Barrett´s Esophagus

High cancer-risk groups, Cardiovascular co-morbidity and interaction with *Helicobacter pylori*

Coverfoto: Geysir - Haukadal Iceland by RAX, Iceland

Publication of this thesis was financially sponsored by:
Jansen-Cilag Iceland, Jansen-Cilag The Netherlands, AstraZeneca Iceland
Is gratefully acknowledged

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Printed by: Svansprent, Iceland

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High cancer-risk groups, cardiovascular co-morbidity and interaction with *Helicobacter pylori*

Barrett-oesophagus

Groepen met een grote kans op carcinoom, bijkomende hart- en vaatziekten en interacties met *Helicobacter pylori*

Proefschrift

ter verkrijging van de graad van doctor aan de Erasmus Universiteit Rotterdam op gezag van de Rector Magnificus

Prof.dr.ir. J.H. van Bemmel

en volgens besluit van het College voor Promoties. De openbare verdediging zal plaatsvinden op

woensdag 15 mei 2002 om 15.45 uur door

Sunna Gudlaugsdottir

geboren te Reykjavik, IJsland

Promotiecommissie

Promotor:	**Prof. J.H.P. Wilson**
Overige leden:	**Prof. dr. E.J. Kuipers**
	Prof. dr. B.H.Ch. Stricker
	Prof. dr. H.W.Tilanus

In memory of my father
To my mother
To Snorri and the children

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Chapter 1 General introduction and outline of the thesis

1.1 Background

Barrett´s esophagus (BE) has come to be regarded as an important premalignant condition (1). In recent years the incidence of adenocarcinoma of the esophagus and of the gastric cardia has risen dramatically (2). Analyses of cancer incidence data from nine areas of the United States revealed steadily rising rates of adenocarcinomas of the esophagus and gastric cardia from 1976 to 1987. The increases among men in this period ranged from 4% to 10% per year, and exceeded those of any other type of cancer (2). The rate of esophageal adenocarcinoma in Denmark has increased eightfold over a 20-yr period (3). In the Netherlands the rate of cardiacarcinoma has increased 35% (4), and since the early 90's mainly (Barrett's related) adenocarcinomas of the esophagus have been on the rise (Ph.D. thesis "Adenocarcinoma of the gastro-oesophageal junction – From gene to clinic" pages 71-73, B.P.L Wijnhoven, 2001). The reasons for this alarming rise are not clear but many believe it to be a consequence of gastroesophageal-reflux disease (GERD) and BE. This has led to an increased interest in research on BE and GERD.

1.2 History

Barrett's esophagus is named after Norman Barrett who described the condition in 1950, but the first known description of islets of ectopic gastric mucosa in the esophagus was in 1805 by Schmidt (5). One century later, in 1906, Tileston attracted attention to peptic ulceration in esophagus, as a rare entity (6). In 1950 Norman Barrett reviewed the literature and described the columnar epithelium lined esophagus(5). He suggested that this represented a congenital short esophagus. Only when gastric-type mucosa was in islands, surrounded on all sides by normal squamous epithel, could it be a part of the esophagus itself. He distinguished between

peptic-type ulcer and other esophageal ulcers. The peptic ulcers were thought to either arise in the islands of ectopic gastric mucosa or as a result of secretion of acid by such islands. Barrett failed to take into account the absence of the musculature and peritoneal covering of the stomach in his theory of a congenital short esophagus (5). In the same period Lortat-Jakob described the same condition, which he named endobrachyesophagus (7). Allison and Johnstone in 1953 showed that anatomically and funtionally the columnar lined esophagus was a part of the esophagus, although they still considered this a congenital condition (8). Strong support for an acquired cause was published during the next decade. In 1970 Bremner and co-workers (9) reported that in dogs with an incompetent lower esophageal sphincter (LES), removal of the squamous epithelium was followed by replacement with columnar epithelium whereas the squamous epithelium recovered in dogs with a competent LES. This was chiefly evident when there was also an induction of gastric hypersecretion in the dog with histamine injections(9). These workers postulated a replacement with mucosa obtained from the gastric or junctional mucosa in persistent GERD. Although the pathogenesis of BE is probably a multifactorial process (10), it is now generally accepted the most important factor is chronic severe (duodeno)gastroesophageal reflux disease (11, 12). (13). Most important evidence for this includes case reports of patients who underwent endoscopy and biopsy before and after developing columnar-lined esophagus(13, 14).

Congenital islands of ectopic gastric mucosa however do occur and are found in up to 10% of individuals undergoing endoscopy (15). These so called "inlet patches" occur principally in the cervical esophagus and are mostly surrounded by normal squamous epithelium (15, 16).

1.3 The definition of Barrett's esophagus

The definition of BE has with time evolved from a macroscopic, usually endoscopic definition (17) to a histologic definition(18, 19). It is generally agreed that the BE of interest as a premalignant condition is a histological diagnosis (19-21) of incomplete intestinal metaplasia (IM) or specialized columnar epithelium that resembles intestinal mucosa with goblet cells between columnar cells with a flat or villiform surface (22, 23). The glands do not contain parietal cells or peptic cells, but esophageal mucous glands are present in the submucosa (24)

This has led to the modern definition of BE, which is: an endoscopically visible segment of columnar mucosa, which on biopsy demonstrates intestinal metaplasia.

1.4 Why does Barrett's esophagus develop?

Barrett's esophagus is probably a late but most severe complication of chronic GERD (11, 12, 14). Only about 5% of patients with chronic symptoms of GERD have BE at endoscopy and IM in a biopsy sample. Patients with BE tend to have more severe reflux disease (10, 25) with greater impairment of LES function and esophageal body motility compared to GERD patients without BE(10, 26). There may be a genetic predisposition to the development of reflux in families of patients with BE (27-29) and esophageal adenocarcinoma (30). For uncomplicated reflux esophagitis, environmental factors such as increasing body mass index appear to be more important (30). Other environmental factors could theoretically also play a role (smoking, alcohol, fatty foods, chocolate, large meals, bedtime snacks and drugs that lowers LES pressure) although this has not been proven (30). The relationship with *H. pylori* infection is discussed below.

In patients with BE, the composition of the refluxed juice is different from that of GERD patients without BE. Patients with reflux of both gastric and duodenal juice, that are potentially carcinogenic(such as bile salts), have a higher prevalence of BE than do those who reflux gastric juice alone (26, 31). There are indications that age of onset, duration of symptoms, and occurrence of complications of GERD (reflux esophagitis, stricture and ulceration) may be markers of increased risk of BE (32). Patients with esophageal atresia seem to be at risk for developing BE (33). This is also true for achalasia, both after esophagomyotomy (34) (34) and without any surgical intervention (35, 36).

1.5 How long does it take for Barrett's esophagus to develop?

Progression of BE with migration of columnar epithelium up to the esophagus as a response to chronic GERD was accepted for many years, in keeping with the suggestion of Bremner et.al. (9). However, evidence from the Mayo Clinic has suggested that BE may develop to its full extent fairly rapidly (37). In a recent study in which ambulatory 24 hour esophageal pH monitoring was used to assess the extent of oesophageal acid exposure, it was found that the length of BE correlates with the duration of acid exposure (38).

1.6 Relationship between Barrett's esophagus and adenocarcinoma

The earliest report of the association of BE with adenocarcinoma was described in the early 1960s (39). More recent studies report the risk of adenocarcinoma in BE to be 30-125 x higher than in the normal population (40-45). A recent meta-analysis suggested an esophageal cancer incidence rate of 0.5% per year as a reasonable estimate (46).

1.7 Natural history of Barrett's esophagus

There appear to be subtypes of BE which do not progress to adenocarcinoma. The factors that initiate changes to an adenocarcinoma, the natural history, and the biological behavior of BE are not well known or understood. It is thought to depend on sequence of genetic alterations that give affected cells growth advantages (47). Before these cells become malignant the genetic changes cause morphologic variation known as dysplasia (48). A major risk factor for adenocarcinoma of the esophagus is dysplasia in IM (48-51). The temporal course of histological progression of dysplasia in surveyed patients supports the theory that adenocarcinoma in BE develops through stages of increasing severity of dysplasia (43, 52). The time intervals during the development of IM, dysplasia and subsequent transition to carcinoma is not known, but any segment of IM is capable of undergoing dysplastic change and ultimately of becoming a focus of adenocarcinoma (21, 53). However, the same morphological alterations can also be seen in non-neoplastic tissue as a reaction to injury, which makes it difficult for a pathologist to be certain of neoplastic changes in BE solely on morphological criteria. The diagnosis is only clear when there is evidence of invasion. High-grade dysplasia in a histologic sample is often associated with the presence of adenocarcinoma if resection is performed (54, 55). Cumulative cancer risk in focal high-grade dysplasia is lower than if diffuse high-grade dysplasia is present (54, 56). However, a recent follow-up study suggests that high grade dysplasia may regress and have a more benign course than earlier reported. (57). Schnell and co-workers reported a 5-year cumulative cancer incidence of only 9% and made it clear that progression to cancer may take years (57).

Even though we are technically able to identify high risk cases, only about 5% of the current cases of esophageal adenocarcinoma occur in patients previously

known to have BE (58). Since there are no population based studies on BE the actual prevalence on BE is not known. A majority of cases (94%) of BE remain unrecognized in the general population (59). Some studies have also reported that only a small fraction of patients with BE actually die from adenocarcinomas (40-42, 60). Taken together, this means that endoscopic cancer surveillance of known cases of BE would neither influence the overall survival rate of patients known to have BE nor have a impact on the rising incidence of adenocarcinoma in BE. And, there is no evidence in the literature that patients with BE benefit from endoscopic surveillance. However, using both clinical information from the BE patient and histological information on the BE we can look for high risk groups. The BE group known to have a high risk of adenocarcinoma are: middle-aged men of Caucasian origin (2, 61), patients with ulceration(42) or stricture formation (62) in a BE, or in relation to smoking, alcohol(63) and obesity (64). The length of the BE segment is a potential risk factor in that there appears to be an increased risk with increasing length of the BE segment (65). Significantly greater esophageal bilirubin exposure has been demonstrated in those with dysplasia or early cancer (66). One study has reported that the widespread use of LES-relaxing drugs may have contributed to the increasing of esophageal adenocarcinoma(67). The combination of achalasia and adenocarcinoma in BE has also been published(68). In recent years the possible interaction of *H. pylori* (*H. pylori*) colonization with GERD and its consequences has received more attention and will be discussed below.

1.8 *Helicobacter pylori* and gastro-esophageal reflux disease

Recently, clinicians have become increasingly aware that *H. pylori* infection may have beneficial effects for the human host, with potential preventive effects on the development of GERD and its complications such as BE and adenocarcinoma of the distal esophagus. Evidence includes the observation in the Western world of opposing time trends in peptic ulcer disease and distal gastric cancer, which are decreasing, and reflux oesophagitis and its outcome and cardia cancer, which are increasing (69). The decrease in the first two is at least partially explained by a decrease in *H. pylori* infection (69).

H. pylori colonisation affects gastric physiology (70, 71) by injuring the mucosa. Epithelial damage plays a key role in the induction and establishment of disease during long-term of *H. pylori* colonization by providing essential nutrients. Ammonia production of *H. pylori* plays a role in epithelial damage and lowers gastric acidity (72). Different *H. pylori* strains and the distribution of *H. pylori*-associated gastritis also determine the effects on acid secretion (72), which later on may play a role in the development to atrophic gastritis.

Clinical epidemiological studies suggest that the severity of gastritis depends mainly on the virulence of *H. pylori* strain(73). The greater the virulence of a particular strain, the greater the epithelial damage. The epithelial damage probably is a factor in the prevention of GERD by reducing acid production and by leading to destruction of glands and replacement by fibrosis and/or metaplasia (74).

1.8.1 Virulence of *H. pylori* strains (73)

1) Expression of Vacuolating cytotoxin A (VacA) is a marker for more virulent strains, with higher cytotoxicity and with a relation to peptic ulcer disease. The relationship with atrophic gastritis and gastric carcinoma is less clear. VacA

expression is found in only 50% of *H. pylori* strains, even though the gene encoding for this cytotoxin (vacA) is present in all strains.

