metaplasia. Intestinal metaplasia was located in the distal part of the stomach (antrum and/ or angulus) in 23/88 patients (26%), in 13/88 patients (15%) in the proximal part of the stomach (corpus and/ or cardia) and in 27/88 patients (31%) in both parts of the stomach. According to the OLGA classification system, stage 0 gastritis was detected in most patients (40%), whereas stage I, stage II, stage III, and stage IV were present in respectively 5%, 24%, 23%, and 9% of patients.

Intragastric extent of intestinal metaplasia

The prevalence of extensive intestinal metaplasia at surveillance endoscopy within the study population varied dependent on the definition used for this diagnosis (multifocal intestinal metaplasia vs. severe grades of intestinal metaplasia) (Table 1). Intestinal metaplasia was present in the biopsies from at least two different intragastric locations (multifocal intestinal metaplasia) in 51 patients (51/88 (58%) of included patients; 51/63 (81%) of patients with histologically confirmed intestinal metaplasia, 6/51 (12%) had gastric dysplasia in the random biopsies. Forty-two patients (respectively 48%; 67%) had moderate or marked intestinal metaplasia in two or more biopsies (severe grades of intestinal metaplasia); five (12%) of whom had gastric dysplasia in the random biopsies. The OLGA gastritis stage at surveillance endoscopy was strongly associated with both intestinal metaplasia in the biopsies from at least two different intragastric locations (multifocal intestinal metaplasia) and moderate or marked intestinal metaplasia in two or more biopsies (severe grades of intestinal metaplasia) (both $p<0.001$).

Patients with multifocal intestinal metaplasia significantly more often had a first-degree relative with gastric cancer ($p=0.05$), moderate or marked intestinal metaplasia ($p=0.005$), and a high OLGA gastritis stage at the index biopsy ($p=0.01$). They also used alcohol more frequently ($p=0.002$) and had a lower mean pepsinogen I to II ratio ($p<0.001$), and lower mean gastrin level ($p=0.04$) as compared to patients with no or only limited intestinal metaplasia (Table 1). Most of these factors were also significantly associated with severe grades of intestinal metaplasia, but most odds ratios were closer to one (Table 1). In multivariable analysis, alcohol use, moderate or marked intestinal metaplasia at index biopsy, and a pepsinogen I to II ratio <3.0 were identified as most important for finding intestinal metaplasia in the biopsies from at least two different intragastric locations (multifocal intestinal metaplasia) and moderate or marked intestinal metaplasia in two or more biopsies (severe grades of intestinal metaplasia) (Table 1).

A predictive score included a family history of gastric cancer (2 points), alcohol use ≥ 1 unit/day (1 point), the grade of intestinal metaplasia at the index biopsy (moderate 1 point; marked 3 points), and a pepsinogen I to II ratio <3 (3 points) (Table 2). With a score ≥ 4 points, multifocal intestinal metaplasia was present in 96% of patients and severe grades of intestinal metaplasia in 92% of patients (Table 2).

The area under the receiver operating characteristic curve (AUC) for having intestinal metaplasia at at least two different intragastric locations (multifocal intestinal metaplasia) was 0.90, which was expected to decrease to 0.86 for future patients according to a bootstrap procedure that included the model selection. For moderate or marked intestinal metaplasia in two or more biopsies (severe grades of intestinal metaplasia), the AUC was expected to decrease from 0.88 to 0.86.

Table 2. Clinical risk score for the prediction of extensive intestinal metaplasia. The score is based on the regression co-efficients in multivariable logistic regression analysis of risk factors for intestinal metaplasia in biopsies from at least two intragastric locations (multifocal intestinal metaplasia).

	At least two locations with IM	Moderate/ marked IM in two or more biopsies
Score 0-1 n=32	8 (25%)	5 (16%)
Score 2-3 n=19	13 (68%)	10 (53%)
Score ≥ 4 n=25	24 (96%)	23 (92%)

Score (0 – 9 points):
a. Family history of gastric cancer: 2 points
b. Alcohol use ≥ 1 unit/ day: 1 point
c. Intestinal metaplasia at index biopsy: moderate =1 point/ marked= 3 points
d. Pepsinogen I to II ratio <3.0: 3 points

DISCUSSION

This study clearly identifies a family history of gastric cancer, a pepsinogen I to II ratio <3.0, the presence of moderate or marked intestinal metaplasia in the index biopsy and alcohol use with an average of at least one unit per day as important predictive parameters for extensive intestinal metaplasia at surveillance endoscopy. Our study adds to existing knowledge of risk factors for progression of pre-malignant gastric lesions to gastric cancer by combining these individual risk factors into a risk stratification rule that can be used as a simple clinical tool to select high-risk patients for endoscopic surveillance. As extensive intestinal metaplasia can be predicted with high sensitivity by a predictive score ≥4, surveillance of intestinal metaplasia can be recommended in routine clinical practice in these patients.

The predictive factors of this study are consistent with observations in various previous studies, yet none of them is routinely used to select patients for endoscopic surveillance.

Firstly, family members of patients with gastric cancer are known to suffer more frequently of pre-malignant gastric lesions. They have for instance been reported to have a seven times higher prevalence of atrophic gastritis as compared to patients with non-ulcer dyspepsia. (18;19) Therefore, prophylactic *H. pylori* screening and eradication has been recommended in these subjects. (18;20-22) Secondly, previous studies have shown that the presence and intragastric extent of atrophic gastritis can be assessed with serological testing of pepsinogen levels. (23-26) In addition, high negative predictive values for intestinal metaplasia and dysplasia have been demonstrated by these serological markers as well. (27) Moreover, a prospective cohort study showed that the combination of serum pepsinogen levels indicative of atrophic gastritis and absence of anti-*H. pylori* antibodies was associated with a more than eight times higher risk to develop gastric cancer, as compared to subjects with normal pepsinogen levels and absence of *H. pylori* antibodies. (28) These results have led to implementation of risk stratification with serological parameters in gastric cancer screening programs in some regions of Japan. (29) Pepsinogen testing is performed with standard ELISA techniques. Thirdly, the severity of intestinal metaplasia according to the Sydney classification system has been described as an important predictor of gastric cancer risk, which seems superior to classification into complete or incomplete intestinal metaplasia. (9;30-32) Fourthly, frequent alcohol use has also been shown to contribute to gastric cancer risk in previous studies. (9)

Although the association between extensive intragastric intestinal metaplasia and the above-mentioned risk factors has been confirmed in this study, an association with a few other risk factors, which would have been expected on the basis of previous study results, has not been demonstrated. Strikingly, we observed no association between extensive intragastric intestinal metaplasia and age, smoking or male sex, which are established risk factors for the development of gastric cancer. (9;33-35) It may well be that these factors are less strongly associated with extensive intestinal metaplasia in this specific selection of patients with pre-existing changes of the gastric mucosa, however, these findings may have also resulted from the relatively limited number of patients included in this study.

Although our study describes a systematic cross-sectional study of several predictive factors of extensive intestinal metaplasia, potential limitations warrant consideration. We used extensive intragastric intestinal metaplasia as a marker of gastric cancer risk. Unfortunately, no definitions of extensive intragastric intestinal metaplasia have been published previously. Current histological classifications provide guidelines to score the severity of intestinal metaplasia in individual biopsy specimens, but do not provide any instructions for combined intragastric scores of both severity and extent of intestinal metaplasia. Therefore, two new definitions were used in this study (multifocal intestinal metaplasia vs. severe grades of intestinal metaplasia). A high correlation was shown between both definitions, and both definitions were also highly associated with the presence of dysplasia and with the gastritis stage according to the OLGA classification system. Therefore, the use of these definitions to identify risk factors for carcinogenic progression seems justified. Nevertheless, a prospec-

tive cohort study should confirm the proposed risk stratification in patients with intestinal metaplasia and validate the definitions of extensive intestinal metaplasia as risk factors for development of gastric cancer, even though such a study may require considerable costs and time as follow-up of a large cohort of patients is required. Also, sampling error and possibly also *H. pylori* eradication are the most likely explanations for the inability to confirm the diagnosis of intestinal metaplasia in a fourth of patients and for the detection of dysplasia in seven patients in this study. As intestinal metaplasia is known to be a multifocal condition and all patients were selected on the basis of their histological abnormalities at baseline, the 'regression' observation was fully according to expectation. A similar phenomenon has been observed in previous studies with a cohort follow-up design. (2) These findings emphasize the need for the development of an accurate biopsy strategy during surveillance endoscopy of pre-malignant gastric lesions. Moreover, a relatively small number of patients was included in the multivariable analysis of this study. From a clinical background perspective, we have categorized the input parameters into a limited number of groups and these showed to be valuable for risk categorization. In the analysis, 16 potential risk factors were considered with a total of 22 degrees of freedom, while we had 51 events in the statistical analyses. Therefore, external validation of our findings is required. Finally, the proposed risk score and its exact cut-off point to omit or perform a surveillance endoscopy need further validation before it can routinely be applied in clinical practice. The discriminative ability remained good (>0.85) at internal validation with bootstrapping, but differences between clinical settings may affect the external validity of the proposed score.

In conclusion, the presence of a family history of gastric cancer, alcohol intake of at least one unit daily, moderate or marked intestinal metaplasia in a routine biopsy, and a low pepsinogen I to II ratio are associated with high risk of extensive intragastric intestinal metaplasia. A high risk score based on the presence of these parameters indicates a severely affected gastric mucosa and the need to consider surveillance endoscopy in due time.

SUMMARY

Patients with extensive intragastric intestinal metaplasia are at increased gastric cancer risk. However, the intragastric extent of intestinal metaplasia is usually unknown at the time of diagnosis. In this study, we showed that a risk score of clinical, histological and serological parameters can predict the presence of extensive intragastric intestinal metaplasia and may serve as a tool to select patients for surveillance endoscopy in routine clinical practice.

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CHAPTER 10

The yield of endoscopic surveillance of pre-malignant gastric lesions: optimalization of biopsy strategies

Submitted

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ABSTRACT

Background: Endoscopic surveillance of pre-malignant gastric lesions may add to gastric cancer prevention. However, the appropriate biopsy regimen for optimal detection of the most advanced lesions remains to be determined. Therefore, we evaluated the yield of endoscopic surveillance by standardized and targeted biopsy protocols.

Methods: In a prospective, multi-center study, patients with intestinal metaplasia (IM) or dysplasia (DYS) underwent a surveillance gastroscopy. Both targeted biopsies from macroscopic lesions and 12 random biopsies from standardized locations (antrum, angulus, corpus, cardia) were obtained. Appropriate biopsy locations and the yield of targeted versus random biopsies were evaluated.

Results: In total, 112 patients with IM (n=101), or low-grade (n=5) and high-grade DYS (n=6) were included. Diagnosis at surveillance endoscopy was atrophic gastritis (AG) in 1, IM in 77, low-grade DYS in 2, high-grade DYS in 3, and gastric cancer in 1 patient. The angulus (40%), antrum (35%) and lesser curvature of the corpus (33%) showed the highest prevalence of pre-malignant conditions. Random biopsies from the lesser curvature had a significantly higher yield as compared to the greater curvature of the corpus in diagnosing AG and IM (p=0.05 and p=0.03). Patients with IM at the cardia were at high risk of a concurrent diagnosis of dysplasia or gastric cancer. High-grade DYS was detected in targeted biopsies only.

Conclusions: Surveillance endoscopies of pre-malignant gastric lesions in a population at an overall low gastric cancer risk require both targeted and random biopsies from antrum, angulus, corpus, in particular along the lesser curvature, and cardia.

INTRODUCTION

Most gastric carcinomas are preceded by a cascade of detectable precursor lesions, i.e. atrophic gastritis, intestinal metaplasia and dysplasia. (1) Endoscopic surveillance of patients with these lesions may lead to early detection of advanced precursor lesions and early cancer. (2;3) Yet, the appropriate biopsy strategy during endoscopic surveillance of pre-malignant gastric lesions is unclear.

Even though image quality of standard video endoscopes has improved considerably over the past decade, the correlation between findings at conventional endoscopy and the histological diagnoses of pre-malignant gastric lesions remains far from satisfactory. (4) Although advanced endoscopic techniques may improve the detection of pre-malignant gastric lesions, current detection and surveillance in routine practice still relies on histological assessment of random biopsies, obtained during conventional endoscopy. (5;6)

The updated Sydney classification system is currently the most widely accepted guideline to classify and grade gastritis. (7) According to this guideline, two biopsies from the antrum, two from the corpus and one from the incisura angularis should be obtained. Although this biopsy protocol generally establishes the correct *Helicobacter pylori* status and the presence of gastritis, it is controversial whether five gastric biopsies are sufficient for an adequate diagnosis of pre-malignant gastric lesions. (8-10) This controversy probably results from variation in the intragastric extent of pre-malignant lesions in different populations. (11-13) It can be assumed that in patients from populations at high risk of gastric cancer the occurrence of extensive atrophic gastritis and intestinal metaplasia is higher. Therefore, fewer biopsies for an accurate diagnosis of precursor lesions are likely to be required in comparison to patients from a population at low risk. In addition, for the detection of gastric dysplasia, it has been argued that random biopsies are insignificant in comparison to targeted biopsies, since dysplastic mucosal changes tend to be focal. (14) Against this background, the appropriate biopsy protocol for endoscopic surveillance of pre-malignant gastric lesions is unclear.

In this study, we aimed to evaluate the yield of endoscopic surveillance with a standardized biopsy protocol in patients with pre-malignant gastric lesions, within a population at an overall low gastric cancer risk. In order to identify the most optimal biopsy strategy during surveillance endoscopy, we evaluated the appropriate biopsy locations and number of biopsies, and the yield of targeted versus random biopsies.

METHODS

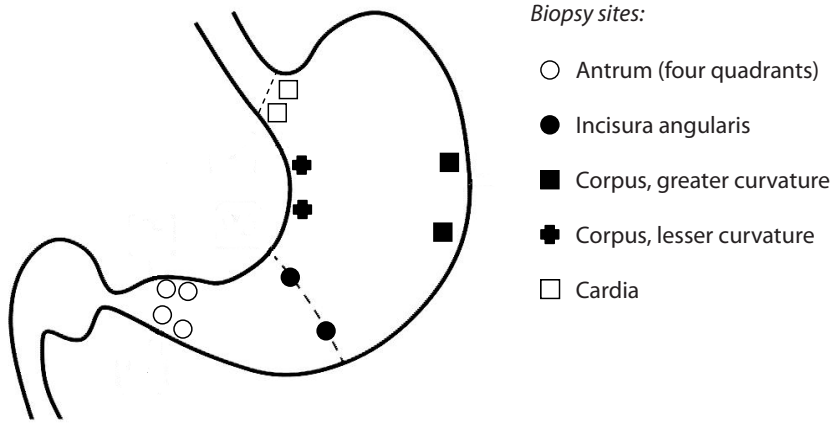
Patients

Consecutive outpatients with a previous histologically confirmed diagnosis of intestinal metaplasia or dysplasia of the gastric mucosa were invited to participate in this prospective, multi-center study. All patients underwent a surveillance endoscopy between March 2006 and June 2007. Patients with a previous diagnosis of upper gastrointestinal malignancy, and/ or a history of oesophageal or gastric surgery were excluded. The institutional review boards of the participating hospitals approved this study and written informed consent was obtained from all patients prior to surveillance endoscopy.