2) Strains carrying the 120 kD cytotoxin-associated-gene A protein (CagA positive phenotype) are more virulent than CagA negative strains and are associated with higher levels of gastric inflammation and greater intramucosal IL-8 production. They are found in around 60% of infected subjects in the Western population. The CagA gene is a 30 kb marker for a pathogenicity island, containing several genes including picA and picB. The virulence of CagA positive strains essentially depends on expression of picA and picB. Nearly all *H. pylori* isolates from patients with peptic ulcers, atrophic gastritis and gastric cancer are CagA positive (75-77).

3) IceA, is a novel gene independent of the CagA and vacA status. Its transcription is induced by contact with epithelium. At present the function of this gene is not fully understood. In a recent report an association was found between peptic ulcers and the presence of iceA1 containing strains .

1.8.2 Acid production.

Hyperacidemia is important in pathophysiology of both duodenal ulcer disease and GERD. Patients with duodenal ulcer tend to have an increased maximal acid output and an increased parietal cell mass due to hypergastrinemia (78-80). The same category are at risk of getting GERD. However, when corpus gastritis is present, hypergastrinemia does not lead to increased acid production. El-Serag et al demonstrated a 54% reduced risk for reflux esophagitis in duodenal ulcer patients compared to controls in subjects with corpus gastritis (74). The *H. pylori* colonization rate was similar in both groups. *H. pylori* possesses factors capable of inhibiting parietal cells (81, 82), while host cytokines, such as TNF-alpha and IL-1ß, resulting

from chronic inflammation, also inhibit parietal cell function (75). It has also been found that the prevalence of *H. pylori* and mainly the more pathogenic form - CagA positive *H. pylori* - is lower in BE than in the rest of the population. Vicari et al prospectively compared the prevalence of CagA serum antibodies in 153 patients with GERD with that in 57 controls, who underwent upper endoscopy for other reasons (83). There was no difference in the carriage of CagA-positive *H. pylori*-strains between controls (46%) and non-erosive GERD patients (41%), but a progressive decrease in the prevalence of antibodies was observed in patients with more severe complications of GERD, such as erosive GERD (31%), Barrett's esophagus (13%) and Barrett's with dysplasia or adenocarcinoma (0%)(83). Similarly, a retrospective study reported that infection with CagA-positive strains was associated with a reduced risk for esophageal and cardia adenocarcinomas (OR 0.4; 95% confidence interval 0.2-0.8), whereas the risk for non-cardiac gastric cancer was not affected by CagA status (84). There is an inverse association between carcinoma in the cardia and lower oesophagus and colonisation with CagA positive *H. pylori*. However, there was little association with CagA negative strains of *H. pylori* for either cancer site (OR 1.0 and 1.1 respectively)(84). In one small study the results suggested that eradication of CagA serotype *H. pylori* was associated strongly with subsequent development of esophagitis (85). These observations provide indirect support for the hypothesis that severe corpus inflammation, being linked to CagA positive organisms, has a protective effect on the entire spectrum of reflux disease through inhibition of acid secretion.

1.9 Treatment of BE and risks of long term acid suppression

No single therapy (surgical or medical) currently has been shown to be superior to others in the treatment of patients with BE. Many cases of progression to cancer in spite of adequate acid suppression with proton pump inhibitors (PPI) or successful surgical antireflux procedures have been documented (86). Nevertheless, it has become customary for patients diagnosed as having BE to be treated with powerful suppressors of acid secretion such as PPI (87). The reason for this are the following.

1) PPIs are superior to any other medical treatment in the healing of severe esophagitis, including esophageal strictures and ulcers, and in maintaining patients with severe forms of esophagitis in remission (88). In recent years doubt regarding the ability of therapy to promote regression of BE once it is formed has risen. This may in part be due to fact that the efficacy of PPI's has been shown to be impaired in BE patients (89). Nevertheless, at present, regression of metaplastic mucosa with adequate acid suppressant therapy appears to be a real but uncommon occurance (89, 90). Acid suppressive therapy needs to be powerful and continous enough to completely abolish any acid pulses in order to effectively diminish cell proliferation and promote cellular differentiation (89, 91-93). The only therapy potentially powerful enough is treatment with PPI's(94). Regression after fundoplication alone has not been convincingly demonstrated (95).
2) PPI's are also theoretically important in novel, nonsurgical experimental treatments for BE. Removal of Barrett's metaplastic mucosa by laser, photodynamic therapy or multipolar electrocoagulation is intended to allow subsequent restoration of the mucosal surface under low acid load to squamous

epithelium(86). Long term studies of such approaches are now being performed, but as yet none has been proven to be ideal (96-98). Complete regression of BE occurs in a minority of patients, primarily in those with no hiatal hernia and shorter segments of BE. Unfortunately IM may persist under the newly developed squamous layer (99). Although patients with high-grade dysplasia and intramucosal adenocarcinoma on biopsy who do not have an endoscopically visible lesion are unlikely to have lymphatic metastases, 7% do have submucosal invasion. Thus, even in these very early tumors, treatment directed only at the mucosa may be inadequate (20). Given the risk of malignant transformation in BE, there is continuing competition between different ablation techniques. Careful data from much larger populations will be needed before ablation reaches the stage of broad clinical application.

Treating all patients with BE with PPI's has its controversial sides and leads to an apparent paradox in the management of the *H. pylori* positive BE patient. In most duodenal ulcer patients, antral gastritis predominates but corpus gastritis often develops during maintenance therapy with acid suppressive drugs (79). It has been suggested if acid production is impaired, for example because of use of acid suppressive drugs or the presence of atrophic gastritis with loss of parietal cells (100), it would consequently possible bring the development of gastric cancer (101). Recentely, a large Japanese study has helped to consolidate the notion that *H. pylori* infection is associated with gastric cancer. Those infected patient with severe gastric atrophy, corpus-predominant gastritis, and intestinal metaplasia were at higher risk for gastric cancer, not those with duodenal ulceration (102). Although there is insufficient evidence at present that long-term proton pump inhibition will indeed increase the risk

of distal stomach cancer (103), there is consensus that patients who are to be given PPI for long periods should be tested for the presence of *H. pylori* and given antibacterial treatment if found to be positive (104). However, if *H. pylori* is eradicated, its inhibitory effects on parietal cells are lost (105, 106), and the increased parietal cell mass may result in a larger volume of titrable acid after normal meal stimulation, and a decrease in the efficacy of proton pump inhibitors (107). This would operate in favour of more reflux symptoms and reflux oesophagitis (107, 108), and moreover could predispose to adenocarcinoma in the esophagus and cardia (109). More reflux symptoms has particularly been observed in patients with duodenal ulcer. Labenz et al published the first study in 1997 concerning the hazard of reflux esophagitis following eradication of *H. pylori* in 460 patients with duodenal ulcer within the next 3 years (107).

1.10 Surveillance of BE patients

The issue of endoscopic surveillance of the BE epithelium is controversial. Consensus surveillance strategies have not yet been clearly established, despite general acceptance of the histological sequence of the development of dysplasia and subsequent transition to carcinoma in BE.

1.10.1 Features supporting the need for endoscopic cancer surveillance

- Since there is no proven method of primary prevention, endoscopy has a crucial role in detecting affected patients and is the reason why some advocate that everyone with endoscopically obvious BE, even shorter than 3 cm in length, should be included in a surveillance programme. More than 96% of responding gastroenterologists in one study recommended endoscopic cancer surveillance (ECS) for BE (110).

- ECS has the potential to detect malignancy at an early and curable stage and thereby reduce mortality from esophageal adenocarcinoma (43, 52).
- Symptoms are unreliable as guides to successful control of reflux (111, 112). The hardest symptom to control is regurgitation and there is concern that continued reflux of altered gastric contents, particularly bile acids in their nonpolar form, may contribute to progression of BE (66).
- Individuals with histologically proven IM at the cardia regio are not included in most surveillance programs because of the low risk of carcinoma (113). However, patients with reflux symptoms and irregular zona serrata might be an exception (114).

1.10.2 PITFALLS in endoscopic cancer surveillance

- Identification of patients at risk. Most of the adenocarcinomas diagnosed in the esophagus occur in individuals not known to have BE(3). ECS in known BE patients will therefore not help in reducing cancer mortality in the whole population.
- Sampling error. Even with multiple biopsies, a degree of sampling error exists, because dysplasia seems to arise in multiple mucosal pits of Barrett's epithelium simultaneously and may only be present focally (54).
- Interobservational cancer. Adenocarcinoma can apparently develop within the space of several months. If the cancer is allowed to invade into the submucosa, 50% of these patients will have lymphatic metastases, thereby negating the purpose of surveillance.

- Patient compliance. During long-term follow-up the dropout rate of the BE population in ECS is high. In one study only 54% had one follow-up examination (50). Another study showed similar results (115).
- Pathologist. There are interobserver discrepancies among pathologists in identification of dysplasia, especially when differentiating low-grade dysplasia from reactive epithelial alterations caused by reflux esophagitis (116).
- High grade dysplasia (HGD). Surgical treatment of all patients with high grade dysplasia has been advocated (117-121), because the group of patients with HGD or early carcinoma in the BE has a high chance of cure following resection. However, the treatment stratigies for HGD might be changing. Recently intensive endoscopic follow-up has been advocated for HGD patients instead of an immediate surgical procedure by one group (57).
- Co-morbidity. Most patients known to have BE do not die from adenocarcinoma of the esophagus(40-42, 60). Most patients with BE would therefore not benefit from endoscopic cancer surveillance, which has also been observed in one observational study (115).

The premalignant potential of Barrett's esophagus and the dramatic increase in incidence of adenocarcinoma of the esophagus in the Western world are matters of concern (2, 3). At present, there is a lack of sufficient evidence to support endoscopic cancer surveillance for all patients with BE(3). The studies described in this thesis were initiated to clarify some areas of uncertainty such as: Whether *H. pylori* infection should be sought and treated if found in BE. Whether an explanation can be found for the increased mortality from cardiovascular diseases in follow-up studies of patients with BE and whether it would-be possible to identify subgroup of individuals

with BE who might benefit from endoscopic cancer surveillance or a low risk of cancer expectancy.

Endoscopic and histological features of BE at initial diagnosis can be predictive of risk of progression to cancer (51). The diagnostic reliability of gastroscopy and histological sampling is fundamental if surveillance protocols are to be proposed. This is even more important if we are to depend only on the index scopy to determine who should be followed. Then errors are not acceptable (122).

1.11 Aims of the thesis

1 To derive guidelines to select patients with known BE who would be likely to benefit from endoscopic cancer surveillance.

2 To find factors likely to be the reason for the lower life-expectancy in the BE population, paying particular attention to cardiovascular co-morbidity.

3 To determine the prevalence of *H. pylori* in the Dutch GERD population, paying particular attention to the BE population and the virulence factor CagA positive *H. pylori* infections.

4 To determine the risk of long-term maintenance treatment with proton pump inhibitors.

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Chapter 2 A majority of patients with Barrett's oesophagus are unlikely to benefit from endoscopic cancer surveillance

Sunna Gudlaugsdottir[1,2], Mark V. Blankenstein[2], Jan Dees[2] and J.H. Paul Wilson[1]

1) Dept. Of Internal Medicine, University Hospital Rotterdam, The Netherlands
2) Dept. Of Gastroenterology and Hepatology, University Hospital Rotterdam, The Netherlands

European Journal of Gastroenterology & Hepatology 2001, Vol 13 No 6, 639-645

Abstract

Background. Endoscopic cancer surveillance has been advocated for patients with Barrett's oesophagus. However, only a small minority of patients dies from adenocarcinoma in Barrett's oesophagus. It has been calculated that endoscopic cancer surveillance will only add to the quality of life of individuals in whom the incidence of adenocarcinoma in Barrett's oesophagus is greater than 1/200 patients-years.

Objective. To determine the proportion of a consecutive cohort of patients, in whom Barrett's oesophagus was diagnosed over a 5-year period, likely to benefit from endoscopic cancer surveillance.

Methods. All patients who had died during the observation period or were over 75 years old and those with diseases likely to impair survival were excluded. Next, all patients in whom the risk of developing adenocarcinoma in Barrett's oesophagus fell below 1/200 patients-year were excluded (including all women, all men under the age of 60 and all men with Barrett's oesophagus of < 3 cm). Patients with dysplasia of any degree and/or presence of an ulcer or stricture in Barrett's oesophagus were reinstated.

Results. Of 335 adult patients diagnosed with Barrett's oesophagus but without adenocarcinoma or high-grade dysplasia, 75 had died from unrelated causes, 47 had other diseases limiting survival and 59 were over 75 years old. After exclusion of all women, all men with Barrett's oesophagus of < 3 cm and all men under 60 years old, 15 patients were left. However, 32 were reinstated because of risk factors and another

five because of insufficient data, resulting in 52 of the original 335 patients (15.5%) being eligible for endoscopic cancer surveillance.

Conclusion. This study suggests that less than 20% of patients identified with Barrett's oesophagus at routine endoscopy would benefit from endoscopic cancer surveillance. Prospective surveillance programmes should be limited to patients with an increased cancer risk and a good health profile.

Introduction

Barrett´s oesophagus is a complication of gastro-oesophageal reflux, in which the distal oesophagus is lined by columnar epithelium [1]. It is found in about one of every 100 oesophageal endoscopic examinations [2]. The prevalence increases with age, and the absolute prevalence among the population also appears to be on the increase [2--4]. Specialized columnar epithelium, also called intestinal metaplasia, is the most common type of mucosa in adults with Barrett's oesophagus, and one that carries an increased risk of adenocarcinoma [5]. The dramatic rise in the incidence of adenocarcinoma in Barrett's oesophagus over the past 20 years [6] has led to an increased interest in this condition and to proposals for endoscopic cancer surveillance in patients with Barrett's oesophagus. The incidence of adenocarcinoma in past studies ranges from 1/46 to 1/441 patients-year [7--30] (Table 1).

Table 1 Results from follow-up studies of the incidence of oesophageal carcinoma in patients with Barrett's oesophagus

Author	Year	Patients	Patient-years	Cancers	Incidence	
Spechler	1984	105	350	2	1:175	[7]
Sprung	1984	41	162	2	1:81	[8]
Cameron	1985	104	882	2	1:441	[29]
Robertson	1988	56	168	4	1:56	[27]
Achtar	1988	62	166	1	1:166	[28]
van der Veen	1989	155	680	4	1:170	[10]
Hameetman	1989	50	260	5	1:52	[11]
Ovaska	1989	32	166	3	1:55	[26]
Polepalle	1990	220	900	6	1:150	[12]
Ollyo	1990	356	1440	9	1:160	[13]
Williamson	1991	176	497	5	1:99	[14]
Watson	1991	45	158	1	1:158	[15]
Sampliner	1991	106	424	2	1:212	[16]
Karras	1991	29	92	2	1:46	[17]
Bonelli	1993	120	198	2	1:99	[18]
Miros	1991	81	289	3	1:96	[19]
Iftikhar	1992	102	462	4	1:115	[20]
van der Burg	1996	155	1440	8	1:180	[21]
Drewitz	1997	177	834	4	1:208	[22]
Katz	1998	102	563	3	1:187	[25]
Sampliner	1999	143	230	1	1:230	[9]
O'conner	1999	136	570	2	1:285	[23]
Weston	1999	108	362	5	1:72	[24]
Böhmer	2000	-	5630	14	1:402	[30]

As only 5% of patients with Barrett's oesophagus are known as such to the medical profession [3], endoscopic cancer surveillance would have a negligible impact on the rising incidence of adenocarcinoma in Barrett's oesophagus in the population. On the other hand, endoscopic cancer surveillance in patients with Barrett's oesophagus is supported by the finding that, with this surveillance, a higher proportion of cases of high-grade dysplasia or early carcinoma are detected than are seen in symptomatic patients [11,31,32]. However, it is questionable whether life-long endoscopic cancer surveillance will, in fact, significantly influence the survival of patients with Barrett's oesophagus, as only a small fraction of these patients actually die from adenocarcinomas [7,10,21,29]. The majority die from unrelated causes, mainly cardio-pulmonary diseases [21]. Endoscopic cancer surveillance of these patients would have caused much discomfort but would have saved few, if any, lives. However, it is possible that surveillance might be effective in subgroups of patients [33]. It therefore seemed rational to test the concept of endoscopic cancer surveillance against the recommendation for surveillance as defined by the World Health Organization (WHO) [34] and, subsequently, to define subgroups with an above-average risk of developing adenocarcinoma who are also free of diseases likely to impair survival or hinder treatment. Obviously, the concept of increased, and therefore also decreased, risk needed some standard. Provenzale and coworkers calculated that patients with Barrett's oesophagus and an expected incidence of adenocarcinoma below 1/200 patients-year would not benefit from endoscopic cancer surveillance [35]. On this basis, guidelines were drawn up for selecting patients who were both fit for and likely to benefit from endoscopic cancer surveillance. These guidelines comprised medical factors likely to impair survival, protective factors which made an incidence in excess of 1/200 patients-year unlikely and risk factors

which mandated endoscopic cancer surveillance. By applying these guidelines to all patients with Barrett's oesophagus, identified over a 5-year period at our endoscopy unit, the proportion of these patients who could potentially have benefited from endoscopic cancer surveillance was established.

Materials and methods

All cases of Barrett's oesophagus in patients over the age of 18 years diagnosed between January 1 1992 and December 31 1996 were identified from computerized endoscopy records. Patients in whom a carcinoma or high-grade dysplasia in Barrett's oesophagus was found were excluded. Barrett's oesophagus was defined as an endoscopic diagnosis of columnar epithelium lining the distal tubular oesophagus, usually more than 3 in length. We also included shorter segments of Barrett's oesophagus because the endoscopic diagnosis of short-segment Barrett's oesophagus is associated with a high prevalence of intestinal-type columnar epithelium (significantly higher than that found in oesophagogastric junctions that appear apparently normal) [36]. There is also a known cancer risk in short-segment Barrett's oesophagus [37]. Information on the age, sex and length of the Barrett's oesophagus segment was obtained from the endoscopic database. Other data, including dysplasia and other medical disorders in these patients, were obtained from the case records.

All patients with Barrett's oesophagus meeting these criteria were subjected to a process of elimination on the basis of a number of factors considered relevant to their suitability for endoscopic cancer surveillance.

Factors influencing the suitability for endoscopic cancer surveillance (Table 2).

Men of Caucasian origin with Barrett's oesophagus have been found in most studies to have a risk of developing adenocarcinoma that is greater than 1/200 per year [4,6,31,38,39]. The risk is higher for Caucasian men than for women or Black people [31,38,39]. There were no Black patients in our study group.

Barrett's oesophagus of 3 cm length or more was chosen as an indication for endoscopic cancer surveillance, as the tendency to malignancy increases with increasing Barrett's oesophagus length [10,20,21,24,38].

Negative prognostic factors leading to exclusion from endoscopic cancer surveillance

1. Concurrent diseases likely to impair survival or effective treatment, including malignancies, severe cardio-pulmonary disease and other diseases expected to limit life expectancy to less than 5 years.

2. Advanced age: the mean age at the endoscopic diagnosis of Barrett's oesophagus was about 63--65 years, which is very similar to that at which adenocarcinoma is diagnosed [2]. In our own hospital the mean age at diagnosis of adenocarcinoma in Barrett's oesophagus patients was 67 years (52--81 years) [21]. The degree of dysplasia and the likelihood of malignancy in Barrett's oesophagus rise with age [11]. On the other hand, surveillance programs have not always been offered to the elderly [33]. Age by itself should not be a limiting factor for endoscopic cancer

surveillance but, because competing causes of death rise with age [40], a cut-off point needs to be drawn. For this study we chose 75 years of age as this cut-off point.

3. Finally, all patients dying within the 5-year period from unrelated diseases were considered unlikely to have benefited from endoscopic cancer surveillance.

Protective factors leading to exclusion from endoscopic cancer surveillance

In the absence of risk factors (see below) the following factors were considered to be associated with an incidence of adenocarcinoma in Barrett's oesophagus of less than 1/200 patients-year:

1. Women: The male to female ratio reported for adenocarcinoma in Barrett's oesophagus ranges between 3:1 and 8:1 [6,30,38]. This ratio was confirmed in a large population of institutionalized, intellectually handicapped individuals who do not smoke or drink alcohol, thus confirming the protective effect of being female [30]. In two observational studies, the incidence of adenocarcinoma in women with Barrett's oesophagus ranged between 1/294 and 1/981 patients-year. After correction for age, these incidences were not significantly different [30; personal communication, CJ Böhmer, 2000] and fell far short of the 1/200 patients-year criterion.

2. Youth: As adenocarcinoma in Barrett's oesophagus practically never occurs below the age of 40, endoscopic cancer surveillance below this age would appear futile [21,30]. However, even above this age the incidence remains low, not meeting the 1/200 patients-year criterion until the age of 65 in men. As the onset of high-grade dysplasia will generally occur years before symptomatic cancer, 60 years of age was taken as a cut-off point.

3. Short-segment Barrett´s oesophagus: Although it may be a risk factor for very distal carcinomas [41], the prevalence of short-segment Barrett´s oesophagus in the population coming to endoscopy is so high (18%) [42] that the incidence of adenocarcinoma in these patients must be far lower than 1/200 patients-year. This was

confirmed in our own observational study in which no adenocarcinomas were found in Barrett's oesophagus of less than 8 cm in length [10,21]. Short-segment Barrett's oesophagus is not seen as an indication for surveillance [43].

Risk factors that override protective factors and necessitate endoscopic cancer surveillance

1. Dysplasia distinguishes Barrett's oesophagus patients particularly at risk of developing cancer in the relatively near future [11,24], while high-grade dysplasia is often a marker of coexistent cancer and therefore often considered an end point in endoscopic cancer surveillance [5]. The degree of dysplasia increases with the age and length of Barrett's oesophagus [20,44] and the time of follow-up [11,45].

2. The presence of ulcerations and/or strictures has been found to be an important predictor of malignancy [1,10,21,33].

Risk factors which were not taken into account

1. Reflux of duodenal juice has been reported to be associated with a significantly higher rate of severe oesophagitis and Barrett's oesophagus [46]. Although not proven, it may be a risk factor for developing adenocarcinoma in Barrett's oesophagus. However, duodenal juice reflux is not routinely tested.

2. Smoking and high alcohol intake are associated with Barrett's oesophagus carcinoma, the relationship being more pronounced for tobacco than for alcohol [7,38,47]. However, this relationship is not very strong, therefore smoking is much

more likely to induce other causes of death before the onset of adenocarcinoma in Barrett's oesophagus [21,30].

3. Obesity has been shown to entail an increased risk of oesophageal adenocarcinoma [48], while raw fruit, vegetable and fibre intake decreases this risk [49].

Table 2 Negative prognostic factors and protective factors leading to exclusion, and risk factors leading to reinstatement, for patients with protective factors, into endoscopic cancer surveillance.

	Males	Females	Total
All patients with Barrett's oesophagus	264	131	395
• Cancer and high-grade dysplasia excluded	52	8	60
Total after excluding cancer and high-grade dysplasia	212	123	335
• Negative prognostic factors (causing exclusion)			
Died during observation	51	24	75
Advanced age	28	31	59
Concurrent disease	34	13	47
Total excluded for negative prognostic factors	113	68	181
Total remaining	99	55	154
• Protective factors (causing exclusion)			
Female gender		55	
Age under 60	66	a)	
Short-segment Barrett's oesophagus	18	b)	
Total excluded for protective factors	84	55	139
Total after all exclusions	15	0	15
• Risk factors (causing reinstatement)			
Ulcer and/or strictures	12	4	
Dysplasia[1]	13	8	
Total reinstated	25	12	
Final total (suitable for ECS)	40	12	52

Factors are based on studies in the literature. [1]Including five hypothetical cases; a) total 29 women under 60 already excluded; b) total 28 women with short-segment Barrett's oesophagus already excluded.

Results

During the 5-year period of studied, 75 patients had died from reasons other than oesophageal carcinoma and would therefore not have benefited from surveillance. The remaining 260 patients (99 women and 161 men) formed the study cohort. Of these, 76% were outpatients and 24% inpatients. There was no significant different in age or sex between outpatients and inpatients.