Endoscopy

All patients underwent a conventional upper gastrointestinal endoscopy using a standard forward-viewing video gastroscope (Olympus GIF-Q160, Olympus Optical Co., Tokyo, Japan). All procedures were performed by experienced senior endoscopists. Biopsy samples were first obtained from any endoscopically detected focal lesion. In addition, twelve biopsies for histological assessment were taken from five standardized intragastric locations: 4 quadrant biopsies from the antrum (2-3 cm proximal to the pylorus), 2 from the angulus, 4 from the mid corpus (2 from the lesser curvature, 2 from the greater curvature) and 2 from the cardia (Figure 1). Furthermore, two additional biopsies (one corpus and one antrum) were used for *H. pylori* culture.

Figure 1. Random biopsy scheme: biopsies were obtained from five standardized intragastric locations. (Adapted from Dixon *et al.* (7))



Histological assessment

Gastric biopsy specimens were fixed in buffered formalin and embedded in paraffin. The slide sections were stained with haematoxylin and eosin (H&E). Two expert gastro-intestinal pathologists assessed all histological sections from the index and surveillance endoscopy (HVD, NVG). In case of disagreement on the presence of intestinal metaplasia or grade of dysplasia, a third expert gastrointestinal pathologist was consulted (GM). The final diagnosis was based on the majority diagnosis, i.e. two of three pathologists agreed upon the diagnosis. The pathologists were unaware of the identity of patients, initial (routine) histological diagnosis of the index biopsy, endoscopic findings, and histological diagnosis of the other pathologists. All histological sections were assessed according to the updated Sydney classification system. The following items were evaluated separately: *H. pylori* density, acute inflammation (neutrophil infiltration), chronic inflammation (mononuclear infiltration), gastric glandular atrophy, and intestinal metaplasia. All items were scored from 0 (absent), to 1 (mild), 2 (moderate), or 3 (marked), as defined in the Sydney classification system. (7) The revised Vienna classification was used for the assessment of neoplasia. (15;16)

Statistical analysis

Continuous data were compared using the Student's t-test; categorical data were analyzed using the chi-square test. Two-sided statistical significance was set at a p-value < 0.05. In order to identify the optimal number and location of random biopsies, the following fictive random biopsy schemes were tested for the accuracy to detect intestinal metaplasia, and dysplasia or gastric cancer in comparison to the study random biopsy scheme: A) conventional Sydney system biopsy regimen (2 antrum, 1 angulus, 1 greater curvature corpus, 1 lesser curvature corpus), B) 7 random biopsies (3 antrum, 1 angulus, 1 greater curvature corpus, 2 lesser curvature corpus), and C) 9 random biopsies (3 antrum, 2 angulus, 1 greater curvature corpus, 2 lesser curvature corpus, 1 cardia). The fictive biopsy schemes were composed of randomly selected biopsies originating from the study biopsy scheme.

RESULTS

Baseline characteristics

A total of 112 patients were included. All had in the past undergone upper gastrointestinal endoscopy with gastric biopsy sampling, and according to the main inclusion criteria all had been histologically diagnosed with gastric intestinal metaplasia (n=101) or dysplasia (n=11; 5 low-grade and 6 high-grade) at baseline (Table 1). The mean interval between the former

Table 1. Baseline characteristics of our study population.

	Intestinal metaplasia n=101	Low-grade dysplasia n=5	High-grade dysplasia n=6
Age (mean) (SD)	60.7 (11.6)	59.5 (9.7)	70.1 (7.7)
Sex (M/ F)	50/ 51	4/ 1	4/ 2
Ethnicity			
- Caucasian	80	3	6
- Non-Caucasian	21	2	0
Smoking			
- Non-smoker	44	2	3
- Current smoker	16	1	0
- Former smoker	37	2	3
Alcohol			
- Non- drinker (<1 unit/day)	63	4	4
- Drinker (≥1 unit/day)	34	1	2
Medication use			
- PPI	54	4	5
- NSAIDs/ Aspirin	18	1	2
Dyspeptic complaints	43	1	2
Family history of gastric cancer (≥ 1 first-degree relative)	10	0	2
H. pylori eradication therapy	41	3	4

endoscopy and the current surveillance endoscopy was 2.3 years (SD 2.4) for patients with intestinal metaplasia, 2.9 years (SD 1.7) for patients with low-grade dysplasia, and 2.6 years (SD 2.7) for patients with high-grade dysplasia.

Outcome at surveillance endoscopy

A total of 37/ 112 (33%) patients had histological evidence of moderate or marked chronic active gastritis. In nine of them the presence of *H. pylori* infection was confirmed by either culture (n=4) or histology (n=5). The remaining 103 (92%) patients had no signs of *H. pylori* infection, 22 (21%) of them had received *H. pylori* eradication treatment prior to the baseline endoscopy of this study and 21 (20%) received *H. pylori* eradication treatment between both study endoscopies. A total of 4 of the 82 patients (5%) who did not receive *H. pylori* eradication treatment between both study endoscopies and had no current evidence of *H. pylori*, still had histological evidence of this bacterium during the previous baseline endoscopy several years before. In these patients *H. pylori* colonization was lost spontaneously in the presence of atrophy and intestinal metaplasia.

The presence of intestinal metaplasia was confirmed at surveillance endoscopy in 72 of 101 patients (71%) with intestinal metaplasia at baseline, in 1/ 101 patient (1%) atrophic gastritis was detected and in 26/ 101 patients (26%) no pre-malignant lesion was diagnosed (Table 2). Two (2%) of 101 patients showed progression to low-grade dysplasia. Amongst the five

Table 2. Cross-tabulation comparing baseline histological diagnoses with diagnoses at surveillance endoscopy.

	Follow-up histology: most advanced (pre-)malignant diagnosis					
Baseline	None	Atrophic gastritis	Intestinal metaplasia	Low-grade dysplasia	High-grade dysplasia	Gastric cancer
Intestinal metaplasia N=101	26	1	72	2	0	0
Low-grade dysplasia N=5	1	0	4	0	0	0
High-grade dysplasia N=6	1	0	1	0	3*	1

Legend: * Histology of resection specimens during follow-up revealed an adenocarcinoma in two patients.

patients with low-grade dysplasia at baseline, intestinal metaplasia was diagnosed as most severe lesion at surveillance endoscopy in all patients and no progression was observed. Amongst the six patients with high-grade dysplasia at baseline, one had at the index endoscopy undergone a mucosal resection of a polypoid lesion, and no further pre-malignant gastric lesion was diagnosed at surveillance endoscopy. A second patient was at follow-up diagnosed with intestinal metaplasia as most advanced lesion, and endoscopic surveillance is being continued. In three patients with high-grade dysplasia at baseline this diagnosis was confirmed at surveillance endoscopy. Subsequently, these patients respectively underwent endoscopic mucosal resection, endoscopic submucosal dissection, and a partial gastrectomy. Histology of the resection specimens revealed an intramucosal well-differentiated adenocarcinoma, high-grade dysplasia and a moderately-differentiated adenocarcinoma with invasion into the muscularis mucosae (TisN0Mx), respectively. One patient with a previous diagnosis of high-grade dysplasia was diagnosed with gastric cancer at the surveillance endoscopy after an interval of 5 years. In this patient, six follow-up endoscopies with random biopsy sampling had been performed in the interval between baseline endoscopy and inclusion in this study, showing only low-grade dysplasia or intestinal metaplasia. After the diagnosis of gastric cancer, this patient underwent a partial gastrectomy. Histology of the resection specimen revealed an adenocarcinoma of the intestinal type with limited invasion into the muscularis propria (T2N0Mx).

In summary, no pre-malignant lesions were diagnosed at surveillance endoscopy in 28 patients, atrophic gastritis in 1, intestinal metaplasia in 77, low-grade dysplasia in 2, high-grade dysplasia in 3, and gastric cancer in 1 patient.

Intragastric locations of pre-malignant gastric lesions

Overall, the highest prevalence of pre-malignant diagnoses (i.e. atrophic gastritis, intestinal metaplasia and dysplasia) was present in random biopsies from the angulus (39%) (86 of 221 random biopsies from the angulus), as compared to 24% in biopsies from the greater

Table 3. The prevalence of pre-malignant gastric lesions per biopsy site, based on most severe diagnosis within each biopsy.

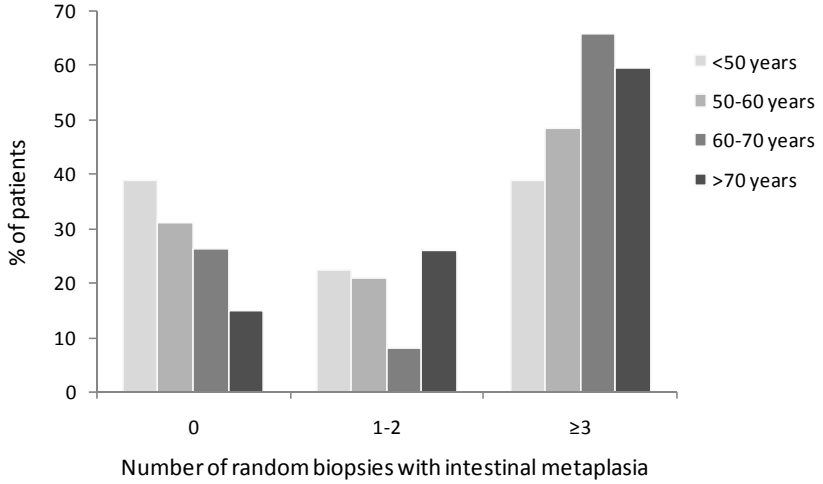
Biopsy location	No. random biopsies	Normal/only mild chronic gastritis	Moderate/ marked chronic gastritis	Atrophic gastritis	Intestinal metaplasia	Dysplasia	Gastric cancer
Cardia	210	140 (67%)	14 (7%)	5 (2%)	51 (24%)	0 (0%)	0 (0%)
Corpus, lesser curvature	219	138 (63%)	11 (5%)	8 (4%)	59 (27%)	1 (0.5%)	2 (1%)
Corpus, greater curvature	224	155 (69%)	16 (7%)	11 (5%)	42 (19%)	0 (0%)	0 (0%)
Angulus	221	121 (55%)	12 (5%)	2 (1%)	84 (38%)	0 (0%)	2 (1%)
Antrum	444	265 (60%)	23 (5%)	2 (0.5%)	152 (34%)	2 (0.5%)	0 (0%)

curvature of the corpus, 27% in biopsies from the cardia, 31% in biopsies from the lesser curvature of the corpus and 35% in biopsies from the antrum (Table 3). Atrophic gastritis was most frequently diagnosed in random biopsies from the lesser curvature of the corpus and angulus, with an overall prevalence of 27% of all random biopsies at both sites. Intestinal metaplasia was most frequently diagnosed in random biopsies from angulus and antrum, with an overall prevalence of respectively 38% and 35%. Random biopsies from the lesser curvature had a significantly higher yield in diagnosing atrophic gastritis and intestinal metaplasia as compared to biopsies from the greater curvature of the corpus (p=0.05 and p=0.03). Within the random biopsy samples, dysplasia or gastric cancer was only detected in random biopsies from the lesser curvature of the corpus, angulus or antrum (prevalence respectively 1.4%, 0.9% and 0.5%).

Intragastric extent of pre-malignant gastric lesions

Atrophic gastritis was present in the random biopsies from 67/ 112 patients (60%) at surveillance endoscopy, either as most severe lesion or concomitant lesion. In 55 (82%) of these patients two or more random biopsies were affected. In comparison, intestinal metaplasia was present in the random biopsies from 82/ 112 patients (73%) at surveillance endoscopy, either as most severe (n=79) or concomitant lesion (n=3). The higher prevalence of intestinal metaplasia (73%) as compared to atrophic gastritis (60%) in the random biopsies was predominantly caused by the diagnosis of focal (mild) intestinal metaplasia within a biopsy with normal glandular structures in the rest of the biopsy. In 72/ 82 (88%) patients two or more random biopsies were affected. In patients with moderate or marked intestinal metaplasia as most severe histological diagnosis at surveillance endoscopy, significantly more intragastric biopsies were affected as compared to patients with only mild intestinal metaplasia (mean number of biopsies 5.2 versus 2.4, respectively) (p=0.02). Patients with three or more random biopsies with intestinal metaplasia were significantly older as compared to patients with no or only limited intestinal metaplasia (63.2 versus 58.7 years, respectively) (p=0.01) (Figure 2).

Figure 2. The number of random biopsies affected by intestinal metaplasia for different age categories.



Low-grade dysplasia was detected as most severe lesion in a single random biopsy in three patients.

In 31 of 82 patients (38%) with intestinal metaplasia in the random biopsies, this lesion was restricted to the angulus and/ or antrum, whereas in 17 (21%) patients the lesser curvature of the corpus and cardia were affected in addition to the angulus and/ or antrum. Patients with intestinal metaplasia at the cardia, lesser curvature of the corpus and angulus and/ or antrum were at significantly higher risk of a concurrent diagnosis of dysplasia as compared to patients with intestinal metaplasia limited to the angulus and/ or antrum (p=0.005).

Random biopsy strategy

Three random biopsy schemes were tested for the accuracy to detect intestinal metaplasia, and dysplasia or gastric cancer, in comparison to the study random biopsy scheme consisting of 12 random biopsies (Table 4). The updated Sydney protocol for random biopsies detected 90% of patients with intestinal metaplasia and only 50% of patients with dysplasia or cancer. A biopsy protocol consisting of seven random biopsies (3 antrum, 1 angulus, 2 lesser curvature of the corpus and 1 greater curvature of the corpus) was able to diagnose intestinal metaplasia in 77/ 79 (97%) cases and low-grade dysplasia or gastric cancer in all four cases that were detected as most severe lesion by the study random biopsy protocol.

Targeted biopsies

In 18 (16%) patients targeted biopsies of endoscopically visible lesions were obtained prior to the random biopsy scheme. In nine patients (50%) the lesions were present in the antrum,

Table 4. The yield of fictive random biopsy protocols in accurately diagnosing intestinal metaplasia, and dysplasia or gastric cancer as most severe histopathological diagnosis at surveillance endoscopy in comparison to the study biopsy protocol.

Biopsy scheme	Intestinal metaplasia n=79* (%)	Dysplasia or gastric cancer n=4* (%)
5 biopsies (according to Sydney system) (2 antrum, 1 angulus, 1 greater curvature corpus, 1 lesser curvature corpus)	71 (90%)	2 (50%)
7 biopsies (3 antrum, 1 angulus, 1 greater curvature corpus, 2 lesser curvature corpus)	75 (95%)	4 (100%)
9 biopsies (3 antrum, 2 angulus, 1 greater curvature corpus, 2 lesser curvature corpus, 1 cardia)	77 (97%)	4 (100%)

*Number of patients with diagnosis after study random biopsy protocol.

in four (22%) in the angulus, in 2 (11%) in the corpus, in 2 (11%) in the cardia and in one (6%) in both antrum and corpus. These biopsies showed no pre-malignant gastric lesion in 4/ 18 (22%), atrophic gastritis in 1/ 18 (6%), intestinal metaplasia in 10/ 18 (56%) and high-grade dysplasia in 3/ 18 (17%) patients.

For the diagnoses of atrophic gastritis or intestinal metaplasia as most severe histological diagnosis at surveillance endoscopy, all diagnoses were made in random biopsies and none were dependent on targeted biopsies only. However, targeted biopsies were indispensable for the diagnosis of high-grade dysplasia in three patients, as the random biopsies showed only intestinal metaplasia in two patients and low-grade dysplasia in one patient. In comparison, the random biopsy scheme was essential for a diagnosis of low-grade dysplasia in two patients and the diagnosis of gastric cancer in one patient. In these patients no macroscopic lesions were seen during endoscopy and therefore no targeted biopsies had been obtained.

DISCUSSION

The understanding of gastric carcinogenesis has largely advanced over the past decades. Especially since the recognition of the key role of *H. pylori* infection and the stepwise progression of pre-malignant lesions to gastric cancer, gastric cancer research has been focused on the development of preventive strategies. Yet, current clinical guidelines principally cover detection and treatment of *H. pylori* infection (17), whereas no clear guidelines are available on detection, surveillance and treatment of pre-malignant gastric lesions. As a consequence, surveillance of pre-malignant gastric lesions is not performed in the vast majority of patients, not even in patients with overt dysplasia. (3) This is remarkable because of the considerable cancer risk in these patients, and the fact that premalignant conditions of the stomach despite a continuing decrease are still highly prevalent. (3;18) The Sydney classification system

currently provides the endoscopic and histological gold standard for the assessment of gastritis. Recently, the OLGA gastritis staging system has been proposed and validated to stratify the histological grading results into stages with increasing cancer risk. (19;20) Both systems strongly rely on histology, with a recommended biopsy sampling protocol which has remained unchanged for more than a decade. Although this biopsy protocol is generally adequate for the diagnosis of *H. pylori* gastritis, it does not sufficiently detect pre-malignant gastric lesions, especially in countries with low gastric cancer incidences. (10)

Therefore, the development of biopsy schemes directed at an accurate diagnosis of pre-malignant gastric lesions is indicated. Our study shows that with the biopsy protocol according to the Sydney classification system at least 10% of patients with intestinal metaplasia and a considerable proportion of patients with dysplasia remain unnoticed. To improve the biopsy strategy during endoscopic surveillance of pre-malignant gastric lesions, this study provides important information on appropriate biopsy locations, number of biopsies and the yield of targeted versus random biopsies. With regard to biopsy locations, pre-malignant gastric lesions associated with *H. pylori* infection have been shown to occur most commonly in the antrum and incisura angularis. (7;21;22) Subsequently, these lesions spread along the lesser curvature and are especially common in the transitional zones (antrum to corpus and corpus to cardia). (23) Thus, the most severe (pre-) malignant lesions predominate at the lesser curvature of the stomach. (21) Nevertheless, biopsies from the corpus are still habitually taken from the greater curvature during routine upper gastrointestinal endoscopy, as these biopsies are most easily obtained. Our study supports previous observations, as it clearly shows that biopsies of the lesser curvature of the corpus carry a significantly higher yield for an adequate histological diagnosis as compared to biopsies from the greater curvature during surveillance of patients with pre-malignant gastric lesions. In this study, biopsies from the cardia never showed a more severe lesion as compared to other intragastric biopsy sites and were therefore not essential for the identification of pre-malignant gastric lesions. However, the presence of intestinal metaplasia in biopsies from the cardia identified patients with extensive lesions who are at increased risk of a concurrent diagnosis dysplasia and gastric cancer. This has also been demonstrated previous studies. (24) Therefore, we still consider these biopsies important in the surveillance of pre-malignant gastric lesions.

From a practical point of view, the ultimate scheme for routine biopsy sampling should limit the number of random biopsies. We performed this study with 12 random biopsies and used this number as the gold standard. With such an approach, we were able to show that the Sydney system biopsy protocol is insufficient for surveillance of pre-malignant lesions within a population at low gastric cancer risk. We showed that a biopsy protocol requires at least 7 biopsies (3 antrum, 1 angulus, 1 greater curvature corpus, 2 lesser curvature corpus) to obtain an accurate histological diagnosis. With the addition of cardia biopsies for an accurate risk estimation of dysplasia or cancer, as mentioned previously, we recommend to obtain a total of 9 biopsies during surveillance endoscopies.

Nevertheless, caution is needed as we cannot exclude that a considerable further increase of the number of random biopsy samples above the 12 specimens per patient would have further increased the yield of pre-neoplastic lesions. This is reflected in our study by a considerable proportion of patients in whom the diagnosis of intestinal metaplasia or dysplasia at index endoscopy was not confirmed at surveillance. This is a common problem in studies evaluating progression of intestinal metaplasia and the effect of *H. pylori* eradication. (25) However, it can be assumed that the majority of patients in whom intestinal metaplasia is not confirmed with this extensive biopsy scheme have a patchy and limited intragastric extent of metaplasia and in these cases gastric cancer risk is generally low. (26)

With regard to random versus targeted biopsies, atrophy has been described to show a more diffuse pattern, whereas intestinal metaplasia and dysplasia tend to be focal. (27) This latter observation has led to controversy with regard to obtaining random biopsies in patients with dysplastic lesions. Although a relatively low number of patients with dysplasia were included, our study shows that random biopsies may be essential to diagnose dysplasia or even gastric cancer. Therefore, our data support the use of random biopsies during surveillance of pre-malignant gastric lesions. In addition, it can be argued that patients with dysplasia require follow-up even though the lesions are not confirmed during surveillance endoscopy, as these lesions may be missed using conventional endoscopy techniques, which is supported by the case of gastric cancer in this study. (3)

In conclusion, our study shows that both random and targeted biopsies are essential during endoscopic surveillance of intestinal metaplasia and dysplasia of the gastric mucosa. An adequate biopsy scheme requires at least 9 random biopsies from the cardia, corpus, in particular along the lesser curvature, angulus, and antrum in a population at an overall low gastric cancer risk.

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CHAPTER 11

Helicobacter pylori eradication for pre-malignant lesions of the gastric mucosa

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ABSTRACT

Background: *Helicobacter pylori* infection is a major risk factor for gastric cancer development. However, the effect of *H. pylori* eradication for prevention of gastric cancer is still controversial, in particular in patients with pre-malignant gastric lesions.

Objectives: To assess the effect of *H. pylori* eradication therapy on different stages of pre-malignant lesions of the gastric mucosa, i.e. atrophic gastritis, intestinal metaplasia and dysplasia.

Search strategy: Trials were identified through electronic searches of the Cochrane Library, MEDLINE and EMBASE databases, using appropriate subject headings and keywords.

Selection criteria: All randomized controlled trials comparing *H. pylori* eradication therapy with placebo or symptomatic treatment in patients with pre-malignant gastric lesions.

Data collection: Data were collected on histological changes of the gastric mucosa and functional parameters of gastric mucosal condition.

Main results: Seventeen randomized controlled trials were included. These trials compared *H. pylori* eradication therapy with placebo or anti-acid inhibitory agents and evaluated the effect on gastric mucosal changes after 8 weeks to 12 years follow-up. Several studies demonstrated less progression or even regression of atrophic gastritis within one to two years after *H. pylori* eradication. Significant less progression and more regression of intestinal metaplasia after *H. pylori* eradication has also been reported by three trials, however, another trial with relatively long-term follow-up did not confirm this finding. The effect of *H. pylori* eradication on the progression of dysplasia was only reported in two trials, which reached contradictory results. Since the outcome measures varied between studies using non-interchangeable parameters, quantification of outcomes was not performed.

Reviewers' conclusions: Clinical evidence for the prevention of carcinogenic progression in patients with atrophic gastritis is highly suggestive, whereas the evidence in patients with intestinal metaplasia and dysplasia is scarce.

BACKGROUND

Gastric cancer is the fourth most common cancer and second leading cause of cancer-related death worldwide. Although the incidence is declining in many populations, the absolute number of new cases per year is increasing, due to ageing of the world population. The estimated incidence of gastric cancer is approximately 934,000 cases per year, with highest rates in Eastern Asia, Eastern Europe and South America. (1)

As symptoms are often absent or non-specific, gastric cancer is frequently diagnosed at an advanced stage, with limited therapeutic options. Consequently, gastric cancer carries a poor prognosis, with overall five-year survival of less than 20 percent. (2)

The vast majority of gastric malignancies are adenocarcinomas, which can be divided into two types: intestinal and diffuse (undifferentiated) type. Intestinal type gastric carcinomas account for at least 60 to 75 percent of cancers; in comparison approximately 30% of the carcinomas are of the diffuse type. (3;4) In contrast to diffuse type carcinomas, intestinal type carcinomas have recognizable precursors: atrophic gastritis, intestinal metaplasia and dysplasia. (5) No international guidelines exist for the surveillance or treatment of patients with these pre-malignant gastric lesions.

Helicobacter pylori infection is considered to be an important initial step in gastric carcinogenesis. Infection with *H. pylori* increases the risk of developing gastric cancer at least six-fold. (6) In the model of gastric carcinogenesis, *H. pylori* causes chronic inflammation of the gastric mucosa, which slowly progresses through the aforementioned pre-malignant stages to gastric adenocarcinoma. It has been estimated that 50 percent of the world population is infected with *H. pylori*. Eradication of this bacterium seems a logical step in the prevention of gastric cancer and generally heals chronic *H. pylori* gastritis. Several studies have shown that eradication of *H. pylori* could be cost-effective for gastric cancer prevention. (7;8) However, despite data from a considerable number of clinical trials, controversy remains whether eradication halts the progression and/or causes the regression of pre-malignant lesions.

OBJECTIVES

To assess the effect of *H. pylori* eradication therapy on different stages of pre-malignant lesions of the gastric mucosa, i.e. atrophic gastritis, intestinal metaplasia and dysplasia.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Inclusion criteria: randomized controlled trials, blinded or unblinded. Both studies evaluating the effect of *H. pylori* eradication on pre-malignant gastric lesions as a primary outcome measure as well as studies evaluating this effect as a secondary outcome measure were included. Abstracts and unpublished studies were also collected with the intention to include these studies in future analysis.

Exclusion criteria: clinical trials without randomization, cross-over studies. We excluded studies in which *H. pylori* eradication was part of a treatment comparison containing additional variables which could not be evaluated separately.

Types of participants

H. pylori-positive subjects with pre-malignant gastric lesions (atrophic gastritis, intestinal metaplasia, dysplasia) were included. From studies that comprised a mixture of participants, with and without pre-malignant gastric lesions, we extracted the data concerning participants with pre-malignant gastric lesions. The *H. pylori* status was considered positive when assessed by any one of histology, rapid urease test, culture (from antral/ corpus biopsies obtained during endoscopy), serology or urea breath test.

Types of interventions

We compared *H. pylori* eradication versus no treatment (or placebo) and *H. pylori* eradication versus symptomatic treatment (anti-acid inhibitory agents).

We only included studies which used an *H. pylori* eradication regimen that had been acknowledged to achieve at least a 50% eradication rate and was defined as one of the following for at least one week:

(1) PPI dual therapy (PPI plus either amoxicillin or clarithromycin)
(2) PPI triple therapy (PPI plus 2 of the following; amoxicillin, macrolide, 5 nitroimidazole)
(3) H2-receptor antagonist triple therapy (H2-receptor antagonist plus 2 of the following; amoxicillin, macrolide, 5 nitroimidazole)
(4) Bismuth triple therapy (bismuth salt and 5 nitroimidazole with either amoxicillin or tetracycline)
(5) Bismuth quadruple therapy (as bismuth triple therapy, but PPI in addition)
(6) Ranitidine Bismuth Citrate dual/triple therapy (as for PPI)

Types of outcome measures

Primary outcome: improvement of pre-malignant lesions of the gastric mucosa, i.e. atrophic gastritis, intestinal metaplasia and dysplasia based on histological assessment.

Secondary outcomes: deterioration of pre-malignant lesions of the gastric mucosa. Other secondary outcomes were functional parameters of gastric mucosal condition (serum pepsinogen level, serum gastrin level, vitamin B12 level, acid secretion), as well as adverse effects.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

A search was conducted to identify all published and unpublished randomized controlled trials.

Trials were identified by searching the following electronic databases - The Cochrane Library, MEDLINE and EMBASE. Reference lists from trials selected by electronic searching were hand searched to identify further relevant trials.

The search strategy for this review was constructed by using a combination of MESH subject headings and text words relating to the use of *H. pylori* eradication therapies in the treatment of pre-malignant lesions of the gastric mucosa. No language restrictions were used.