A progressive process of exclusion from endoscopic cancer surveillance was implemented, producing the following results. Twenty-eight men and 31 women over the age of 75 were excluded from surveillance on the grounds of age, leaving 201 patients. Of these, 47 (34 men and 13 women) had other diseases (see Table 3), which limited survival, leaving 154 patients (99 men and 55 women).

Table 3 Causes of exclusion from endoscopic surveillance of 47 patients with Barrett's oesophagus because of an unrelated medical disorder

Malignancy	**patient (n)**
Larynx cancer	4
Colon cancer with peritonitis carcinomatosis	1
Lung cancer with pericarditis carcinomatosis	1
Pulmonary carcinoma	1
Pancreatic carcinoma	1
Non-Hodgkin's lymphoma	2
Multiple myeloma stage IIIB	1
Peritonitis carcinomatosis (unknown primary)	1
Thyroid cancer	1
Gastric cancer with hepatic metastases	1
Malignant melanoma	1
Pheochromocytoma with metastases	1
Prostate cancer with metastases	2
Breast carcinoma	1
Other diseases	**patient (n)**
Diffuse atherosclerosis and cardiac disease	6
Autoimmune hepatitis and cirrhosis	1
Primary biliary cirrhosis	1
Cystic fibrosis	1
Congestive heart failure and renal failure	1
Alcoholic liver cirrhosis and Wernicke--Korsakoff syndrome	2
Alcoholic liver cirrhosis	2
Interstitial lung fibrosis	1
Hypertension and renal failure	1
Heart transplantation	1
Renal transplantation	2
Cardiomyopathy and heart failure	1
Cerebro-vascular accident	3
Polyarteritis nodosa	1
Diabetis mellitus with complications	1
Psychiatric diseases	2
Chronic pancreatitis and multiple laparotomies	1

The women were excluded, leaving 99 men. Of these remaining 99 individuals (all men), 66 were under the age of 60 and, from the remaining 33 patients, there were 18 with short-segment Barrett's oesophagus. Only 15 had Barrett's oesophagus segments of 3 cm or longer and therefore remained eligible for endoscopic cancer surveillance. Histology was available in 89% of Barrett's oesophagus segments of 3 cm or longer but not available in about 50% of short-segment Barrett's oesophagus.

In the eliminated groups there were eight women and eight men with dysplasia; in addition, four women and 12 men had ulcers or strictures. These patients, totaling 32, were reinstated because of these risk factors, leaving a total of 47 patients with an average age of 54.5 years who were eligible for endoscopic cancer surveillance. However, based on the prevalence of dysplasia and because no histology was available in 11% of patients with Barrett's oesophagus and about 50% of patients with short-segment Barrett's oesophagus, we estimated that an extra five patients should have been reinstated. This resulted in a final total of 52 patients eligible for endoscopic cancer surveillance out of the original 335 (15.5%).

Discussion

Only about 5% of the current cases of oesophageal adenocarcinoma occur in patients already known to have Barrett's oesophagus [50]. The seemingly obvious solution to the challenge of the rapid rise in the incidence of adenocarcinoma in Barrett's oesophagus is endoscopic population screening for Barrett's oesophagus. However, both practical problems in providing endoscopic services and failure to meet the WHO 'principles of early disease detection', specifically principles 2, 6, 8 and 9 [34], are powerful arguments against population screening (Table 4).

A number of experimental treatments for Barrett's oesophagus have been launched, such as removal of Barrett's metaplastic mucosa by laser, photodynamic therapy or multipolar electrocoagulation and subsequent restoration of the mucosal surface under low acid load to squamous epithelium. However, none of these treatments has, as yet, been proven to be feasible or safe in long-term studies [51--53].

On the other hand, endoscopic cancer surveillance in cases of Barrett's oesophagus identified at routine endoscopy to detect dysplasia or early carcinoma does not violate any of the WHO principles, although principles 6 and 9 may again present some problems. Here, the most important principle -- an acceptable treatment for patients with recognized disease[34] -- can be met.

Table 4 WHO criteria or points that might be regarded as guides to planning case-finding

Principles of early disease detection:
• The condition sought should be an important health problem • There should be an accepted treatment for patients with recognized disease • Facilities for diagnosis and treatment should be available • There should be a recognizable latent or early symptomatic stage • There should be a suitable test or examination • The test should be acceptable to the population • The natural history of the condition, including its development from a latent to a declared disease, should be adequately understood • There should be an agreed policy on whom to treat as patients • The cost of case-findings (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole • Case-finding should be a continuing process and not a 'once and for all' project

Surveillance is a word used as a synonym for screening and is defined as, 'an individual approach with close and continous observation of a person not complaining of the disease for which screening is performed'

Oesophagectomy for high-grade dysplasia or early cancer detected by surveillance is often curative and therefore should improve long-term survival [5,39,54], although this advantage would be partly counterbalanced by mortality from oesophagectomy. However, both laser-ablation and photodynamic therapy may provide effective treatment for those patients with high-grade dysplasia or early cancer who are unsuitable or unwilling to undergo surgery [51--53]. If endoscopic cancer surveillance of known cases of Barrett's oesophagus is acceptable, the question remains whether it should be applied universally. In view of the fact that the great majority of patients with Barrett's oesophagus die from unrelated diseases [21], it became obvious that endoscopic cancer surveillance should be limited to a sub-group combining a relatively high cancer risk with an otherwise good life expectancy.

The aim of the present study was to define guidelines for identifying this sub-group and, by applying these guidelines, to establish the proportion of patients with Barrett's oesophagus, diagnosed at routine endoscopy in our unit over a 5-year period, who would have been eligible for endoscopic cancer surveillance. This was achieved by taking into account that the clinical, endoscopic and histological features of Barrett's oesophagus patients at initial diagnosis are probably predictive of cancer risk [24], and by retrieving data on all patients diagnosed with Barrett's oesophagus over this period. Patients in whom high-grade dysplasia or adenocarcinoma in Barrett's oesophagus was found at the inclusion endoscopy were excluded. The remaining patients were subjected to a process of elimination, first those with poor prognosis, then those with a low cancer risk. Finally, those found at the inclusion endoscopy to have an increased cancer risk on the basis of previously defined risk factors were reinstated. In no case were data other than those from the inclusion endoscopy taken

into account. The poor prognosis category included all those who had died during the 5-year recruitment period from causes unrelated to adenocarcinoma in Barrett's oesophagus. They would obviously not have benefited from endoscopic cancer surveillance but would have been exposed to needless discomfort. Patients with diseases unrelated to Barrett's oesophagus but likely to preclude long-term survival were also excluded. It could be argued that in a university hospital this category could be larger than in a general hospital. On the other hand, in this retrospective study the prevalence of mild or as yet asymptomatic cardio-pulmonary disease is likely to have been underestimated, while cardiopulmonary disease constitutes the major cause of death in patients with Barrett's oesophagus [21].

The last group in the poor prognosis category were patients over the age of 75 years. In the light of recent insight into the operability of fit elderly patients and newer non-surgical treatment options, this exclusion criterion could be questioned. However, in view of the slow progression from high-grade dysplasia to symptomatic cancer, it seems unlikely that even non-surgical eradication of high-grade dysplasia would add to the life expectancy of these patients.

The low cancer risk group was less simple to define. Refraining from treating patients too ill or too frail to survive treatment for a meaningful period is a generally accepted principle. However, where to draw the line in screening or surveillance of healthy, low-risk individuals is a contentious issue. The reported risk of developing adenocarcinoma in Barrett's oesophagus varies from 1/46 to 1/441 patients-year of follow-up [7--30,35]. The higher incidences may be the result of overestimation in smaller studies, which have received undue attention in the literature because of publication bias [55]. This risk (or incidence) of adenocarcinoma in patients with

Barrett's oesophagus is of obvious importance as it determines the number of endoscopies -- with their attendant risks, discomfort and expense -- needed to identify one case of high-grade dysplasia or early cancer. Although the precise cancer risk remains unclear, Shaheen *et al.* [55] suggest that an oesophageal cancer incidence rate of 0.5% per year might be a reasonable estimate. If both length and quality of life are considered, it has been calculated that if the incidence of cancer is less than 0.5% (1/200 patients-year), the preferred strategy is no surveillance [35]. The same author recently published a revised study assuming a cancer incidence of 1/227 patients-year [56]. She concluded that endoscopic cancer surveillance once every 5 years increases life expectancy by 0.1 years at a cost of $9800 per annum, resulting in a quality-adjusted life year of $98.000. In view of this excessive cost (by European standards), we decided to stay with the 1/200 patients-year limit for endoscopic cancer surveillance. In practice, the low cancer risk category included all women, men under the age of 60 and patients with short-segment Barrett's oesophagus without dysplasia. The exclusion of women was based on the fact that the incidence of adenocarcinoma in Barrett's oesophagus in women was found to be no higher than 1/294 patients-year [21,30]. This is supported by the ratio of incidence of adenocarcinoma in Barrett's oesophagus in men and women, which ranges between 3:1 and 8:1 [6,38]. In principle, Black people should also be excluded on this basis; there were however no Black patients in our Barrett's oesophagus population. Similarly, in men the 1/200 patients-year limit was not exceeded before the age of 60 [21,30]. In principle, healthy men with Barrett's oesophagus on reaching the age of 60 could be enrolled in endoscopic cancer surveillance.

Although it is now thought likely that most, if not all, cases of adenocarcinoma of the gastric cardia and the distal oesophagus arise from short-segment Barrett's

oesophagus [57], this condition is so common that it was considered to be associated with a cancer incidence far short of 1/200 patients-year. However, these exclusions on the basis of low cancer risk were reversed in the presence of one or more factors associated with an increased risk of cancer in Barrett's oesophagus, which could be identified at routine initial endoscopy. These factors include dysplasia other than high-grade dysplasia and an active or healed ulcer (resulting in a stricture) in Barrett's oesophagus [5,7,31,33]. Heavy smoking, which is the only other prognostic factor consistently associated with an increased risk of endoscopic cancer surveillance, was considered to be a self-defeating prognostic sign as these patients are much more likely to die from cardio-pulmonary disease than from cancer.

At the final analysis of 335 patients qualifying for entry into the study, only 52 (15.5%) could have benefited from endoscopic cancer surveillance. Assuming a 100% compliance with endoscopic cancer surveillance, these 52 patients, with an average age of 54.5 years, would, on reaching the age of 75, together have completed almost 1100 years under surveillance. Assuming an incidence of adenocarcinoma in Barrett's oesophagus of 1/112 patients-year for males over 45 years [21], slightly less than 1100 annual endoscopies would have discovered 10 cancer cases or, approximately, one cancer case would be discovered per 110 endoscopies. A crude estimate can be made as to the cost. Upper-gastrointestinal endoscopy with histology costs about 300 Euros. The cost of identifying one case of adenocarcinoma in Barrett's oesophagus is therefore about 33&th;600 Euros. High-grade dysplasia, being diagnosed a few years earlier, would be somewhat cheaper. In both cases, however, these amounts are considerably in excess of the costs of identifying one cancer in current public screening programs.

In conclusion, this study suggests that only 15.5% of patients identified as having Barrett's oesophagus at routine upper-gastrointestinal endoscopy would benefit from endoscopic cancer surveillance. This benefit would arise from early, pre-symptomatic diagnosis of high-grade dysplasia or adenocarcinoma in Barrett's oesophagus giving a greater chance of successful treatment in individuals. However, such surveillance is unlikely to reduce the death rate from oesophageal adenocarcinomas in the general population.

Rational selection, based on clinical, endoscopic and histological features in Barrett's oesophagus patients at initial endoscopy, should prevent futile surveillance in those unlikely to develop cancer or unfit for treatment.

Until long-term prospective follow-up studies have been performed, we recommend limiting surveillance to high-risk, physically fit patients as defined by guidelines used in this study (Table 2).

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Chapter 3 Cardiovascular risk factors and history of myocardial infarction in patients with Barrett's esophagus

Sunna Gudlaugsdottir[1,2], Jacqueline CM Witteman[3], Frank JA van Rooij[3], Jan Dees[2], Theo Stijnen[3], JH Paul Wilson[1].