To identify randomized controlled trials, the following search was combined with the Cochrane highly sensitive search strategy phases one, two and three as contained in the Reviewer's Handbook (Clarke 2000).

exp Precancerous Conditions/
(pre adj2 (neoplas$ or carcino$ or cancer$ or malignan$ or
cursor)).tw.
(preneoplas$ or precarcino$ or precancer$ or premalignan$ or
precursor).tw.
1 or 2 or 3
exp Gastric Mucosa/
(gastric adj2 mucosa).tw.
5 or 6
4 and 7
(gastric adj2 (lesion$ or tissue$ or change$ or alter$)).tw.
Gastritis, Atrophic/
(atroph$ adj2 gastr$).tw.
(intestinal adj2 metaplas$).tw.
exp Metaplasia/
exp Intestinal Neoplasms/
13 and 14
dysplasia.tw.
(correa$ adj1 cascade).mp. [mp=title, original title, abstract,name of substance word, subject heading word]
8 or 9 or 10 or 11 or 12 or 15 or 16 or 17
Helicobacter pylori/

Helicobacter Infections/
(helicobacter adj3 pylori).tw.
(h adj1 pylori).tw.
(pylori adj3 infect$).tw.
(pylori adj3 therap$).tw.
(pylori adj3 eradicat$).tw.
(pylori adj3 treat$).tw.
(pylori adj3 positive).tw.
(pylori adj3 cure).tw.
(pylori adj3 inhibit$).tw.
(pylori adj3 coloni$).tw.
19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
exp Proton Pumps/
(proton adj3 pump adj3 inhibit$).mp. [mp=title, original title,abstract, name of substance word, subject heading word]
ppi.tw.
esomeprazole.mp.
lanzoprazole.mp.
Omeprazole/
omeprazole.mp.
pantoprazole.mp.
rabeprazole.mp.
exp Histamine H2 Antagonists/
(histamine adj1 h2 adj1 antagonist$).tw.
(h2 adj1 receptor adj2 antagonist adj1 triple).tw.
burimamide.mp.
cimetidine.mp.
famotidine.mp.
metiamide.mp.
nizatidine.mp.
ranitidine.mp.
exp Amoxicillin/
amoxycillin.mp.
amoxicillin.mp.
exp Macrolides/
macrolide$.mp.
Clarithromycin/
clarithromycin.mp.
exp Erythromycin/
erythromycin.mp.
azithromycin.mp.
telithromycin.mp.
(bismuth adj1 salt$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
(bismuth adj1 citrate$).tw.
(bismuth adj1 subcitrate$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
(colloidal adj1 bismuth).tw.
(bismuth adj3 therap$).tw.
Nitroimidazoles/
nitroimidazole$.mp.
("5" adj1 nitroimidazole$).mp.
Metronidazole/
metronidazole.mp.
Tinidazole/
tinidazole.mp.
(tripotassium adj1 dicitratobismuthate).mp.

Tetracycline/
tetracycline.mp.
or/32-75
31 or 76
18 and 77
randomized controlled trial.pt.
controlled clinical trial.pt.
randomized controlled trials.sh.
random allocation.sh.
double blind method.sh.
single blind method.sh.
clinical trial.pt.
exp clinical trials/
(clin$ adj25 trial$).ti,ab.
((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
placebos.sh.
placebo$.ti,ab.
random$.ti,ab.
research design.sh.
comparative study.sh.
exp evaluation studies/
follow up studies.sh.
prospective studies.sh.
(control$ or prospectiv$ or volunteer$).ti,ab.
or/79-97
(animals not humans).sh.
98 not 99
78 and 100

METHODS OF THE REVIEW

Study selection

The title and abstract of all retrieved references was scanned. The full-text of relevant, eligible studies was collected and further assessed.

Data extraction

The following data were extracted:

General information: title, authors, source, year of publication, full text/ abstract, published/ unpublished, language

Trial characteristics: RCT, blinding, duration (follow-up), setting

Study population: in- and exclusion criteria (in particular coexisting gastro-oesophageal diseases), number of patients, baseline characteristics, similarity of groups at baseline, region (Asian/ non-Asian)

Intervention: *H. pylori* eradication method, therapy after eradication failure, treatment of control group (no eradication/ placebo/ symptomatic treatment)

Outcome measurement: method of assessment of gastric mucosa (histology, endoscopy, functional parameters), method of diagnosing *H. pylori* infection, method of diagnosing *H. pylori* eradication, number and timing of follow-up gastroscopies, number and site of biopsies per gastroscopy

Outcome:

- Improvement of pre-malignant lesions of the gastric mucosa
- Deterioration of pre-malignant lesions of the gastric mucosa
- Change in functional parameters of gastric mucosal condition (pepsinogens, gastrin, vitamin B12, acid secretion)
- Adverse effects of *H. pylori* eradication therapy

Quality assessment

The quality of included studies was assessed according to the Cochrane Reviewer's handbook.

The quality assessment criteria include:

1. Method of randomization
   A. Truly random: computer generated random numbers, coin toss etc.
   B. Quasi random: birth-date, patient registration-number etc.
   C. Not stated/unclear
2. Allocation concealment
   A. Adequate: trialist unaware of each participant's allocation, by for instance central randomization systems or serially numbered opaque envelopes etc.
   B. Inadequate: trialist aware of allocations at recruitment
   C. Not stated/ unclear
3. Blinding
   A. Double blind
   B. Patient/ Doctor blinded
   C. Unblinded
4. Blinding of outcome assessment
   A. Blinded
   B. Unblinded
5. Participant flow
   A. Loss to follow-up described
6. Intention to treat analysis

DESCRIPTION OF STUDIES

A total of 2036 articles were identified by the search strategy. We excluded 1940 clearly irrelevant references or unrandomized studies through reading abstracts. Accordingly, 96 references were retrieved for further assessment. After further assessment, a total of 71 references were excluded, mostly because they were not randomized, or duplicated (the data of) other references. One additional reference was identified through scanning reference lists of the identified randomized trials and relevant reviews. (9) Five references described the study design of ongoing or unpublished trials. (10-14) In addition, one study is awaiting assessment after translation from Chinese to English. (15) In total, 20 references fulfilled the inclusion criteria. (9;16-34) Five references described different periods of follow-up of two original study cohorts. (18;24;26;31;34) Therefore, 17 relevant randomized controlled trials were identified. Details of the included trials are shown in Table 1 'Characteristics of included studies'.

Methodological quality of included studies

An overview of the methodological quality of included randomized controlled trials is provided in Table 2 'Methodological quality of included studies'. Nine trials mentioned the method of randomization and were truly randomized, and seven studies mentioned adequate concealment of allocation. Nine studies had a double-blind design, in three studies only the doctor or patient was blinded, whereas five studies did not mention any details on blinding. In 14 studies the pathologist was blinded to the treatment allocation of study subjects when assessing the outcome measures. The loss to follow-up varied from 0% after eight weeks to three years follow-up (9;20;23) to 35% after 6 years follow-up (18). Seven studies evaluated the effect of *H. pylori* according to *H. pylori* status at the end of follow-up, whereas ten studies performed an intention to treat analysis.

RESULTS

Baseline characteristics

Six trials were performed in Asian countries; the other eleven trials were performed in various parts of the world (Table 1). Only four studies aimed to evaluate the effect of *H. pylori* on pre-malignant gastric lesions as a primary outcome measure and only included patients with these conditions (16;18;23;25;26), whereas the other trials were either population-based studies or included patients with various gastro-intestinal conditions at baseline. The number of patients with pre-malignant gastric lesions that were randomized to the *H. pylori*

Table 1. Characteristics of included studies.

Author	Region	Baseline condition	Hp diagnosis	Hp eradication confirmation	Intervention			Hp eradication rate in treatment group (overall)	Method of assessment of pre-malignant changes of gastric mucosa
					Treatment group	Length of treatment	Control group		
Arkkila	Finland	Peptic ulcer and AG	Rapid urease test and histology	Rapid urease test, Histology and Culture (all negative)	Bismuth quadruple therapy; PPI triple therapy; PPI dual therapy	2 weeks	Placebo +PPI	97%	Histology
You	China	General population	Serology	UBT	PPI dual therapy	2 weeks	Placebo	73%	Histology
Ley	Mexico	General population, antibodies to CagA and gastrin levels ≥25 ng/ml	Histology	Histology	PPI triple therapy	1 week	Placebo	79%	Histology
Befrits	Sweden	Gastric ulcer	Culture or Histology	Culture and Histology	PPI triple therapy	1 week	Placebo + omeprazole	88%	Histology
Wong	China	General population	Rapid urease test and Histology	UBT	PPI triple therapy	2 weeks	Placebo	84%	Histology
Kuipers	Western-Europe and Australia	GORD	Culture/ Histology	Culture and Histology	PPI triple therapy	1 week	Omeprazole	88%	Histology
Kamada	Japan	Dyspepsia	Histology	Histology and UBT	PPI triple therapy	1 week	Placebo	82%	Histology; Gastrin and pepsinogen serology; Gastric acid secretion
Correa[#]	Colombia	AG, IM, DYS	Histology	Histology and UBT	Bismuth triple therapy	2 weeks	No treatment	74%	Histology
Mera[#]	Colombia	AG, IM, DYS	Histology	Histology	Bismuth triple therapy	2 weeks	No treatment*	51%	Histology
Sung[##]	China	General population	Rapid urease test and Histology	UBT	PPI triple therapy	1 week	Placebo	89%	Histology

Author	Region	Baseline condition	Hp diagnosis	Hp eradication confirmation	Intervention			Hp eradication rate in treatment group (overall)	Method of assessment of pre-malignant changes of gastric mucosa
					Treatment group	Length of treatment	Control group		
Zhou[##]	China	General population	Rapid urease test and Histology	UBT	PPI triple therapy	1 week	Placebo	89%	Histology
Leung[##]	China	General population	Rapid urease test and Histology	UBT	PPI triple therapy	1 week	Placebo	75%	Histology
Mones	Spain	Duodenal ulcer	Rapid urease test and Histology and UBT	UBT	PPI triple therapy	1 week	Placebo + omeprazole	78%	Histology
Schenk	the Netherlands	GORD	Rapid urease test and Histology, or Culture	Culture and Histology (in case indecisive: serology)	PPI triple therapy	2 weeks	Placebo + omeprazole	85%	Histology
Miwa	Japan	Dyspepsia	Histology or UBT	Histology and UBT	PPI triple therapy	1 week	Placebo + omeprazole	85%	Histology
Gisbert	Spain	Duodenal ulcer	Rapid urease test and Histology, or Culture	Culture and Histology	H2-receptor antagonist triple therapy/ Bismuth triple therapy	2 weeks	Ranitidine	48%	Histology
Moayyedi	United Kingdom	Moderate oesophagitis	UBT and Rapid urease test/ Culture/ Histology	UBT	PPI triple therapy	1 week	Placebo + omeprazole	78%	Histology
Leri	Italy	Dyspepsia and AG	Serology positive, Histology negative	Serology	PPI triple therapy	10 days	No treatment	86%	Histology
Ohkusa	Japan	Hyperplastic gastric polyp	Culture, Histology, UBT, Rapid urease test (2/4 tests positive)	Culture, Histology, UBT, rapid urease test (all negative)	PPI triple therapy	NS	No treatment	88%	Histology; Gastrin serology
Lazzaroni	Italy	Gastric ulcer	Rapid urease test and histology	Histology	PPI dual therapy	2 weeks	Placebo + omeprazole	62%	Histology

Author	Follow-up endoscopy	Biopsy scheme (histological evaluation)	Total N randomized (treatment/ control group)	N with pre-malignant lesions (treatment/ control group) (most severe diagnosis)	Outcome	GC cases in patients with pre-malignant lesions at baseline (treatment/control group)
Arkkila	8, 52 weeks	2 A, 4 C	92	92 IM	Reduction of AG score in antrum in Hp eradicated patients as compared to Hp positive patients. No significant effect for IM.	NS
You	5, 9 years	4 A, 1 Ang, 2 C	285/286	NS	Larger proportion of patients with regression and smaller proportion with progression of AG and DYS in treatment as compared to control group. No significant effect for IM.	NS (Hp eradication study population: 18)
Ley	6 wk and 1 yr	3 A, 1 Ang, 3 C	161/155	10/14 AG, 63/59 IM, 2/2 DYS	Reduction of stomach index score (weighted combination of number of sites affected and histopathology) in treatment as compared to control group between score at 6 weeks and 1 year follow-up.	NS (total study population: 1)
Befrits	6, 12, 24 months	2 A, 2 C	64/61	NS	Reduction of proportion of patients with AG in both antrum and corpus (statistical significance not mentioned), no reduction of IM.	NS (total study population: 3)
Wong	5 years	2 A, 1 Ang, 1C	817/813	72/57 AG, 243/234 IM, 4/5 DYS	No significant reduction of gastric cancer incidence in treatment as compared to control group.	12 (7/5)
Kuipers	1, 2 years	NS	111/120	NS	Larger proportion of patients with regression of AG in corpus in treatment as compared to control group. No significant difference for IM.	1
Kamada	1, 2, 3 years	2 A, 2 C	45/45	45/45 AG	Reduction of AG scores in antrum and fundus antrum in Hp eradicated patients as compared to baseline. Serum gastrin decreased significantly and the pepsinogen I/II ratio increased significantly in Hp eradicated patients as compared to baseline. Gastric pH decreased significantly in Hp eradicated patients as compared to baseline.	NS
Correa[#]	3 and 6 years	3A, 1C	120/117	NS	Larger proportion of patients with regression of AG and IM in treatment as compared to control group. No significant changes for DYS.	NS (total study population: 5)
Mera[#]	12 years	3A, 1C	NA*	NS	More regression and less progression after Hp eradication as compared to Hp positive patients (average histopathological score). No significant differences in intention to treat analysis.	9 (5/4)
Sung[##]	1 year	2 A, 2 C	295/292	NS (110/121 AG, 107/121 IM)	Smaller proportion of patients with progression of AG in corpus after Hp eradication as compared to Hp positive patients. Significant reduction of IM score in antrum in Hp eradicated patients as compared to baseline.	NS