1. Dept. Of Internal Medicine, University Hospital Rotterdam, The Netherlands
2. Dept. Of Gastroenterology and Hepatology, University Hospital Rotterdam, The Netherlands
3. Institute of Epidemiology and Biostatistics, Erasmus University Rotterdam, The Netherlands

Submitted

Preliminary results of this study were presented at the Netherlands society of Gastroenterology meeting in Veldhoven, the Netherlands in March 2000, and published in the form of an abstract in the European Journal of Gastroenterology and Hepatology – December 2000.

Abstract

Background. In a previous follow-up study of patients with Barrett's esophagus we found an excess mortality of 50% in the Barrett´s Esophagus (BE) population, one-third because of cardiovascular diseases. As a part of an epidemiological study on the prevalence of *Helicobacter pylori* in a BE population, we studied verified history of myocardial infarction and cardiovascular risk factors and in BE patients compared to controls.

Methods. Forty-seven patients aged 55-79 years with upper gastrointestinal complaints in whom BE was diagnosed at routine endoscopy were examined. A standard questionnaire including age, sex, verified history of myocardial infarction, and its risk factors was used. Blood pressure, body mass index (kg/m2), total- and HDL cholesterol were measured. Data from a population-based prospective cohort study of the same age range and living in the same area were used for comparison.

Results. Mean blood pressure was higher and hypertension significantly more frequently present in the BE population than in the control group. Mean body mass index was higher, although not significantly so. Obesity (BMI ≥30 kg/m2) was significantly more often observed in the BE group. The prevalences of smoking and hypercholesterolemia were not different. A validated history of myocardial infarction was significantly more frequent in the BE population.

Conclusion. This study suggests that BE diagnosed in patients with upper gastrointestinal complaints is associated with an increased prevalence of hypertension, obesity and a history of myocardial infarction. If true, this should be taken into account when designing or evaluating surveillance studies of BE.

Introduction

Barrett's esophagus (BE) is a complication of gastro-esophageal reflux disease [1]. It is found in about 1 of every 100 endoscopic examinations [2], and is a risk factor for adenocarcinoma of the esophagus. Because of the dramatically rising incidence of adenocarcinoma in the esophagus in the past decade[3], several groups have proposed endoscopic biopsy surveillance for BE patients to detect malignancy at an early and curable stage[4, 5]. However, doubt has been cast on the effectiveness of endoscopic biopsy surveillance as few patients diagnosed as having BE actually die from adenocarcinoma of the esophagus [6-9]. In a follow-up study of 166 patients from this hospital in whom the diagnosis BE had been established between 1973 – 1986 during a mean follow-up of 9.3 years (amounting to 1440 patient years) 8 patients developed esophageal cancer at various times, giving one case in 180 patient years [6]. Seventy nine patients had died, one-third because of coronary heart disease (CHD). This mortality was 50% above the expected mortality in an age/sex matched control population. In only 2 cases was esophageal cancer the cause of death [6]. These results raised the hypothesis that BE patients have an increased risk of CHD.

The aim of this study was to determine the prevalence of risk factors for CHD and prevalence of myocardial infarction in patients with BE compared to the general elderly population. The study was a part of epidemiological analysis on prevalence of *Helicobacter pylori* in BE patients.

Methods

For this study we used BE patients between 55-80 years of age. The invitation was from January 1998 to August 1999. The computerised endoscopic and medical data of all patients with BE found at routine endoscopy in the University Hospital Rotterdam in the years 1992 to 1996 were scrutinised to recruit patients with BE. Information on the length of BE and histological definition of a biopsy sample from the BE was noted. Patients were included if the BE met the definition of columnar mucosa in the tubular esophagus found at endoscopy with histological proof of intestinal metaplasia (IM) [10]. If the patient had no upper gastrointestinal malignancies at endoscopy, he or she was sent a standard questionnaire and informed consent form together with a request to participate. Of 335 BE patients without adenocarcinoma, a total of 212 (137 men and 75 women) where alive, in the age-range 18 – 80 years, and were sent an invitation. One hundred and nine reacted to the invitation with agreement to participate. The study subjects were given an appointment for an esophagogastroduodenoscopy (EGD) with biopsy to confirm the diagnosis of BE. If the patient refused a new EDG we used previous data for information about the length of the Barrett's segment and histology. Forty-seven patients were eligible in the age-category 55-79 years with proven BE.

Weight and height were mostly self-reported in the standard questionnaire and checked at the outpatient visit. If it was not known or not reported in the standard questionnaire, height and weight were measured with the patient wearing indoor clothes. At the outpatient visit a non-fasting blood sample was taken for laboratory tests. We also ascertained by a simple check-list the following demographic characteristics of the study cohort: age, gender, residence, ethnicity, date of first diagnosis of BE and date of last endoscopy. A standard questionnaire filled in at home

about the presence of CHD and its risk factors, and list of current medication use was collected at the outpatient visit. Fifteen BE patients reported taking anti-hypertensive medication. Two did not report what they used. Most frequently used as treatment for hypertension were ACE inhibitors (n=7), followed by beta-blockers (n=5) and calcium channel antagonists (n=3). Three patients were on combination treatment. The questionnaire included the following questions; 1) Have you ever had a myocardial infarction? 2) Have you ever had hypertension? 3) Do you use medication for hypertension? If answered with "yes" the medications listed were checked and verified. 4) Have you ever smoked? 5) Do you still smoke? 6) Have you never smoked?) 7) Do you use medication for high cholesterol? If answered with "yes" it was verified in the patients-list of medication. 8) Are cardiovascular diseases known in your family, and if answered yes, we later checked by telephone to determine if it was CHD and in which family member. Only those with known first-degree family member with CHD were noted as having positive family history of CHD and used as such for comparison. 9) Are you known with diabetes mellitus? Body mass index was calculated as weight (kg)/height(m)^2, and obesity was defined as $\geq$30 kg/m^2. Blood pressure was measured once after 5 minutes rest in sitting position at the end of the outpatient visit by a mercury sphygmomanometer. The diastolic reading was taken at the level when sounds disappear (Korotkoff phase V). Blood was taken for determination of serum total and high-density lipoprotein (HDL) cholesterol concentrations by an automated enzymatic procedure. All cholesterol determinations were performed at the Clinical Chemistry Laboratory of the University Hospital in Rotterdam, which is the coordinator of the Dutch National Cholesterol Standardisation Program.

In the BE group all self-reported infarcts were verified in our own hospital documents or through information from the general practitioner.

A reference population was derived from a population-based prospective cohort study on chronic diseases in the elderly; the Rotterdam Study. The rationale of the Rotterdam Study has been described extensively elsewhere [11]. In short, all residents of the suburb Ommoord of Rotterdam over 55 years of age were invited to participate in the study. Sixty seven percent from the whole group participated in both the home interview and two visits to the research centre.

The baseline phase of the study comprised a home interview and two visits to the research centre and was conducted from 1990 to1993. Height and weight were measured with participants wearing light clothes and without shoes. Information on current health status, medical history, current medication use, smoking behaviour and family history was obtained using a computerised questionnaire during the home interview. We used the following questions for the current study; 1) Have you ever had a myocardial infarction? 2) Have you ever had hypertension? 3) Do you use medication for the indication hypertension? 4) Have you ever smoked? 5) Do you still smoke? 6) Have you never smoked? 7) Are your mother, father or siblings known with MI? 8) Do you use medication for DM. Body mass index (BMI) was calculated as weight (kg)/height(m)^2, and used to evaluate obesity defined as >30 kg/m^2. At the research centre, the systolic and diastolic blood pressures, were measured twice on the right arm in all subjects in a sitting position by a mercury manometer (random zero sphygmomanometer). The diastolic reading was taken at the level when sounds disappear (Korotkoff phase V). In the current study we used only the first measurement for reasons of comparison. A non-fasting blood sample was taken for

determination of serum total and high-density lipoprotein (HDL) cholesterol concentrations by an automated enzymatic procedure. All cholesterol measurements were performed in the laboratory of the Department of Epidemiology and Biostatistics (Erasmus University Medical School), which participated in the Dutch National Cholesterol Standardisation Program.

Subjects were asked to take all medication they were currently using to the research center for registration. Medication for hypercholesterolemia and hypertension were obtained from that notification

Hypercholesterolemia was defined in both studies as serum cholesterol of more than 8 mmol/L or treatment with cholesterol lowering medication or both.

The definition for hypertension used in both studies was the presence of at least one of the following factors: systolic blood pressure measured ≥ 160mmHg, diastolic blood pressure measured ≥ 95 mmHg, or use of antihypertensive medication for the indication to lower the blood pressure. According to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) and World Health Organization defined and classified hypertension in adults, this blood pressure limit is mild to moderate hypertension [12, 13]. Self-reported myocardial infarction in the Rotterdam study was verified by hospital discharge data, written information from the subject's general practitioner or electrocardiogram measurements.

The medical ethical committee of the Erasmus University Medical Center Rotterdam approved the studies. Written informed consent was obtained from all participants.

Statistical analysis

From all subjects between 55 years and 80 years of age from the Rotterdam study we selected 3 reference subjects per Barrett patient, matched for gender and age in strata of 5 years. This resulted in 144 subjects in the reference group.

Differences in continuous variables between the BE group and the controls were analysed by using the Student's t-test and differences in categorical variables by using the chi-square test. A two-sided p-value < 0.05 was considered statistically significant.

Results

The mean age of BE patients was 67.4 years (range 55 – 79). The gender distribution was 35 male (72.9%), all of Caucasian origin. All were offered repeat EDG, and 90% (42 of 47) underwent this procedure. The mean length of Barrett's mucosa in the enrolled group was 4.0 cm (range 0.5 – 10 cm). All included cases had intestinal metaplasia in a biopsy sample. In total 9 patients (19%) had dysplasia. There were 6 cases of mild dysplasia (13%) and 3 cases of high-grade dysplasia (6%). The mean length of BE segment with mild dysplasia was 3.9 cm (range 3-6 cm), but for high-grade dysplasia the length was 8.3 cm (range 5-10 cm).

Cardiovascular risk factors in both groups are present in table 1. A significantly higher mean blood pressure was present in the BE patients than in the controls ($p<0.01$). Hypertension was also found more frequently in the BE group than in the controls (71.7% vs 33.6%, $p <0.001$). Individuals in the BE group received treatment for hypertension more often than the control group (43.8% vs 31.4% respectively), but the difference was not significant. When the groups were compared on the single

question "have you ever had hypertension? 56.3% answered "yes" in the BE population compared to 28.9% in the control group ($p = 0.001$). Hypercholesterolemia defined as a serum cholesterol of more than 8 mmol/L or treatment with cholesterol lowering medication or both, resulted in prevalence of hypercholesterolemia that did not differ between the two groups (table 1). Mean total cholesterol was lower in the BE group than in the control group (5.95 vs 6.64; $p = 0.001$), but on the other hand treatment for high cholesterol was significantly more frequent in the BE group (18.8% vs 3.5%, respectively, $p < 0.001$). Mean body mass index was higher in BE patients than in controls, but the difference did not reach statistic significance. However, obesity (BMI $\geq 30 kg/m^2$) was significantly higher in the BE group (18.3% vs 5.6%, respectively, $p < 0.01$). Smoking habits were the same in both groups. The prevalence of diabetes mellitus was somewhat higher in the Barrett's population (8.3%) than in the control group (5.6%) but this was not significant. In the BE group the prevalence of self-reported history with subsequent validation of myocardial infarction was 27.1% and in the control population it was 13.4% ($p=0.03$). A history of CHD in the first-degree relatives, was found significantly more often in the Barrett's population than in the control group, (65.0% vs 36.1% respectively, $p < 0.05$).

Table 1

Risk factors	Barrett Group	Rotterdam-control group*	p-value
Age-years (range)	67.4 (55-79)	68.1 (55-80)	-
Gender (% men)	72.9%	72.9%	-
Systolic blood pressure, mmHg	143(18)	141(22)	0.53
Diastolic blood pressure, mmHg	84(11)	76(13)	<0.01
Hypertension*	71.7%	33.6%	<0.001
Treatment for hypertension used	43.8%	31.4%	0.121
High cholesterol**	18.8%	17.4%	0.827
Body mass index, kg/m²	27.4(7.5)	25.8(3.1)	0.157
Obesity (body mass index ≥ 30 kg/m²)	18.3%	5.6%	<0.01
Smoking			
Current	27.1%	23.6%	0.628
Past	50%	55.6%	0.503
Never	22.9%	19%	0.530
Diabetes mellitus	8.3%	5.6%	0.5
Verified history of MI***	27.1%	13.4%	0.03
Family history of coronary heart disease	65.0%	36.1%	<0.05

Adjusted for age and gender. Values are means with standard deviations or percentages.
**Hypertension is defined as the presence of at least one of the following factors: systolic blood pressure measured ≥ 160mmHg, diastolic blood pressure measured ≥ 95 mmHg, or use of antihypertensive medication for the indication to lower the blood pressure.*
***High cholesterol is defined as serum cholesterol > 8.0 mmol/Land/or drug treatment for hypercholesterolemia.*
****Myocardial infarction.*

Discussion

The present study is the first to examine the prevalence of verified history of myocardial infarction in BE patients. It was found to be significantly more frequent in the BE population than the control group. We also looked at risk factors for CHD. Blood pressure was significantly higher and hypertension was significantly more frequently present in the BE population than in controls. Obesity (BMI $\geq 30 kg/m^2$) was significantly more prevalent in the BE group. . Hypercholesterolemia or treatment for hypercholesterolemia and the prevalence of smoking and diabetes mellitus was not significantly different between the groups.

Before interpreting the data several methodological issues need to be discussed. The invitation for participation in this study was not to detect CHD in BE patients but to look for prevalence of *Helicobacter pylori* infection. The invitation included a notice that we would like to assess general health status of participants with a standard questionnaire at the same time. Therefore, it is not likely that the response of BE patients is influenced by the presence of history of myocardial infarction or CHD risk factors. Although BE can be found at any age [2], we limited the analyses to the older population ($\geq$55 years) to enable a comparison with a sample of the Rotterdam Study [11]. We thought this age-limit was reasonable because BE is most often diagnosed within this age-range. Mean age at diagnosis of BE is 63 years in subjects without carcinoma and 64 years in patients with adenocarcinoma (range30-89)[2]. The diagnosis of BE in the patients included in this study was originally made by diagnostic endoscopy, almost always performed for upper gastrointestinal complaints. All patients with BE diagnosed in the above-mentioned period willing to participate were included in the study, also those who had only come for diagnostic endoscopy and had not been followed as outpatients. This group

represents thus the great majority of patients now known to have BE, as screening upper GI endoscopy is not generally performed in an otherwise healthy population. The cohort of the Rotterdam Study was considered a valid control group because participants were derived from the general population and living in the same area. The majority of subjects in both groups were Caucasians. However, there was a difference in period of measurements 1990 to 1993 in the Rotterdam group versus 1998 to 1999 in the BE group. Treatment of hypercholesterolemia in the elderly has increased in the Netherlands. In 1990-1993 treatment for hypercholesterolemia was used in 2.8% of subjects between 60 and 80 years participating in the Rotterdam study, while in 1997-1999 this percentage is 14.8%. Therefore the difference in frequency of cholesterol-lowering medication use can be explained by the time difference in data collection between the groups.

The comparability of the two sets of data was achieved by only using the same items from the standard questionnaire of the reference group and the BE population on presence of CHD and its risk factors. For myocardial infarction we verified self-reported histories in both the BE and the reference population.

Our study, shows a higher prevalence of hypertension and treatment for hypertension in the BE group than the reference Rotterdam population. It could be argued that the difference in prevalence of those factors was due to selection bias as the BE group, being hospital outpatients, might conceivably be a group requiring more frequent medical attention. This would increase the chance of detection of hypertension, myocardial infarction, hypercholesterolemia and BE and therefore treatment of both hypertension and hypercholesterolemia. However, the higher blood pressure level in the BE group than in the controls, despite the more frequent use of antihypertensive medication, is difficult to explain purely by selection bias. The

current study might have two limitations with respect to blood pressure measurement. Firstly, we cannot exclude the possibility that the higher levels in the BE group are due to the circumstances of measurement (white coat effect) [14], as the blood pressure was measured by physician in the BE study and by a research assistant in the Rotterdam study. However, the phenomenon of white coat hypertension, possibly refers to a health care institute hypertension or office hypertension phenomenon, because it depends on multiple factors and does not correlate with the pressure response to the doctor [13]. If this is true, it should imply that the isolated office hypertension, which might also be the earliest manifestation of real hypertension [15], is evenly important in both cases and the reference group. Secondly, since an individual person's blood pressure can vary substantially, a single measurement might not accurately represent a person's average, or usual, blood pressure level. It is likely to lead to overestimation of the prevalence of hypertension. However, by depending only on the first measurement in both cases and controls we believe the comparison between the groups is made trustworthy.

In the BE group, weight and height were often self-reported, in contrast to the Rotterdam study. Self-reporting tends to give 5–7% lower BMI´s than measured BMI´s, which tend to be more biased in older and overweight groups [16]. This could mean that BMI and obesity in the BE population defined as BMI $\geq$30 kg/m^2 was underestimated in the present study. The different protocols for measuring family history of CHD between the two groups indicate that the more frequent occurrence of CHD in first degree relatives of BE patients than controls may be biased and needs to be interpreted with caution.

Only a small fraction of patients known to have BE actually die from adenocarcinomas [6-9], and the most likely causes of death are cardio-pulmonary diseases [6]. A recent observational study from a University Hospital in the United Kingdom found in 266 BE patients who where too frail or because of other reasons not suitable for surveillance only one death from oesophageal cancer and 103 from other causes[17]. The main cause of death in that study were also cardiovascular diseases [17]. The findings in present study suggest differences in prevalence of hypertension, obesity and validated history of myocardial infarction. Obesity might contribute to hypertension and increased prevalence of myocardial infarction. If the findings are true it may explain part of the 50% higher than expected cardiovascular mortality in the BE population. However, the underlying mechanisms are unknown. Because smoking habits did not differ between the two groups the difference in myocardial infarction between the two cohorts could not be explained through difference in smoking habits. Recently, on the basis of clustering of gastro-esophageal reflux disease (GERD) in families, it has been suggested that there might be a GERD gene [18, 19]. It should be considered whether the same causative factors - genetic or environmental factors – or both might be operative in BE and CHD. Another possibility is that the GERD is related to co-medication. Lagergren *et al.* has provided epidemiological evidence for a causal role for medications known to cause lower esophageal sphinchter relaxations in the rising incidence of adenocarcinoma in the esophagus [20]. Medications used to treat hypertension might predispose to reflux esophagitis and BE. Further studies need to be performed to establish this possibility.

A new carefully designed prospective study is needed to confirm our results. If our results can be confirmed, it would imply that the increased risk of hypertension, obesity and myocardial infarction in patients with Barrett's esophagus diagnosed because of upper gastrointestinal complaints should be taken into account when designing prospective studies or selecting patients for surveillance. By taking clinical features into account, rational selection of individuals for prospective studies and surveillance would be limited to physically fit patients.

Acknowledgments

We thank Mark van Blankenstein MD for advice

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Chapter 4 Hypertension is a frequent co-morbidity in patients with reflux oesophagitis or Barrett's oesophagus but not in nonulcer dyspepsia.

Sunna Gudlaugsdottir[1,2], WM Monique Verschuren[3], Jan Dees[2], Theo Stijnen[4], JH Paul Wilson[1].

1. Dept. Of Internal Medicine, University Hospital Rotterdam, The Netherlands
2. Dept. Of Gastroenterology and Hepatology, University Hospital Rotterdam, The Netherlands
3. National Institute of Public Health and the Environment (RIVM), The Netherlands
4. Institute of Epidemiology and Biostatistics, Erasmus University Rotterdam, The Netherlands

In press in European Journal of Internal Medicine 2002

Abstract

Background. An excess mortality due to cardiovascular disease has been reported for patients with Barrett's oesophagus. We compared the prevalence of risk factors for cardiovascular disease in patients with Barrett's oesophagus, reflux oesophagitis or non-ulcer dyspepsia with that of the general population.

Methods. Patients with upper gastrointestinal complaints and Barrett's oesophagus (34), reflux oesophagitis (31) or non-ulcer dyspepsia (21) were compared with an matched cohort of the general population, using a questionnaire, and blood pressure and cholesterol measurements.

Results. Hypertension occurred more frequently in Barrett's oesophagus (odds ratio 5.1, $P<0.0001$) and reflux oesophagitis patients (odds ratio 3.8, $P<0.001$), but not in non-ulcer dyspepsia. Serum total cholesterol was higher in Barrett's oesophagus ($P=0.02$), borderline higher in reflux oesophagitis ($P=0.06$) but not in non-ulcer dyspepsia. Mean HDL cholesterol levels and body mass index, and smoking were not different.

Conclusions. This study suggests that Barrett's oesophagus and reflux oesophagitis found at diagnostic endoscopy are associated with an increased prevalence of hypertension and a higher total cholesterol level than the general population. If true this provides an explanation for the increased mortality during follow-up of Barrett's oesophagus patients, and should be taken into account when designing or evaluating surveillance studies of Barrett's oesophagus.

Introduction

The prevalence of endoscopically confirmed oesophagitis in the community is thought to be up to 2%[1]. Oesophagitis can progress to complications such as deep ulceration, stricture formation, and the development of Barrett's oesophagus(BO)[2]. Because BO has a premalignant potential [3] and because of the dramatically rising incidence of adenocarcinoma in the oesophagus in the past decade[4], several groups have proposed endoscopic biopsy surveillance for BO patients to detect malignancy at an early and curable stage[5, 6]. However, earlier studies have cast doubt on the effectiveness of endoscopic biopsy surveillance as few patients diagnosed as having BO actually die from adenocarcinoma of the oesophagus [7-10]. In a follow-up study of 166 patients in whom the diagnosis BO had been established between 1973 - 1986, we found an excess mortality of 50%, compared to what was expected in an age/sex matched control population [10]. During a mean follow-up of 9.3 years (amounting to 1440 patient years) 8 patients had developed oesophageal cancer at random intervals, giving one case in 180 patient years. Seventy nine patients had died, one-third because of cardiovascular disease, and in only 2 cases was oesophageal cancer the cause of death [10]. These results raised the hypothesis that patients with gastroesophageal reflux disease (GORD) or, at least a subgroup with BO, have an increased risk of cardiovascular disease (CVD) with an increased prevalence of one or more CVD risk factors. This study was undertaken to investigate the prevalence of the main risk factors for CVD (blood pressure, cholesterol, smoking) in patients with reflux oesophagitis, BO and in patients without endoscopic abnormalities and to compare these with the normal population. The study was a part of an epidemiological investigation into the prevalence of *Helicobacter pylori* in reflux oesophagitis, BO and NUD patients.

Materials and Methods

For this study we used patients with reflux oesophagitis, BO and NUD patients – aged 20 to 59.9 years. Two sources of data were used: One was by reviewing computerised endoscopic and medical data of all patients with BO found at routine endoscopy in the University Hospital Rotterdam in the years 1992 to 1996. Information on the length of BO and histological definition of a biopsy sample from the BO was noted. Patients were included if the BO met the definition of columnar mucosa of at least 3 cm in the tubulair oesophagus found at endoscopy or histological proof of intestinal metaplasia (IM) when the columnar mucosa was less than 3 cm[11]. The study subjects were offered repeat oesophagogastroduodenoscopy (OGD) with a biopsy to confirm the diagnosis of BO. If the patient refused ODG we used the older data for information about the length of the Barrett's segment and histology. Secondly, all consecutive patients with GORD or no endoscopic abnormalities referred for diagnostic upper gastrointestinal endoscopy to the University Hospital Rotterdam - Dijkzigt, during the period January 1999 to July 2000 were asked to participate. GORD was defined as the presence of endoscopic signs of reflux oesophagitis, BO or both. Reflux oesophagitis was scored according to the Savary-Miller system [12], as follows: grade 0, normal oesophageal mucosa with no abnormalities; grade 1, mucosal erythema or diffusely red mucosa, with or without friability; grade 2, linear erosions extending from the gastroesophageal junction upward in relation to the folds; grade 3, confluent erosions extending around the entire circumference; grade 4, frank ulcer, stricture or BO.