Author	Follow-up endoscopy	Biopsy scheme (histological evaluation)	Total N randomized (treatment/ control group)	N with pre-malignant lesions (treatment/ control group) (most severe diagnosis)	Outcome	GC cases in patients with pre-malignant lesions at baseline (treatment/control group)
Zhou[##]	2, 5 years	2 A, 2 C	276/276	NS	Smaller proportion of patients with progression of IM in antrum after Hp eradication as compared to Hp positive patients.	NS
Leung[##]	5 years	2 A, 2 C	295/292	4 AG, 194 IM	Smaller proportion of patients with progression of IM in treatment as compared to placebo group.	8
Mones	12 months	2 A, 2 C	42/43	NS (32 IM)	Significant reduction of IM score in Hp eradicated patients as compared to Hp positive patients. No significant effect for AG.	NS
Schenk	3, 12 months	3 A, 4 C	NS (in analysis: 27/30)	NS	No significant differences in AG and IM scores between Hp eradicated and Hp positive patients. Reduction of AG score in antrum in Hp eradicated patients as compared to baseline.	NS
Miwa	12 weeks	1 A, 1 C	50/40	NS	Increase of AG score in antrum in treatment group as compared to baseline.	NS
Gisbert	3, 6, 12, 18 months	2 A	45/45/45	NS (46 AG, 18 IM)	No significant reduction of AG and IM scores after Hp eradication.	NS
Moayyedi	2, 12 months	2 A, 2 C	21/20	NS	Increased proportion of patients with AG in control as compared to treatment group. No significant differences for IM.	NS
Leri	8 weeks	2 A, 1 C	10/10	10/10 AG	No significant difference in AG scores before and after treatment within treatment and control group.	NS
Ohkusa	1-3, 7-9, 12-15 months	NS	17/18	17/18 AG (IM NS)	No significant reduction of AG and IM scores in treatment group as compared to control group. Significant decrease of serum gastrin levels in treatment group as compared to control group.	NS
Lazzaroni	2 years	2 A, 3 C	29/30	NS	No significant reduction of AG or IM scores in Hp eradicated patients as compared to baseline.	NS

Legend: NS= not stated, NA= not applicable, Hp= *H. pylori*, UBT= urea breath test, A= antrum, C= corpus, Ang= angulus, AG= atrophic gastritis, IM= intestinal metaplasia, GC= gastric cancer, * at 6 years all *H. pylori* positive subjects received *H. pylori* eradication

[#]studies desribing the same study cohort

[##]studies desribing the same study cohort

eradication treatment or control groups was not clearly mentioned in several studies. This has probably resulted from the evaluation of different primary outcome measures, variations in presentation of data, for instance, separate evaluation of lesions in corpus and antrum (21), and in a few studies from the evaluation of *H. pylori* eradication in combination with dietary supplements. (18;26;33)

Study design

The *H. pylori* eradication regimens resulted in eradication rates ranging from 48% (19) to 97% (16). In all trials, histology was used for the diagnosis of pre-malignant gastric lesions. Only two studies also used pepsinogen or gastrin serology to evaluate the effect of *H. pylori* eradication on the gastric mucosa (9;20), and one of these studies reported details on the effect of *H. pylori* eradication on gastric acid secretion (20). The biopsy schemes to obtain his-

Table 2. Methodological quality of included studies.

Author	Method of randomization (A/B/C)*	Allocation concealment (A/B/C)*	Blinding (A/B/C)*	Blinding of pathologist (A/B/C)*	Partcipant flow (n lost to follow-up of total study population) (%)	Intention to treat analysis
Arkkila	A	C	B	A	16/92 (17%)	No
You	A	A	A	A	440/3365 (13%)	Yes
Ley	A	A	A	A	69/316 (22%)	Yes
Befrits	C	C	A	A	2/125 (2%)	No
Wong	A	A	B	A	192/1630 (12%)	Yes
Kuipers	A	C	C	A	NS	Yes
Kamada	C	C	A	A	0 (0%)	No
Correa[#]	A	C	C	A	345/976 (35%)	Yes
Mera[#]	A	C	C	A	186/795 (23%)	Yes
Sung[##]	A	A	A	A	72/587 (12%)	No
Zhou[##]	A	A	A	A	109/552 (20%)	No
Leung[##]	A	A	A	A	152/587 (26%)	Yes
Mones	A	A	A	C	2/85 (2%)	No
Schenk	C	C	B	A	17/100 (17%)	No
Miwa	C	A	A	A	5/90 (6%)	Yes
Gisbert	C	C	C	A	13/135 (10%)	No
Moayyedi	A	A	A	A	8/41 (20%)	Yes
Leri	C	C	C	C	0 (0%)	Yes
Ohkusa	C	C	C	A	0 (0%)	Yes
Lazzaroni	C	C	A	C	10/59 (17%)	No

Legend: * A/B/C-coding as described in 'Quality assessment'.
[#]studies desribing the same study cohort
[##]studies desribing the same study cohort

tological specimens varied greatly between the trials, from two (27) to seven gastric biopsies (33). Similarly, the follow-up period varied greatly, as the effect of *H. pylori* eradication on the gastric mucosa was evaluated after 8 weeks (23) to a maximum of 12 years (26). However, the latter study was unblinded after six years and all subjects who were *H. pylori* positive at that time received *H. pylori* eradication.

Effect of *H. pylori* eradication on pre-malignant gastric lesions

Several studies demonstrated less progression or even regression of atrophic gastritis within one to two years after *H. pylori* eradication (16-18;20;21;25;28;30;31;33), although some relatively small studies of overall low to moderate methodological quality showed no significant difference (9;19;22;23;27;29). Significant less progression and more regression of intestinal metaplasia after *H. pylori* eradication has also been reported by three trials after five months, five and six years follow-up. (18;24;29;34) However, another trial did not confirm this finding after nine years follow-up. (33) The effect of *H. pylori* eradication on the progression of gastric dysplasia was only reported in two trials, which reached contradictory results after six and nine years follow-up. (18;33) Unfortunately, two other studies with relatively long-term follow-up do not report data on progression or regression of the different categories of pre-malignant gastric lesions. (26;32) Only Wong *et al.* analyzed the effect of *H. pylori* eradication on the development of gastric cancer in patients with pre-malignant gastric lesions. This study demonstrated no significant difference in gastric cancer development between the *H. pylori* eradication and control group. In this study, gastric cancer within patients with pre-malignant gastric lesions at baseline only occurred in patients who had been diagnosed with intestinal metaplasia and dysplasia previously.

DISCUSSION

Unfortunately, several factors hinder overall evaluation of these randomized controlled trials. For instance, the number of included patients with pre-malignant lesions was generally low, frequently even unclear, and follow-up in most studies was relatively short. Furthermore, the number of biopsies obtained in individual patients was mostly small, leading to imprecise results as a consequence of sampling errors. In addition, study outcomes were by some evaluated in an intention-to-treat analysis and by others according to *H. pylori* status at the end of follow-up. Most importantly, outcome measures varied between studies using non-interchangeable parameters such as prevalence changes, histological scores and transition percentages. Quantification of the outcomes is therefore difficult.

REVIEWERS' CONCLUSIONS

Implications for practice

H. pylori eradication harbours great potential for prevention of gastric cancer. Clinical evidence for the prevention of carcinogenic progression in patients with atrophic gastritis is highly suggestive, whereas the evidence in patients with intestinal metaplasia and dysplasia is scarce. Possibly, frequent loss of *H. pylori* colonization in these patients indicates limited benefit from *H. pylori* eradication. At this moment, we advise to consider *H. pylori* eradication for prevention of gastric cancer at the earliest stage of gastric carcinogenesis. However, it must be realized that *H. pylori* eradication may be insufficient to halt gastric carcinogenesis in patients with intestinal metaplasia and dysplasia.

Implications for research

Although several randomized controlled trials are available on the effect of *H. pylori* eradication on pre-malignant gastric lesions, overall evaluation and quantification of the effect are hindered by the heterogeneity of the outcome parameters. A meta-analysis of the available trials is needed. In this meta-analysis histological improvement of the lesions versus no improvement (no change or deterioration) and histological deterioration versus no deterioration (no change or improvement) need to be investigated. In addition, additional randomized controlled trials with long-term follow-up on the effect of *H. pylori* eradication on intestinal metaplasia and dysplasia are required.

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CHAPTER 12

Helicobacter pylori eradication and gastric cancer: when is the horse out of the barn?

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ABSTRACT

Helicobacter pylori infection is a major risk factor for gastric cancer development. Therefore, *H. pylori* eradication may be an important approach in the prevention of gastric cancer. However, long-term data proving the efficacy of this approach are lacking. This report describes two patients who developed gastric cancer at respectively 4 and 14 years after *H. pylori* eradication therapy. These patients were included in a study cohort of *H. pylori*-infected subjects who received anti-*H. pylori* therapy during the early years of development of *H. pylori* eradication therapy, and underwent strict endoscopic follow-up for several years. In both patients, gastric ulcer disease and pre-malignant gastric lesions, i.e. intestinal metaplasia at baseline and dysplasia during follow-up, were diagnosed before gastric cancer development. These case reports demonstrate that *H. pylori* eradication does not prevent gastric cancer development in all infected patients after long-term follow-up. In patients with pre-malignant gastric lesions, in particular in patients with a history of gastric ulcer disease, adequate endoscopic follow-up is essential for early detection of gastric neoplasia.

INTRODUCTION

The development of gastric cancer is strongly associated with *Helicobacter pylori* infection. (1;2) This is in particular true for the development of distal gastric cancer, for which the presence of *H. pylori* may be a conditio sine qua non, as in more than 90% of patients current or past *H. pylori* colonization can be demonstrated. (3-5) The association between cancer of the gastric cardia appears partly related to *H. pylori* and partly to other conditions, in particular gastro-esophageal reflux disease. (6;7) In the multi-step pathogenesis of intestinal type gastric cancer, *H. pylori*-induced chronic active gastritis slowly progresses through the pre-malignant stages of atrophic gastritis, intestinal metaplasia and dysplasia to gastric adenocarcinomas. (8-10)

Given its central role in gastric carcinogenesis, eradication of *H. pylori* may be an effective approach for prevention of gastric cancer. This hypothesis was firstly supported by the concept that gastritis is a key feature in gastric carcinogenesis, and that *H. pylori* eradication virtually always leads to a gradual, complete resolution of chronic active gastritis. (11) Further studies showed that *H. pylori* eradication can also lead to regression of atrophic gastritis. (12-17) Therefore, *H. pylori* eradication has been accepted by many for treatment of atrophic gastritis aiming at prevention of gastric cancer. (18) Nevertheless, in patients with lesions that have progressed beyond the stage of atrophic gastritis, i.e. patients with intestinal metaplasia or dysplasia, *H. pylori* eradication may have little beneficial effect to prevent gastric cancer. (19) These lesions are often associated with decreased colonization density, and ultimately even with frequent loss of *H. pylori* colonization even without active intervention. Therefore, further progression of pre-malignant lesions may be less dependent on *H. pylori* infection. These findings implicate that *H. pylori* eradication would in particular have a long-term preventive effect for the development of gastric cancer over the time-frame that it takes to progress from non-atrophic gastritis to intestinal metaplasia and gastric dysplasia.

To prove this concept, truly long-term studies are needed. Such long-term data will only slowly become available given the fact that *H. pylori* eradication was only first given twenty years ago, in the mid eighties. (11;20) In this case report we describe two patients who received eradication therapy for peptic ulcer disease in the first years after the discovery of *H. pylori*, but nevertheless developed gastric cancer during long-term follow-up. Both patients belonged to a cohort of patients who were endoscopically diagnosed in the period of 1985 – 1987 with peptic ulcers or histological evidence of chronic active gastritis, and had a positive *Campylobacter pylori* culture. (21) These patients were among the first worldwide to be treated for *H. pylori* and they were followed periodically after *H. pylori* eradication as part of a study protocol. (22;23)

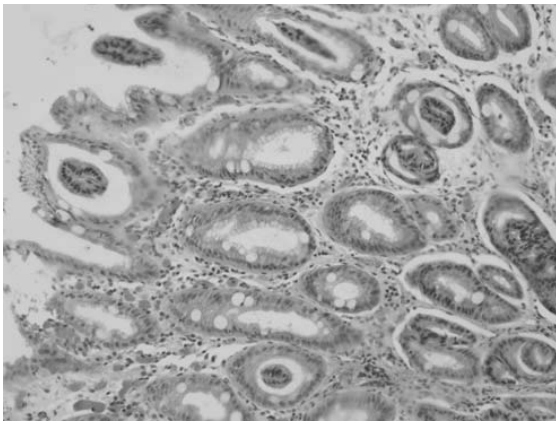
CASE 1

A 58-year-old female patient with a past medical history of gastric ulcer disease, underwent endoscopic examination because of upper abdominal pain in 1984. Gastroscopy showed an erythematous mucosa without erosions or ulcerations, and antral biopsies revealed chronic active gastritis with *Campylobacter pylori* micro-organisms and intestinal metaplasia. An attempt to eradicate this bacterium with bismuth subcitrate mono-therapy failed, but subsequent treatment with a combination of ranitidin and furazolidone led in 1985 to *H. pylori* eradication as demonstrated by a negative *Campylobacter pylori* culture and confirmed by repeatedly negative histology and culture results in subsequent years. Between 1984 and 1989, she underwent a total of 23 surveillance endoscopies with intervals ranging from 1 to 4 months. During follow-up, in 1985, an ulcer was detected at the angulus, which persisted for several years despite the absence of *H. pylori* bacteria. Biopsies from this ulcer were obtained during several follow-up endoscopies and repeatedly showed intestinal metaplasia and low-grade dysplasia. In 1989, four years after *H. pylori* eradication, a well-differentiated intramucosal adenocarcinoma (T2N0M0) was diagnosed in biopsies from this persistent ulcer. Subsequently, she underwent an intentionally curative total gastrectomy. In 1993, she presented with metastasized primary lung cancer and deceased at the age of 67 years, eight years after *H. pylori* eradication.

CASE 2

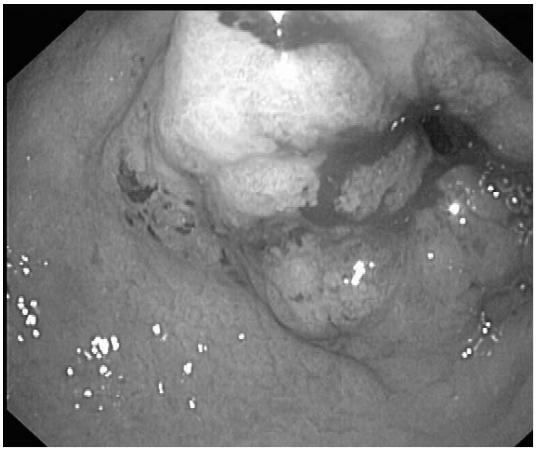
A 35-year-old male patient presented with dyspeptic complaints in 1985 and was subsequently diagnosed with a gastric angular ulcer at gastroscopy. Biopsies from the angulus and antrum

Figure 1. Case 2: Histological examination of initial antral biopsy (1985) only shows intestinal metaplasia without dysplasia. Original magnification 100x, H&E staining.



showed active chronic gastritis with presence of *Campylobacter pylori* micro-organisms and intestinal metaplasia (Figure 1). Various treatment attempts to eradicate the infection were performed, using H2-receptor antagonists, bismuth subcitrate, sucralfate, and triple therapy consisting of a combination of bismuth subcitrate, amoxicillin and metronidazole. After five years of repeated treatment, *H. pylori* was eradicated in 1990 as confirmed by histology showing disappearance of the bacteria and resolution of gastritis, and the angular ulcer finally healed. Within ten years of follow-up after initial treatment, this patient underwent 19 follow-up endoscopies with histological evaluation at intervals ranging from 1 to 12 months. During further follow-up, no macroscopic abnormalities of the gastric mucosa were detected at endoscopy and antral biopsies showed no *H. pylori* bacteria or active chronic gastritis. However, intestinal metaplasia and low-grade dysplasia were repeatedly observed. In 2004, 14 years after *H. pylori* eradication, he was endoscopically re-examined because of recurrent complaints of dyspepsia and heartburn. At this endoscopy, a pyloric ulcer was detected (Figure 2), and histological examination of biopsies showed a poorly-differentiated adenocarcinoma of the intestinal type (T4N1M0) (Figure 3). Subsequently, an intentionally curative distal gastric resection with subtotal pancreaticoduodenectomy was performed. However, in 2006 at the age of 56 years, he presented with distant liver metastases and deceased shortly thereafter, 16 years after *H. pylori* eradication.

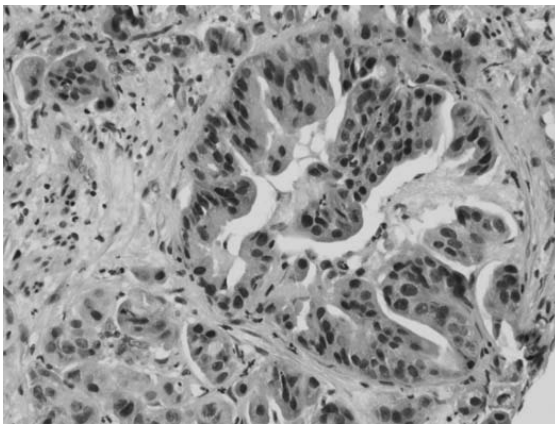
Figure 2. Case 2: Endoscopic image of the ulcerative, pyloric lesion during follow-up (2004).



DISCUSSION

This report describes two patients who were once included in one of the first study cohorts that underwent *H. pylori* eradication treatment for gastritis or peptic ulcer disease. The length and intensity of follow-up of these patients is therefore unique, even more so because data from Western populations on the effect of *H. pylori* eradication for gastric cancer prevention

Figure 3. Case 2: Histological examination of biopsies of ulcerative, pyloric lesion (2004) shows a poorly-differentiated adenocarcinoma of the intestinal type. Original magnification 150x, H&E staining.



are scarce. These case reports show that *H. pylori* eradication does not prevent the development of gastric cancer in all patients during long-term follow-up, in particular not in patients who already developed pre-malignant gastric lesions prior to *H. pylori* eradication.

As progression from *H. pylori* gastritis to gastric cancer generally takes years to decades, evaluation of long-term follow-up after eradication, such as provided in these case reports, is essential to assess the true impact of *H. pylori* eradication on gastric carcinogenesis. The reported follow-up in previous studies that assessed the effect of *H. pylori* eradication on the development of gastric cancer as primary endpoint varied between 5 years to 12 years, which is too short to adequately assess the true progression to cancer and the preventive effect of *H. pylori* eradication. (16;19;24)

Both patients presented in this report suffered from gastric ulcer disease before the development of gastric cancer. It has been described previously that patients with gastric ulcers are at increased risk of gastric cancer development, whereas patients with duodenal ulcers seem to be protected. (3;25) This probably results from the presence of atrophic gastritis and corpus-predominant gastritis in patients with gastric ulcers, whereas these conditions are commonly absent in patients with duodenal ulcers.

In case *H. pylori* eradication therapy is prescribed in patients with pre-malignant gastric lesions aiming at gastric cancer prevention, proof of eradication should be obtained. The reduced colonization density in these patients may impair the sensitivity of histology and culture, as well as that of urea breath testing. Further confirmation of eradication can therefore be sought by demonstration of resolution of gastritis or negative seroconversion. The latter rarely occurs without active intervention, unless the bacterium spontaneously disappears when severe atrophy and intestinal metaplasia have occurred. (26) In addition, the combination of *H. pylori* eradication with endoscopic surveillance and histological follow-up is crucial to detect gastric neoplasia at an early and potentially curative stage. At this moment,

guidelines for follow-up of patients with pre-malignant gastric lesions are lacking in Western countries. We recommend no follow-up for patients with atrophic gastritis, yet surveillance endoscopy with biopsy sampling at a 2-3 year interval for patients with intestinal metaplasia, a 1 year interval for low-grade dysplasia, and direct re-evaluation for patients with high-grade dysplasia. (9) This recommendation is based on previous observations of very similar cancer incidences in these patients as in patients with Barrett's esophagus. (9) However, the yield of such surveillance, and the optimal intervals require further investigation, in which the appropriate biopsy protocols, additional risk stratification to identify high-risk patients, and the potential of serological surveillance need to be addressed.

Our report is in line with the observation in the large randomized study of Wong *et al.* in which *H. pylori* eradication in patients with pre-malignant gastric lesions did not prevent the development of gastric cancer. (19) Our data add to this important study by extending the follow-up from a maximum of five years to a maximum of 16 years after *H. pylori* eradication. This suggests that the progress from atrophy and intestinal metaplasia to invasive cancer is truly an autonomous, *H. pylori*-independent process. This is consistent with previous observations that *H. pylori* colonization and even the serological evidence of previous infection may completely disappear once marked atrophy and metaplasia have occurred. At this point, molecular changes may be too severe to be reversed. The progress towards cancer may then occur via different pathways in which several gene regions associated with oncogene overexpression, tumor suppressor loss, and defective DNA mismatch repair appear to be involved. (27) Recent studies have suggested that *H. pylori* induces repopulation of the stomach with bone marrow-derived cells, which may play a crucial role in gastric carcinogenesis. (28)

The importance of our report, albeit a description of cases, lies in the observation that this autonomous process can take more than a decade. This means that we have to revise the general concept suggested by previous intervention studies that the preventive effect of *H. pylori* eradication becomes complete beyond the first few years, when patients at an advanced stage towards cancer have progressed to this disease.

In conclusion, this report emphasizes the need for further systematic data collection, preferably by randomized controlled trials in different geographical areas, to elucidate the role of *H. pylori* eradication in patients with intestinal metaplasia or dysplasia to prevent gastric cancer after long-term follow-up. Our data confirm that *H. pylori* eradication is insufficient in these patients as single management modality and should be combined with strict endoscopic surveillance, and if needed endoscopic treatment.

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CHAPTER 13

General discussion and conclusions

INTRODUCTION

The understanding of gastric carcinogenesis has advanced largely over the past decades. Since 1994, *Helicobacter pylori* has been identified as a definite carcinogen in the pathogenesis of distal gastric cancer. (1) *H. pylori* causes chronic active gastritis which can progress through several pre-malignant stages, i.e. atrophic gastritis, intestinal metaplasia and dysplasia, to eventually gastric cancer. (2;3) Especially since the recognition of the key role of *H. pylori* infection and the stepwise progression of pre-malignant lesions to gastric cancer, the development of preventive strategies has become an important focus in gastric cancer research. Current clinical guidelines principally cover detection and treatment of *H. pylori* infection. (4) Yet, no clear guidelines are available on detection, surveillance and treatment of subsequent pre-malignant gastric lesions.

EPIDEMIOLOGY

Epidemiology of pre-malignant gastric lesions

Since most subjects with pre-malignant gastric lesions are asymptomatic, these lesions remain unrecognized in the majority of individuals. For this reason, data on the epidemiology of pre-malignant lesions are scarce, especially from populations with an overall low incidence of gastric cancer. (5) According to a recent population-based study from Germany, the prevalence of a serological diagnosis of atrophic gastritis, as defined as serum pepsinogen I < 25 ng/ml, increased from approximately 5% in the age group from 50 to 54 years to 9% in the age group from 70 to 74 years. (6) Pre-malignant gastric lesions are also common diagnoses in routine biopsies obtained during upper gastro-intestinal endoscopies in a Western population, especially in the elderly. (Chapter 3) From 1991 to 2005, the average incidence (world standardized rate) was 2944/100,000 for atrophic gastritis, 4891/100,000 for intestinal metaplasia, and 614/100,000 for dysplasia relative to the total number of patients with a first gastric biopsy. (Chapter 3)

Although these data show that diagnoses of pre-malignant gastric lesions are common, the occurrence of these lesions has declined significantly over the past decades. A study with repeated cross-sectional endoscopic examination within the same Finnish population showed that the prevalence of chronic *H. pylori*-induced gastritis (both non-atrophic and atrophic) declined by 18% in the period from 1977 to 1992. (7) However, the prevalence rates of chronic *H. pylori* gastritis were stable in the same birth cohorts over the study period. So the decline was only caused by lower *H. pylori* prevalences in younger birth cohorts (cohort effect), a phenomenon which has also been observed in a prospective Ducth cohort study. (8) In our research, we showed that from 1991 to 2005, the incidence of atrophic gastritis,

intestinal metaplasia and dysplasia in the Netherlands declined with 8.2%, 8.1% and 2.4% per year, respectively. (Chapter 3) These incidence changes were caused by both cohort and period effects, since a declining incidence in men born after 1920 as well as an accelerating decline in the number of diagnoses of atrophic gastritis and intestinal metaplasia after 1996 were demonstrated. These phenomena are probably related to a decrease in the prevalence of *H. pylori* infection in younger age cohorts, the introduction of histological classification systems, and the widespread introduction of *H. pylori* diagnosis and treatment in the early nineties. (9-11) Since the decline in the incidence of pre-malignant gastric lesions is stronger than the current decline of gastric cancer and changes in the incidence of pre-malignant lesions predict similar changes in gastric cancer occurrence in the next 10-15 years, we predict a more rapid further decline of gastric cancer incidence of approximately 24% within the next decade. (12)

With regard to cost-effectiveness and burden for patients, the declining incidence of pre-malignant gastric lesions and expected decline of gastric cancer incidence emphasize the need for selective screening and surveillance in Western populations. In these populations, an approach with several screening stages with stepwise increasing burden for subjects in proportion to gastric cancer risk is required. In this approach, the selection of a population sample of the general population that should be offered non-invasive serological screening could be the initial step. This selection should primarily be based on epidemiological risk factors, as symptoms cannot predict the presence of pre-malignant lesions or early gastric cancer. A risk profile could be defined based on known epidemiological risk factors, as for instance low socioeconomic class, blood group A and familial occurrence of gastric cancer. (2;13;14) In addition, migrant communities constitute a high risk population as we observed a high *H. pylori* infection rate in a population-based sample in the Netherlands. (Chapter 4) In addition, more infections with CagA-positive *H. pylori* strains and serological evidence of atrophic gastritis, as defined as either a pepsinogen I<70 µg/L in combination with a pepsinogen I/II ratio <3.0, or a pepsinogen I <28 µg/L, were observed in subjects from foreign origin (48% and 5.2%, respectively) as compared to subjects from Dutch origin (25% and 0%, respectively). Serological screening is attractive to identify a population at high risk of gastric cancer in low incidence countries, since costs and burden for patients are acceptable and thereby a large population sample can be screened. By combining pepsinogens I and II and gastrin levels with *H. pylori* serology in a decision algorithm, it is possible to estimate the presence of *H. pylori* gastritis, distinguish atrophic gastritis and locate atrophic changes with high sensitivity and specificity. (15) The aim of serological screening would be to identify patients at risk of pre-malignant gastric lesions that require histological confirmation after endoscopy. Finally, long-term endoscopic surveillance should be offered to individuals with pre-malignant lesions at high risk of progression.

Association between pre-malignant gastric lesions and other gastro-esophageal diseases

In addition to gastric cancer, an association with chronic *H. pylori* infection has been investigated for several gastro-esophageal and duodenal disorders, such as Barrett's esophagus, esophageal adenocarcinoma, and peptic ulcer disease. (16-20) In addition, recent studies have demonstrated an elevated risk of oesophageal squamous cell carcinomas (ESCC) in patients with atrophic changes of the gastric mucosa. (20-23) Our large, nationwide study confirms a positive association between these conditions, with an overall relative risk of 2.2 for the development of ESCC in patients with gastric atrophy as compared to the general Dutch population. (Chapter 5) However, as the risk of ESCC in our population did not increase with the severity of gastric atrophy, a causal relationship between gastric atrophy and ESCC seems unlikely. Moreover, as we demonstrated a similar association between gastric atrophy and the anatomically unrelated small cell lung carcinoma (relative risk 1.8), these associations are best explained by confounding factors, such as smoking.

H. pylori infection has also been recognized in the pathogenesis of gastric Mucosa-Associated Lymphoid Tissue (MALT) lymphomas. In patients with gastric MALT lymphomas, increased progression of pre-malignant gastric lesions has been observed, but the association with gastric cancer remained unknown. (24;25) Our long-term data presented in this thesis show that gastric MALT lymphoma patients indeed have a six times higher risk of developing gastric cancer as compared to the general Dutch population. (Chapter 6) In the majority of cases (53%), gastric cancer was diagnosed within one year prior to or after the diagnosis of MALT lymphoma. This means that strict endoscopic surveillance with careful inspection of the gastric mucosa after diagnosis or treatment of gastric MALT lymphoma is indicated.