If the patient had no malignancies or active peptic ulcer disease, he or she was asked to fill in a standard questionnaire about the presence of risk factors of CVD, current medication use and smoking behaviour. One patient with BO was excluded because he was unable to travel.

We ascertained with a simple check-list the following demographic characteristics of all three study cohorts: age, sex, weight, height, smoking (current, past, never), date of first diagnosis of BO and date of last endoscopy.

A blood sample for laboratory tests was taken at the outpatient care for most of the BO patients but for other participants on the day of endoscopy. The study populations (reflux oesophagitis, BO and NUD) answered the following questions used for comparison in present study: 1) Do you currently use medication for hypertension 2) Have you ever smoked? If yes → 3) Do you still smoke? Answering categories: yes (→ current smokers); If no (→ ex-smokers) 4) Have you never smoked? Answering categories: no, never (→ never smokers). Body mass index (BMI) was calculated as weight(kg)/height(m)^2. The blood pressure was measured once at rest in the end of the outpatient visit by a mercury sphygmomanometer. Systolic pressure was recorded at the first Korotkoff phase and diastolic pressure at the fifth Korotkoff phase.

The Medical Ethics committee of the University Hospital Rotterdam approved the study. Informed consent was obtained from all participating patients, before the endoscopy was performed.

A reference population was derived from the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN-project). This project has been carried out in the Netherlands from 1993 to 1997. The general purpose was to determine both the prevalence of risk factors for chronic disease (e.g. plasma cholesterol, blood pressure, smoking habits), and the prevalence of some specific chronic conditions in a random sample of the general population [13]. Information on current health status, medical history, current medication use, smoking behaviour and family history was obtained using a self-administered questionnaire at home. We used the following questions for comparison with the study groups; 1) Do you currently use medication for hypertension? 2) Do you smoke? Answering categories: Yes (→ current smokers), No, not

anymore (→ ex-smokers), No, and never have smoked (→ never smokers). Height and weight were measured with participants wearing indoor clothes, without shoes and with empty pockets. Body mass index was calculated as weight (kg)/height(m)^2. At the research centre, the systolic and diastolic blood pressures, were measured twice on the right arm by all subjects in sitting position by a mercury manometer (random zero sphygmomanometer). Systolic pressure was recorded at the first Korotkoff phase and diastolic pressure at the fifth Korotkoff phase.The average of the two measurements was used in the original analysis, but we used in present study the first measurement for reasons of comparison.

In both studies the participants were asked to write down all medication used and, blood was taken for determination of serum total and high-density lipoprotein (HDL) cholesterol concentrations by an automated enzymatic procedure.

In both studies all cholesterol determinations were performed at the clinical chemistry laboratory of the University Hospital in Rotterdam, which is the coordinator of the Dutch National Cholesterol Standardisation Program. All respondents sat down 5 minutes before the blood pressure measurement was taken. The definition for hypertension used in all groups (both studies) was at least one of the following factors: systolic blood pressure measured ≥ 160mmHg, diastolic blood pressure measured ≥ 95 mmHg, or use of antihypertensive medication. According to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) and the World Health Organization which defines and classifies hypertension in adults, this blood pressure limit is mild to moderate hypertension [14,15]. In present study, a systolic blood pressure of ≥ 160 mmHg and a diastolic blood pressure of ≥ 95 mmHg was chosen as we only have single measurements in these cohorts, and these values have previously been used as a cut off point for the definition of hypertension in a population study. The current systolic blood-pressure threshold for hypertension treatment is 140

mmHg for all adults. WHO and the International Society of Hypertension have proposed that normal pressure be lower than 130 mm Hg, with an optimum pressure of less than 120 mm Hg[14,15]. The cutoff limit of our study might miss individuals with mild hypertension but is however unlikely to missclassify normotensive persons.

Stastistical analysis

For the continuous potential risk factors (BMI, SBP, DBP, total and HDL cholesterol) the study group was compared with the reference population as follows. The reference population was stratified by sex and 5-years age categories. Per stratum the mean was computed. From the observed value of each patient in the study group, the mean of the corresponding stratum of the reference group was subtracted, and the average difference was determined. A 95% confidence interval was computed and the null hypothesis of no mean difference was tested with Student's one-sample test. Since the stratum sizes of the reference group were large (more than 1000), there was no need to account for the uncertainty in the stratum specific means. To investigate whether the difference between study and reference population depended on age and/or sex, multiple linear regression analysis was used with (continuous) age and sex as independent variables. For the categorical potential risk factors (smoking behavior and hypertension), both the study and the reference group were stratified by sex and 5-years age categories, followed by computing the Mantel-Haenszel odds ratio, the 95% confidence interval and the Mantel-Haenszel test. A homogeneity test was performed to investigate whether the odds ratio differed between strata.

Results

Eighty six patients aged 20-59.9 years with upper gastrointestinal complaints in whom BO (n=34), reflux oesophagitis (n=31) or nonulcer dyspepsia (n=21) was diagnosed at routine endoscopy took part in the study and were evaluated. We found 212 (137 men and 75 women), diagnosed with BO whom were alive and without adenocarcinoma, in the age range 18 – 80 years. One hundred and nine responded to the invitation to participate. Of these, 88 were found to have BO with repeat endoscopy and 34 of them were eligible in the age category 20 – 59.9 years.

Table 1 Demographic characteristics of the study individuals in the three subgroups.

	Reflux Oesophagitis	**Barrett's Epithelium**	**Nonulcer Dyspepsia**
Age	44 ±10	48 ±8.4	44 ±11
Number of subjects	31	34	21
Male	21	26	11
*Weight kg	81±18	77±15	76±11
*Height cm	175±10	175±10	175±10

**Means ±SD.*

The other participating individuals were all consecutive patients with GORD or no endoscopic abnormalities referred for diagnostic upper gastrointestinal endoscopy to the University Hospital Rotterdam - Dijkzigt, during the period January 1999 to July 2000. Demographic characteristics are given in table 1, with endoscopic features in table 2.

Table 2 Endoscopic features

	Reflux Oesophagitis	**Barrett's Epithelium**
**Grade I	5	
**Grade II	11	
**Grade III	-	
**Grade IV	15	
Length BO*,mean(range)		4,7cm (0.8-8.5)
No Intestinal Metaplasia (%)		‡30 (88)
Dysplasia(%)		‡6(17.6)

*Number of subjects per grade according to the Savary Miller endoscopic scoring features** of the reflux oesophagitis group and the endoscopic features of the *Barrett's epithelium group. ‡From two subjects information is not available.*

Twenty seven(79%) of the patients in the BO group were using proton pump inhibitors (mostly omeprazole). This was less frequent in the reflux oesophagitis group 17(55%) and only 4(19%) in the NUD group ($p<0.0001$).

The prevalence of risk factors for CVD are shown in table 3 and 4. Body mass index were not significantly different between groups. The mean systolic blood pressure was significantly higher in the BO and reflux oesophagitis group than controls (see table 3, which shows the mean blood pressures of all patients within a group, whether or not on antihypertensive treatment). The mean systolic blood pressure in the NUD group was higher than the reference population, although the difference was not statistically significant. The mean diastolic blood pressure was significantly higher in the reflux oesophagitis group but it was not different in the BO or NUD groups. Frequencies of hypertension in study groups and controls are given in table 4. Hypertension occurred significantly more frequently among the BO ($P<0.0001$) (odds ratio 5.1) and reflux oesophagitis ($P<0.001$) (odds ratio 3.8) patients than in controls, but not in the NUD group ($P=0.34$) (odds ratio 1.7).

Table 3 Mean level of cardiovascular risk factors.

Variable	Study group Mean (SD)	Controle Group	p-value	95% CI@
Body-mass index*				
Barrett's group	25.5(3.6)	26.0(0.9)	0.5	-1.7-0.8
Reflux oesophagitis group	26.1(6)¶	25.5(0.6)	0.6	-1.7-2.9
Nonulcer dyspepsia group	24.6(4.4)	25.5(0.3)	0.3	-2.8-1
Systolic blood pressure mmHg (SD)**				
Barrett's group	136(17)	127(5)	0.004	3.4-16
Reflux oesophagitis group	134(16)	124(6)	0.002	4.2-16.5
Nonulcer dyspepsia group	129(14)	124(6)	0.07	-0.5-11
Diastolic blood pressure mmHg (SD)**				
Barrett's group	82(11)	80(3)	0.4	-2.4-5.3
Reflux oesophagitis group	83(14)	79(3)	0.05	5.8-10
Nonulcer dyspepsia group	80(9)	78(3)	0.2	-1.6-5.7
Serum total cholesterol (SD)#				
Barrett's group	6.0 (1.2)	5.5 (0.3)	0.02	6.8-0.9
Reflux oesophagitis group	5.7 (1.0)	5.4 (0.4)	0.06	-1.5-0.7
Nonulcer dyspepsia group	5.8 (1.5)	5.4 (0.5)	0.3	-0.3-1
Serum HDL cholesterol (SD)				
Barrett's group	1.38(0.4)	1.26(0.4)	0.08	-2.3-0.3
Reflux oesophagitis group	1.27(0.5)	1.29(0.1)	0.3	-0.2-0.2
Nonulcer dyspepsia group	1.35(0.3)	1.34(0.2)	0.9	-0.2-0.2

**:Body-mass index was calculated as the weight in kilograms divided by the square of the height in meters. **:Blood pressure is given in mmHg with SD. #:Cholesterol values are given in millimoles per liter. P values were calculated by the one-sample Student's t-test. @:95% Confidence interval of the difference. ¶:One subject was not available for analysis.*

Table 4 Prevalence of hypertension

	Hypertension% (total group)	P-value	Odds ratio	95% CI@
Barrett's Epithelium	47 32	<0.0001	5.61	2.5-10.0
Reflux Oesophagitis	19 8	<0.001	3.76	1.7-8.3
Nonulcer Dyspepsia		0.34	1.7	0.5-5.0
Reference group		-	-	-

Values for hypertension are shown as percent of hypertension in the three study and in the reference population. The three study groups were compared to the reference group as described under methods. P-values were calculated by the Mantel-Haenszel test stratified on age and sex.
@ 95% confidence interval of the difference.
Hypertension is defined as the presence of at least one of the following factors: systolic blood pressure measured ≥ 160mmHg, diastolic blood pressure measured ≥ 95 mmHg, or use of antihypertensive medication for the indication to lower the blood pressure.

Most frequently given treatment for hypertension in the three study groups were beta blockers in 10(29%) BO patients, 2(6%) reflux oesophagitis patients and 2(9.5%) NUD patients followed by ACE inhibitors; 4(12%), 1(3.3%) and 1(5%) respectively. In the third and fourth place came; Calcium antagonists 2(6%), 2(6.4%),1(5%), and hydrochloorthiazide 2(6%), 2(6.4%) and 3(14%) respectively. Combination treatment with beta blockers and calcium antagonists was being used by 2 BO patients, 1 reflux oesophagitis patient and 1 NUD subject. Two BO individuals were on the combination of an ACE inhibitor and a beta blocker, and by one reflux oesophagitis subject. Five of the patients with GERD or 1 with NUD diagnosed as having hypertension had a history of myocardial infarction. An additional 3 normotensive individuals had a history of myocardial infarction. Five patients were known to have diabetes mellitus, no new cases were identified by blood sugar measurements. Two of the diabetics were also hypertensive.

Two known hypertensives had a serum creatinine slightly above the normal limit, as did one normotensive patient. One normotensive patient had a serum creatinine of 310 mcmol/l. Serum creatinine values were normal in all other cases.

Serum total cholesterol levels (see table 3) were significantly higher in the BO (P=0.02) group, with a trend in the reflux oesophagitis (P=0.06) patients, but were not different in the NUD group. HDL cholesterol levels and the prevalences of smoking habits were not different between the study groups and controls. The prevalence of both current smoking and non smoking tended to be highest in the younger age category (almost 50 percent in both categories), but decreased with age to the lowest level of 30 percent and 20 percent respectively in the 55-59,9 years of age category. Past smoking was lowest in the youngest age category - around 10% - and highest in the 55-59,9 category - almost 50%. Mean blood glucose level was lower in the reflux oesophagitis and NUD groups.