DETECTION AND SURVEILLANCE

Gastric cancer risk of pre-malignant gastric lesions

The efficacy of endoscopic re-evaluation or surveillance of patients with pre-malignant gastric lesions in the prevention of gastric cancer is highly controversial. (26-28) As a result, the performance of endoscopic surveillance largely depends on the personal experience of clinicians and is frequently omitted in current clinical practice, even in patients with overt dysplasia. In our nationwide cohort study of patients with pre-malignant gastric lesions, at least one re-evaluation upper gastro-intestinal endoscopy with histological re-evaluation was performed in only 26% of patients with atrophic gastritis, in 28% with intestinal metaplasia, and in 38% with mild or moderate dysplasia. Although the frequency of surveillance was significantly higher in patients with severe dysplasia (61%; $p<0.001$) as compared to the other pre-malignant diagnoses, still more than one-third of patients with severe dysplasia

and thus at presumed very high risk for invasive gastric cancer, did not receive surveillance. (Chapter 8)

The most important reason for the controversy on the importance of endoscopic surveillance in patients with pre-malignant gastric lesions is that quantification of gastric cancer risk in these patients is unclear. Previous studies that investigated the progression rate of atrophic gastritis, intestinal metaplasia and dysplasia to gastric cancer have reached conflicting results. (Chapter 7) These variations can probably be explained by a variety of factors, such as differences in study design and included populations, and variations in criteria for diagnosis of intestinal metaplasia and dysplasia. The largest prospective study was performed in China and included 1240 patients with severe gastritis and/or atrophic gastritis, 842 with intestinal metaplasia and 546 with dysplasia. (29) Progression rates to gastric cancer were 0.02% per year for severe gastritis and/or atrophic gastritis, 0.4% per year for intestinal metaplasia and 0.6% per year for mild dysplasia and 1.4% for severe dysplasia within 5 years follow-up. In our Western study population, we studied 22,365 patients with atrophic gastritis, 61,707 with intestinal metaplasia, 7,616 with mild to moderate dysplasia, and 562 with severe dysplasia. Within this cohort, we observed remarkably similar progression rates. Within 5 years follow-up, the annual incidence of gastric cancer was 0.1% for patients with atrophic gastritis, 0.25% for intestinal metaplasia, 0.6% for mild to moderate dysplasia, and 6% for severe dysplasia. (Chapter 8) The difference in progression rate of severe dysplasia between both studies may be explained by differences between Western and Asian gastro-intestinal pathologists in classification of gastric dysplasia and cancer. (30)

These findings on progression to gastric cancer indicate that endoscopic follow-up of all patients with atrophic gastritis or intestinal metaplasia is not indicated, as only a small proportion of patients eventually develops gastric cancer. However, a diagnosis of low-grade dysplasia warrants endoscopic surveillance at short intervals. In addition, in patients with high-grade dysplasia thorough endoscopic and histological re-evaluation shortly after initial diagnosis and subsequent long-term surveillance are strongly indicated, and endoscopic resection needs to be considered. (31;32)

Surveillance of atrophic gastritis and intestinal metaplasia of the gastric mucosa should preferably be limited to patients at high risk of gastric cancer. Previous studies have identified the severity, extent, and the intragastric location of the lesions, as well as the concomitant presence of associated lesions, in particular MALT lymphoma or gastric ulcer, as risk factors for progression of these lesions. (24;26;33) Furthermore, the risk is influenced by *H. pylori* virulence factors, a family history of gastric cancer, host genetics and environmental factors, in particular cigarette smoking and alcohol use. (34-39) In our nationwide cohort study, we identified male sex as an important independent risk factor for progression to more advanced lesions and gastric cancer. (Chapter 8) In addition, we performed a prospective study to identify risk factors for extensive intragastric intestinal metaplasia as a marker for increased gastric cancer risk. (Chapter 9) A total of 88 patients with a previous diagnosis of intestinal

metaplasia underwent a surveillance endoscopy with biopsies for histological assessment taken from five standardized intragastric locations (antrum, angulus, lesser curvature and greater curvature of corpus, and cardia) In accordance with previous studies, we identified a family history of gastric cancer, alcohol use ≥ 1 unit/ day, moderate or marked intestinal metaplasia at the index biopsy, and a pepsinogen I to II ratio <3.0 as the most important predictors of extensive intestinal metaplasia, as defined as intestinal metaplasia in the random biopsies from at least two different intragastric locations. A simple risk score based on these factors could identify extensive intestinal metaplasia with 96% sensitivity.

Endoscopic surveillance strategy of pre-malignant gastric lesions

Although advanced endoscopic techniques may improve the detection of pre-malignant gastric lesions, current detection and surveillance in routine practice still relies on histological assessment of random biopsies, obtained during conventional endoscopy. (40) The Sydney classification system currently provides the endoscopic and histological gold standard for the assessment of gastritis. (9) According to this system five gastric biopsies need to be obtained (two antrum, two corpus and one angulus). However, this biopsy schedule insufficiently acknowledges the intragastric distribution of pre-malignant lesions, which should guide biopsy sampling during surveillance endoscopy. (41-43) Pre-malignant gastric lesions associated with *H. pylori* infection have been shown to occur most commonly in the antrum and incisura angularis. (44) Subsequently, these lesions spread along the lesser curvature and are especially common in the transitional zones (antrum to corpus and corpus to cardia). (45)

We performed a prospective study to identify the most optimal biopsy strategy during surveillance of intestinal metaplasia or dysplasia of the gastric mucosa. A total of 112 patients with a previous diagnosis of intestinal metaplasia or dysplasia underwent surveillance endoscopy and biopsy samples were obtained from any endoscopically detected focal lesion and 12 random biopsies were taken from five standardized intragastric locations (antrum, angulus, lesser curvature and greater curvature of corpus and cardia). Random biopsies from the lesser curvature had a significantly higher yield in diagnosing atrophic gastritis and intestinal metaplasia as compared to biopsies from the greater curvature of the corpus ($p=0.05$ and $p=0.03$). In addition, intestinal metaplasia in biopsies from the cardia identified patients at increased risk of a concurrent diagnosis of dysplasia or gastric cancer. Targeted biopsies were indispensable for the diagnosis of high-grade dysplasia in three patients. In comparison, the random biopsy scheme was essential for a diagnosis of low-grade dysplasia in two patients and the diagnosis of gastric cancer in one patient. Therefore, an adequate biopsy protocol requires 2 random biopsies from the cardia, 1 from the greater curvature of the corpus, 2 from the lesser curvature of the corpus, 1 from the angulus, and 3 from the antrum in a population at an overall low gastric cancer risk. Moreover, both random and

targeted biopsies are essential for an adequate diagnosis during endoscopic surveillance of intestinal metaplasia and dysplasia of the gastric mucosa.

TREATMENT

Helicobacter pylori eradication for pre-malignant gastric lesions

With advancing insights into the pivotal role of *H. pylori* in gastric carcinogenesis, the prevention of gastric cancer by eradication of infection seems increasingly important. However, the effect of *H. pylori* eradication for prevention of gastric cancer is still controversial. Only one randomized controlled trial has been published on the effect of *H. pylori* eradication to prevent gastric cancer in subjects with chronic *H. pylori*-induced gastritis without pre-malignant gastric lesions. (46) This Chinese trial demonstrated a significantly reduced incidence of gastric cancer after *H. pylori* eradication (0% in *H. pylori* eradication group versus 1.2% in placebo-group, p=0.02). However, a significantly reduced incidence of gastric cancer by *H. pylori* eradication in patients with pre-malignant gastric lesions at baseline could not be demonstrated (2.2% in *H. pylori* eradication group versus 1.7% in placebo-group, p=0.67).

Gastric cancer prevention through *H. pylori* eradication in patients with pre-malignant gastric lesions has been studied in several other randomized controlled trials. (46-64) (Chapter 11) These studies evaluated the progression and regression of pre-malignant gastric lesions as surrogate parameters for the development of gastric cancer. Unfortunately, several factors hinder overall evaluation of these randomized controlled trials. For instance, the number of included patients with pre-malignant lesions was generally low, follow-up in most studies was relatively short and outcome measures varied between studies. Nevertheless, conclusions can be drawn with cautiousness. In patients with atrophic gastritis, lesions regress within one to two years after *H. pylori* eradication. (Chapter 11) However, the effect of *H. pylori* eradication in patients with intestinal metaplasia and dysplasia is highly uncertain, as was illustrated by the development of gastric cancer long after *H. pylori* eradication in two case reports. (Chapter 12) In these patients progression of the lesions probably occurs independent of *H. pylori* colonization. Therefore, *H. pylori* eradication is insufficient in these patients as single management modality and should be combined with long-term endoscopic surveillance.

FUTURE DIRECTIONS

Although the detection, surveillance and treatment of pre-malignant gastric lesions can contribute to the prevention of gastric cancer, its potential is not fully explored as yet.

For the detection of pre-malignant gastric lesions, several steps of a preventive strategy need further investigation in case gastric cancer screening is considered in low incidence countries. First of all, accurate initial selection of individuals for screening for pre-malignant gastric lesions in the general population is important, since most subjects with pre-malignant gastric lesions are asymptomatic. However, this is an almost undeveloped research area. Therefore, large population-based studies are necessary to identify adequate risk profiles. Moreover, the diagnostic options for detection of pre-malignant gastric lesions in this stage need to be further explored, for instance serological screening to estimate the presence of intestinal metaplasia and dysplasia. Lastly, all steps of screening and surveillance need further investigation on cost-effectiveness.

In addition, surveillance programs of pre-malignant gastric lesions need further evaluation too, as these lesions are frequently diagnosed in random biopsies after routine upper gastrointestinal endoscopy. The appropriate endoscopic surveillance frequency in these patients needs to be established, preferentially by individual risk stratification. For this stratification, clinical, serological, including new serological markers as ghrelin and leptin, and histological markers, as well as genetic markers (polymorphisms) need to be evaluated. In addition, advanced endoscopic techniques may improve the detection of pre-malignant gastric lesions during surveillance endoscopy, for instance narrow band imaging or endomicroscopy. Therefore, the yield of endoscopic surveillance with these techniques needs to be investigated, and these techniques need to be studied separately in populations with an overall high and low gastric cancer risk.

For the treatment of pre-malignant gastric lesions, the long-term results of ongoing randomized controlled clinical trials on the effect of *H. pylori* eradication are eagerly awaited. In particular the effect of *H. pylori* eradication in patients with intestinal metaplasia and dysplasia after long-term follow-up needs further investigation in well-designed randomized controlled trials.

CONCLUSIONS

The progression of chronic *H. pylori*-induced gastritis through several pre-malignant stages to gastric cancer harbours great potential for gastric cancer prevention. Although the occurrence of pre-malignant gastric lesions has declined significantly over the past decades, diagnoses of these lesions are still common. Pre-malignant gastric lesions carry a significant gastric cancer risk, which is insufficiently acknowledged in current clinical practice. Therefore, the development of clinical guidelines for management of pre-malignant gastric lesions is required.

In general, *H. pylori* eradication prevents progression along the carcinogenic cascade in patients with *H. pylori*-induced chronic active gastritis and atrophic gastritis. However, in

patients with intestinal metaplasia and dysplasia *H. pylori* eradication is insufficient to prevent gastric cancer development. In these patients endoscopic surveillance with histological biopsy sampling is essential for early detection and treatment of advanced precursors and gastric cancer. Endoscopic surveillance needs to be considered in all patients with intestinal metaplasia and dysplasia of the gastric mucosa, although decisions on follow-up frequency require individual adjustment according to intragastric extent of pre-malignant lesions and the presence of additional risk factors.

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Summary

Gastric cancer is usually diagnosed at an advanced stage, since symptoms are often absent or non-specific in patients with an early stage of disease. As curative options are often limited at an advanced stage of disease, gastric cancer usually portrays a poor prognosis. In the multi-step cascade of gastric carcinogenesis, *Helicobacter pylori*–induced gastritis slowly progresses through the pre-malignant stages of atrophic gastritis, intestinal metaplasia and dysplasia to gastric adenocarcinoma. The progression of pre-malignant gastric lesions to gastric cancer generally takes decades. Therefore, this cascade may provide a basis for cancer prevention by early intervention, such as *H. pylori* eradication, and potentially also for early detection and treatment of advanced precursor lesions and gastric adenocarcinomas.

The general aims and outline of this thesis are described in **Chapter 1**.

Chapter 2 provides an overview of current knowledge on the epidemiology of pre-malignant gastric lesions. Geographical variations and risk factors of pre-malignant gastric lesions and gastric cancer are described. In addition, their implications for the development of screening and surveillance strategies are discussed.

Chapter 3 describes a nationwide study of epidemiological trends of pre-malignant gastric lesions in the Netherlands in the period from 1991 to 2005. In this study, 23,278 patients with a first diagnosis of atrophic gastritis, 65,937 patients with intestinal metaplasia, and 8,517 patients with dysplasia were included. The incidence of atrophic gastritis declined similarly in men and women with 8.2% per year [95% CI 7.9-8.6], and dysplasia with 8.1% per year [95% CI 7.5-8.6]. The incidence of intestinal metaplasia declined with 2.9% per year [95% CI 2.7-3.1] in males and 2.4% [95% CI 2.2-2.6] in females. The declining incidence of pre-malignant gastric lesions resulted from a combined period and cohort effect. Based on these findings, a further decrease in incidence of gastric cancer of 24% can be expected in the next decade.

In **Chapter 4** the prevalence of *H. pylori* infection and atrophic gastritis was studied in a Dutch migrant community. The prevalence of *H. pylori* infection was high in a population-based sample of 288 subjects, even in autochthonous inhabitants. In addition, mean pepsinogen I level and pepsinogen I/II ratio were significantly lower in subjects from non-Dutch origin as compared to Dutch subjects (both $p<0.001$). Serologic evidence of atrophic gastritis was observed in 12 subjects from non-Dutch origin, whereas Dutch subjects were not affected ($p=0.13$). Therefore, these migrant communities may constitute a target group for serologic screening to prevent *H. pylori*-related complications in Western countries.

An association between esophageal squamous cell carcinomas and atrophic changes of the gastric mucosa has been demonstrated by several studies. However, the mechanism for this association remained unclear. In **Chapter 5** a relative risk of 2.2 [95% CI 1.8-2.6] for developing esophageal squamous cell carcinomas was demonstrated in a nationwide cohort of patients with gastric atrophy as compared to the general Dutch population. The risk of

esophageal squamous cell carcinomas did not increase in parallel with the severity of gastric atrophy (p=0.90). In addition, a similar association was demonstrated between small cell lung carcinomas and gastric atrophy. Therefore, a causal relation between esophageal squamous cell carcinomas and gastric atrophy seems unlikely, and this association is probably best explained by confounding factors, such as smoking.

In order to evaluate gastric cancer risk in patients with gastric MALT lymphoma, a nationwide cohort of 1419 patients with gastric MALT lymphoma was studied in **Chapter 6**. A total of 34 (2.4%) patients were diagnosed with gastric cancer, which corresponds with a six times higher risk of gastric cancer as compared to the general Dutch population. In the majority of cases (53%), gastric cancer is diagnosed within one year prior to or after the diagnosis of MALT lymphoma. Accurate endoscopic re-evaluation after diagnosis and treatment of gastric MALT lymphoma is therefore indicated.

In **Chapter 7** an overview is provided on current knowledge on the detection, surveillance and treatment of patients with pre-malignant gastric lesions. The available literature on histological classifications, natural history, serological and endoscopic detection, pharmacological and endoscopic treatment of pre-malignant gastric lesions is summarized and discussed.

Chapter 8 describes a nationwide cohort study of 22,365 patients with atrophic gastritis, 61,707 with intestinal metaplasia, 7,616 with mild to moderate dysplasia, and 562 with severe dysplasia. At least one follow-up upper gastro-intestinal endoscopy with histological re-evaluation was performed in only 26% of patients with atrophic gastritis, in 28% with intestinal metaplasia, and in 38% with mild or moderate dysplasia, compared to 61% with severe dysplasia ($p<0.001$). Within 5 years follow-up, the annual incidence of gastric cancer was 0.1% for patients with atrophic gastritis, 0.25% for intestinal metaplasia, 0.6% for mild to moderate dysplasia, and 6% for severe dysplasia. As current surveillance of pre-malignant gastric lesions is discrepant with the substantial gastric cancer risk of these lesions, development of clinical guidelines on endoscopic surveillance or treatment of pre-malignant gastric lesions is strongly indicated. These data show that routine endoscopic surveillance at short intervals is warranted in patients with gastric dysplasia, whereas surveillance at larger intervals should be considered for patients with atrophic gastritis and intestinal metaplasia.

In **Chapter 9** the value of clinical characteristics, histological assessment of routine gastric biopsies, and serological markers as predictors for the intragastric extent of intestinal metaplasia was investigated. A total of 88 patients were included in a prospective, multi-center study and underwent a surveillance endoscopy with extensive biopsy sampling. Multivariate logistic regression analysis identified a family history of gastric cancer, a pepsinogen I to II ratio <3.0, the presence of moderate or marked intestinal metaplasia in the biopsy at baseline, and alcohol use with an average of at least one unit per day as important predictive parameters for extensive intestinal metaplasia at surveillance endoscopy. A high risk score based on the presence of these parameters indicates a severely affected gastric mucosa and the need to consider surveillance endoscopy.

In **Chapter 10** the appropriate biopsy regimen for optimal detection of pre-malignant gastric lesions during surveillance endoscopy was investigated. In a prospective, multicenter study, 112 patients with intestinal metaplasia or dysplasia underwent a surveillance endoscopy. During endoscopy, both targeted biopsies from macroscopic lesions and twelve random biopsies from standardized locations (antrum, angulus, corpus, cardia) were obtained. This study showed that both random and targeted biopsies are essential during endoscopic surveillance of intestinal metaplasia and dysplasia of the gastric mucosa. An adequate biopsy scheme requires at least random biopsies from the cardia, corpus, in particular from the lesser curvature, angulus, and antrum in a population at an overall low gastric cancer risk.

A total of 17 randomized controlled trials on *H. pylori* eradication in patients with pre-malignant gastric lesions were systematically reviewed in **Chapter 11**. Several studies demonstrated less progression or even regression of atrophic gastritis within one to two years after *H. pylori* eradication. However, as evidence on the effect of *H. pylori* eradication in patients with intestinal metaplasia or dysplasia is scarce, the effect in these patients is unclear.

Chapter 12 describes two case reports of patients who developed gastric cancer at respectively four and twelve years after *H. pylori* eradication. In both patients, gastric ulcer disease and pre-malignant gastric lesions, i.e. intestinal metaplasia at baseline and dysplasia during follow-up, were diagnosed before the development of gastric cancer. These cases demonstrate that *H. pylori* eradication is insufficient as a single treatment modality in these patients and should be combined with endoscopic surveillance for early detection of gastric neoplasia.

The main findings of this thesis and directions for future research are discussed in **Chapter 13**.

Samenvatting

Maagkanker wordt doorgaans pas in een laat stadium gediagnosticeerd, aangezien symptomen in een vroeg stadium van de ziekte vaak ontbreken of aspecifiek zijn. Doordat de mogelijkheden voor een op genezing gerichte behandeling in een laat stadium van de ziekte beperkt zijn, is de gemiddelde prognose van patiënten met maagkanker slecht. Tijdens de stapsgewijze ontstaanswijze van maagkanker, schrijdt *Helicobacter pylori*-geïnduceerde gastritis langzaam voort via de pre-maligne stadia van atrofische gastritis, intestinale metaplasie en dysplasie, tot uiteindelijk maagkanker. De progressie van pre-maligne maagafwijkingen tot maagkanker duurt doorgaans tientallen jaren. Derhalve zou deze cascade van afwijkingen een basis kunnen vormen voor de preventie van kanker door vroegtijdige interventie, zoals *H. pylori* eradicatie, alsmede voor vroegtijdige detectie en behandeling van ernstige voorloperafwijkingen en maagkanker.

In **Hoofdstuk 1** staan de algemene doelstellingen van dit proefschrift beschreven.

In **Hoofdstuk 2** wordt een overzicht gegeven van de huidige kennis over de epidemiologie van pre-maligne maagafwijkingen. Geografische verschillen en risicofactoren voor de ontwikkeling van pre-maligne maagafwijkingen en maagkanker worden beschreven. Daarnaast worden de implicaties van deze gegevens voor de ontwikkeling van screening en surveillance strategieën bediscussieerd.

Hoofdstuk 3 beschrijft een landelijke studie naar epidemiologische trends van pre-maligne maagafwijkingen in Nederland gedurende de periode van 1991 tot 2005. In deze studie werden 23.278 patiënten met atrofische gastritis, 65.937 patiënten met intestinale metaplasie, en 8.517 patiënten met dysplasie geïncludeerd. De incidentie van atrofische gastritis daalde zowel bij mannen als bij vrouwen met 8.2% per jaar [95% betrouwbaarsheidsinterval (BI) 7.9-8.6], en van dysplasie met 8.1% per jaar [95% BI 7.5-8.6]. De incidentie van intestinale metaplasie daalde met 2.9% per jaar [95% BI 2.7-3.1] bij mannen en 2.4% [95% BI 2.2-2.6] bij vrouwen. De dalende incidentie van pre-maligne maagafwijkingen was het gevolg van een gecombineerd periode en cohort effect. Op basis van deze gegevens kan een verdere afname van de incidentie van maagkanker van 24% worden verwacht gedurende de komende tien jaar.

In **Hoofdstuk 4** werd de prevalentie van *H. pylori* infectie en atrofische gastritis bestudeerd in een Nederlandse migranten populatie. De prevalentie van *H. pylori* was hoog in de onderzochte steekproef van 288 personen, zelfs bij autochtone personen. Daarnaast waren de gemiddelde pepsinogeen I waarde en pepsinogeen I/II ratio significant lager bij personen van niet Nederlandse afkomst in vergelijking tot Nederlandse personen (beide $p<0.001$). Er waren geen Nederlandse personen met serologische aanwijzingen voor atrofische gastritis, in vergelijking tot 12 personen van niet Nederlandse afkomst ($p=0.13$). Concluderend kunnen deze migranten populaties een doelgroep vormen voor de serologische screening ter preventie van *H. pylori*-gerelateerde complicaties in Westerse landen.

Eerdere studies toonden een associatie tussen plaveiselcelcarcinomen van de slokdarm en atrofie van het maagslijmvlies aan. Echter, het mechanisme van deze associatie bleef onduidelijk. In **Hoofdstuk 5** werd een relatief risico van 2.2 [95% BI 1.8-2.6] voor het ontwikkelen van plaveiselcelcarcinomen van de slokdarm aangetoond in een landelijk cohort van patiënten met atrofie van het maagslijmvlies in vergelijking tot de algemene Nederlandse bevolking. Het risico van plaveiselcelcarcinomen van de slokdarm nam niet toe met de ernst van atrofie van het maagslijmvlies (p=0.90). Bovendien werd een vergelijkbare associatie aangetoond tussen kleincellige longcarcinomen en atrofie van het maagslijmvlies. Een causale relatie tussen plaveiselcelcarcinomen van de slokdarm en atrofie van het maagslijmvlies is derhalve onwaarschijnlijk, en deze associatie wordt meest waarschijnlijk verklaard door de aanwezigheid van gedeelde risicofactoren, zoals roken.

Ter evaluatie van het risico van maagkanker bij patiënten met MALT lymfomen van de maag werd een landelijk cohort van 1419 patiënten bestudeerd in **Hoofdstuk 6**. In totaal werd bij 34 (2.4%) patiënten maagkanker vastgesteld. Het risico van maagkanker bij patiënten met MALT lymfomen was 6 keer verhoogd ten opzichte van de algemene Nederlandse bevolking. In het merendeel van de gevallen (53%) werd maagkanker in het jaar voorafgaand aan of na de diagnose MALT lymfoom gesteld. Nauwkeurige endoscopische follow-up na diagnose en behandeling van MALT lymfomen van de maag is daarom aangewezen.

In **Hoofdstuk 7** wordt een overzicht gegeven van de huidige kennis over detectie, surveillance en behandeling van patiënten met pre-maligne maagafwijkingen. De beschikbare literatuur over histologische classificatie, natuurlijk beloop, serologische en endoscopische detectie, medicamenteuze en endoscopische behandeling van pre-maligne maagafwijkingen werd samengevat en bediscussieerd.

Hoofdstuk 8 beschrijft een landelijke cohort studie van 22.365 patiënten met atrofische gastritis, 61.707 met intestinale metaplasie, 7.616 met milde tot matige dysplasie, en 562 met ernstige dysplasie. Tenminste één her-evaluatie endoscopie met afname van biopten werd uitgevoerd bij slechts 26% van patiënten met atrofische gastritis, 28% met intestinale metaplasie en 38% met mild tot matige dysplasie, in vergelijking tot 61% van patiënten met ernstige dysplasie (p<0.001). Binnen 5 jaar follow-up betrof de jaarlijkse incidentie van maagkanker 0.1% voor patiënten met atrofische gastritis, 0.25% voor patiënten met intestinale metaplasie, 0.6% voor patiënten met mild tot matige dysplasie en 6% voor patiënten met ernstige dysplasie. Aangezien de huidige surveillance van patiënten met pre-maligne maagafwijkingen niet in overeenstemming is met het substantiële risico van maagkanker, is de ontwikkeling van klinische richtlijnen voor endoscopische surveillance of behandeling van pre-maligne maagafwijkingen aangewezen. De data uit deze studie benadrukken dat routinematige surveillance van patiënten met dysplasie van de maagmucosa op korte termijn dient te worden verricht, terwijl surveillance op langere termijn overwogen dient te worden bij patiënten met atrofische gastritis en intestinale metaplasie.

In **Hoofdstuk 9** werd de voorspellende waarde van klinische karakteristieken, histologische beoordeling van maagbiopten en serologische markers voor de aanwezigheid van uitgebreide intestinale metaplasie onderzocht. In totaal werden 88 patiënten geïncludeerd in een prospectief, multi-center onderzoek en zij ondergingen een surveillance endoscopie met uitgebreide biopt afname. Multivariate logistische regressie analyse identificeerde een positieve familie-anamnese, pepsinogeen I tot II ratio <3.0, de aanwezigheid van matig tot ernstige intestinale metaplasie in het biopt bij inclusie, en alcohol gebruik van tenminste één eenheid per dag als belangrijke voorspellende parameters voor uitgebreide intestinale metaplasie bij de surveillance endoscopie. Een hoge risico score gebaseerd op de aanwezigheid van deze factoren maakt de aanwezigheid van uitgebreide intestinale metaplasie aannemelijk en in deze gevallen dient endoscopische surveillance te worden overwogen.

In **Hoofdstuk 10** werd de meest geschikte strategie voor het afnemen van maagbiopten tijdens surveillance endoscopie ter detectie van pre-maligne maagafwijkingen onderzocht. In een prospectieve, multicenter studie ondergingen 112 patiënten met intestinale metaplasie of dysplasie een surveillance endoscopie. Tijdens deze endoscopie werden zowel gerichte biopten genomen van macroscopische lesies, alsmede twaalf willekeurige biopten van gestandaardiseerde locaties (antrum, angulus, corpus, cardia). Deze studie toonde aan dat zowel gerichte biopten als willekeurige biopten essentieel zijn tijdens endoscopische surveillance van intestinale metaplasie en dysplasie van de maagmucosa. Een optimale strategie voor het afnemen van biopten vereist de afname van willekeurige biopten van de cardia, kleine curvatuur van het corpus, angulus en antrum binnen een populatie met een gemiddeld laag maagkanker risico.

Hoofdstuk 11 beschrijft een systematische beschouwing van 17 gerandomiseerde, gecontroleerde onderzoeken over het effect van *H. pylori* eradicatie bij patiënten met pre-maligne maagafwijkingen. Verscheidene onderzoeken toonden significant minder progressie of zelfs regressie aan van atrofische gastritis binnen één tot twee jaar na *H. pylori* eradicatie. Echter, doordat het beschikbare bewijs zeer schaars is, is het effect van *H. pylori* eradicatie bij patiënten met intestinale metaplasie en dysplasie nog onvoldoende duidelijk.

In **Hoofdstuk 12** worden twee casus beschrijvingen gepresenteerd van patiënten die maagkanker ontwikkelden, respectievelijk vier en twaalf jaar na *H. pylori* eradicatie. Bij beide patiënten werden een maagulcus en pre-maligne maagafwijkingen, d.w.z. intestinale metaplasie bij initiële endoscopie en dysplasie tijdens vervolg onderzoek, gediagnosticeerd voorafgaand aan de ontwikkeling van maagkanker. Deze casus tonen aan dat *H. pylori* eradicatie onvoldoende is als enige behandeling bij deze patiënten en gecombineerd dient te worden met endoscopische surveillance teneinde neoplasieën van de maag vroegtijdig te ontdekken.

De belangrijkste bevindingen uit dit proefschrift en aanbevelingen voor toekomstig onderzoek worden beschreven in **Hoofdstuk 13**.

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Curriculum vitae

Annemarie Charlotte de Vries werd op 30 maart 1981 geboren te Groningen. In 1999 behaalde zij het gymnasium eindexamen aan Het Gelders College te Arnhem. Vervolgens studeerde zij geneeskunde aan de Universiteit Utrecht. Na een semi-arts stage en wetenschappelijke stage op de afdeling Maag-, Darm- en Leverziekten van het UMC Utrecht werd in 2005 het artsexamen behaald. In september 2005 startte zij met promotie-onderzoek naar pre-maligne maagafwijkingen op de afdeling Maag-, Darm- en Leverziekten van het Erasmus MC te Rotterdam onder begeleiding van professor dr. E.J. Kuipers. Per december 2007 is zij met de opleiding tot Maag-Darm-Leverarts begonnen (opleiders dr. R.A. de Man, professor dr. E.J. Kuipers). De vooropleiding interne geneeskunde wordt thans verricht in het Sint Franciscus Gasthuis te Rotterdam (opleiders drs. A.P. Rietveld, dr. H.C.T. van Zaanen).