Discussion

This is the first study to consider the issue of the prevalence of risk factors for CVD in patients with all grades of GORD. It was undertaken in patients with endoscopically confirmed and clearly defined subgroups of GORD and patients without endoscopic abnormalities, classified as NUD. We observed a higher blood pressure in the reflux oesophagitis and BO group compared to the reference population, which was not found in the NUD group. Whether hypertension occurred before or after the start of gasto-intestinal complaints could not be assessed by this study (the questions asked did not specify the chronology of complaints). We also observed a significantly higher serum total cholesterol in the BO group, with trend in the reflux oesophagitis patients, but not in the NUD group. The mean HDL cholesterol level was borderline significantly higher in the BO group. However, this was not different between the two other study groups and the reference group. Although BMI was higher in BO patients than in controls, the difference did not reach statistical significance.

To appreciate the findings of this study, certain methodological aspects should be considered. The diagnoses in the study groups were originally made with diagnostic endoscopy in patients with upper gastrointestinal complaints. All patients meeting our criteria for reflux oesophagitis, BO or NUD and diagnosed in the above-mentioned periods were asked to participate in a study to look for the prevalence of *Helicobacter pylori* infection. They were not asked to participate in a study to detect risk factors for CVD. A notice was included in the invitation that we would like to know a few things about general health status. Therefore, it is not likely that the response of the three study groups patients is influenced by the presence of CVD risk factors. The individuals participating in the MORGEN study were considered a valid control group because participants were derived from the general population and living in the same area with same period of measurements. The comparability of the two sets of data was achieved by using the

same items from the standard questionnaire of the reference group and the three study populations on presence of CVD risk factors. We therefore could not use questions about known family-history of CVD for comparison because of differences in the phrasing of the questions used.

The criterion for hypertension was based on both a blood pressure measurement and treatment for hypertension. Therefore, it could be argued that the difference in prevalence of hypertension was due to selection bias, as the study groups, many being hospital outpatients, might conceivably be a group requiring more frequent medical attention which would increase the chance of detection and treatment of hypertension. However, the invitation included also those who had only come for diagnostic endoscopy but were not known as outpatients at our hospital. It should therefore represent the great majority of patients today diagnosed with reflux oesophagitis, BO, or NUD . The difference is therefore difficult to explain purely by selection bias. In all participants blood pressure was measured once with a sphygmomanometer in sitting position after 5 minutes rest. We cannot exclude the possibility that the higher levels of blood pressure in the reflux oesophagitis and the BO group compared to control is due to circumstances of the measurements (white coat effect of a physician in the study groups but an research assistant in the MORGEN project)[16]. However, the phenomenon of white coat hypertension, refers to a health care institute hypertension or office hypertension phenomenon, because it depends on multiple factors and does not correlate with the pressor response to the doctor [15]. Thus, it should imply that isolated office hypertension which might also be the earliest manifestation of real hypertension [17], s evenly important in both cases and controls. The same remarkable outcome was not seen in the NUD group compared to controls, which makes a white coat effect than unlikely as a reason for higher blood pressure measurements in the other groups. A single measurement does not exactly represent a person's average, or usual blood pressure [18], leading to overestimation of the prevalence of hypertension in both the cases and controls.

We believe that by depending only on the first measure in both the patient and the reference group, the comparison that we made is reliable.

In the reflux oesophagitis, BO and NUD groups, weight and height were often self reported, in contrast to the MORGEN study. Self-reporting tends to give 5–7% lower BMI's than measured BMI's, which tend to be more biased in older and overweight groups [19]. However, self-reporting on BMI is more reliable when used on a younger population[20]. Our three study populations are relatively young, mean age 44 years in the reflux oesophagitis and NUD groups and 48 years in the BO group, but due to the broad age range (20 to 59.9 years), it could mean that BMI might have been underestimated in the present study, although less likely in the younger age group.

If the findings are true the underlying mechanisms are not known. Although high cholesterol might contribute to an increased risk of CVD, differences in the prevalence of hypertension in the present study were statistically more striking. As we matched for age and gender, age does not play a role in the comparison. Since BMI did not differ between groups, obesity as hypertensive factor in the reflux oesophagitis and BO groups seems unlikely. We did not include any additional investigations in this study to determine whether the patients had secondary hypertension and other factors known to increase blood pressure such as insuline resistance, high alcohol and salt intake, and perhaps sedentary lifestyle, stress, low potassium and calcium intake were not examined. One might hypothesize that genetic factors play a role. The influence of genes on blood pressure has been suggested by family studies and mutations in at least 10 genes have been shown to raise or lower blood pressure [18]. Recently, on the basis of clustering of GORD in families, it has also been suggested that there might be a GORD gene [21, 22]. The same causative factors - either genetic or environmental factors or both - might be operative in GORD diseases and hypertension. However, further studies need to be performed to establish this possibility.

In an earlier follow-up study at our university hospital we found surprisingly high mortality rates from CVD in a cohort of 166 patients in whom the diagnosis BO had been established between 1973 and 1986[10]. In retrospect, those patients would not have benefited from endoscopic surveillance because of their excess mortality was in one-third due to CVD. This is in agreement with a recently published long term observational study from MacDonald *et al.* on BO patients in University Hospital in the United Kingdom [23]. This high mortality from cardiovascular diseases rather than cancer was recently reported as a surprising finding in a long-term follow-up study of GORD patients treated surgically or medically[24]. Recently we found in an elderly population with BO a higher prevalence of myocardial infarction with a notably higher prevalence of hypertension in the same group[25]. The present study was performed in a younger category of the whole spectrum of GORD patients and compared with another age and sex matched reference population. Again we noticed a noteworthy high prevalence of hypertension in the GORD population, particularly the BO group. Cardiovascular and overall mortality are known to increase continuously with increasing blood pressure [18]. If our findings are true, they may possibly explain part of the observed higher mortality in the BO population in the follow-up study from our hospital performed some years ago[10]. Further studies are needed. These should be prospective and include multiple measurements of blood pressure, examination for end-organ damage such as retinopathy, and an evaluation of factors which might contribute to the raised blood pressure such as salt intake.

In conclusion, Barrett's oesophagus and reflux oesophagitis found at diagnostic endoscopy are associated with an increased prevalence of hypertension and possibly a higher total cholesterol level than the general population. If our results can be confirmed, this provides an explanation for the increased mortality during follow-up of Barrett's oesophagus patients, and should be

taken into account when designing or evaluating surveillance studies or selecting patients with BO for surveillance.

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Chapter 5 The prevalence of CagA strains of *Helicobacter pylori* in nonulcer dyspepsia, reflux oesophagitis and Barrett's oesophagus.

Sunna Gudlaugsdottir[1,2], Jan Francke[1], Felix de Rooij[1], Jan Dees[2], Theo Stijnen[3], JH Paul Wilson[1].

1. Dept. Of Internal Medicine, University Hospital Rotterdam, The Netherlands
2. Dept. Of Gastroenterology and Hepatology, University Hospital Rotterdam, The Netherlands
3. Institute of Epidemiology and Biostatistics, Erasmus University Rotterdam, The Netherlands

Submitted

Abstract

Background. The hypothesis that colonisation with *CagA*-positive *H.pylori* strains protects against the development of complications of gastro-oesophageal reflux disease (GORD) was tested with present study.

Methods. Patients with reflux oesophagitis and Barrett's oesophagus were studied. Two corpus and 4 antral biopsy specimens were obtained for detection of *H.pylori*. A serum sample was obtained for determination of IgG and IgA antibodies to *H.pylori* and to the *CagA* protein.

Results. Of 233 patients studied, 68 patients had reflux oesophagitis, 83 had Barrett's oesophagus, 82 had no macroscopic abnormalities (the control group) and no signs of GORD. The 151 patients with reflux disease had a trend to lower prevalence of *H.pylori* (35%) than did the 82 controls (43%) (P=ns). Among 83 *H.pylori*-positive patients from whom serum was available, colonisation with *CagA*-positive strains was detected in 35% in the control group versus 26% in the reflux oesophagitis group (ns), and 19% in the Barrett's oesophagitis group (P=0,02).

Conclusion. Patients with reflux oesophagitis and Barrett's oesophagus tend to have a lower prevalence of *H.pylori* colonisation than controls. Patients with Barrett's oesophagus have a significantly lower prevalence of colonisation by the *CagA*-positive type *H.pylori* than did controls. These data suggest that colonisation with *CagA*-positive *H.pylori* strains may protect against the development of Barrett's oesophagus.

Introduction

Helicobacter pylori (*H. pylori*) cause long-term infection of the gastric and duodenal mucosa in human's [1]. Colonisation predisposes for peptic ulcer disease, atrophic gastritis and distal (antral) stomach cancer [2], with varied effects on gastric acid secretion. Genetic variability of *H. pylori* is high [3]. Several genes have been identified that may play a role in the pathogenicity [4, 5]. Most important is the cytotoxin-associated gene A (*CagA*), which is associated with peptic ulcer disease [6], and intestinal type adenocarcinoma of the stomach [7]. Patients with duodenal ulcer often have high basal gastrin levels, high peak acid output and high 24-hour intragastric acidity [8-10]. In contrast, patients with *H. pylori*-associated gastric ulcer often have hypochlorhydria [11]. Several reports suggest that the prevalence of *H. pylori* and especially the more pathogenic form – *CagA* might be lower in patients with GORD including Barrett's oesophagus (BO) than in the rest of the population [17, 18]. One explanation for the negative association between colonisation with *H. pylori* and GORD is the effect of *H. pylori* on acid production, since extensive gastritis involving the corpus may lower acid secretion by impairing parietal function.

We conducted a cross sectional study in consecutive patients over the age 18 years coming for routine endoscopy at our endoscopic unit, to determine the prevalence of *H. pylori* infection and subsequently *CagA* phenotype in subgroups of patients with reflux oesophagitis and proven BO to compare with patients without endoscopic abnormalities. We tested the hypothesis that colonisation with *CagA*-positive *H. pylori* strains protects against the development of gastro-oesophageal reflux disease (GORD) and it's complications.

Materials and Methods

Patients

All patients referred for upper gastrointestinal endoscopy from January 1, 1999 to July 31, 2000, with dyspeptic complaints and not known to have peptic ulcer disease by previous radiology or endoscopy were asked to participate. Our institutional medical ethics review board approved the study and informed consent was obtained from each patient. On the basis of visual examination of the oesophagus, stomach and duodenum, patients were subdivided into study groups. If an ulcer or a cancer was found the patients were excluded from the study. The first study group was formed by patients without endoscopic abnormalities or gastritis only (the same category). They were classified as nonulcer dyspepsia (NUD). The second study group comprised patients with reflux oesophagitis meeting the criteria of the Savary-Miller oesophagitis grading scheme, as defined by Little *et al.* [19]. The third group was formed by patients with BO defined as an endoscopic diagnosis of columnar epithelium lining the distal tubular oesophagus of at least 3 cm in length. We also included shorter segments of BO (SSBO) in the BO cohort if proved histologically to be intestinal type columnar epithelium [20]. BO patients were largely derived from a recall study based on records between January 1, 1992 to December 31, 1996 and reached by letter. Patients in whom a carcinoma or high-grade dysplasia in BO was found were excluded. Patients with SSBO at endoscopic examination, but without that histological proof were categorised as reflux oesophagitis grade IV, according to the Savary-Miller oesophagitis grading scheme [19]. Serum samples were obtained from each patient on the day of the endoscopic procedure for serology testing for *H. pylori* and *CagA*.

Histologic sample

Hematoxylin-eosin- and modified Giemsa-stained microscope slides bearing 4-μm histologic section were prepared using the original paraffin blocks of biopsy specimens from antrum, angulus and corpus of the stomach. All specimens were independently evaluated. The presence of the *H. pylori* colonisation was evaluated separately.

Serology

Specific serum IgG and IgA antibody levels against *H.pylori* were determined using an ELISA technique (Pyloriset EIA-G III and Pyloriset EIA-A III, Orion Diagnostica, Espoo, Finland). The assays were performed according to the instructions of the manufacture. The absorbance of the ELISA samples was quantified at 405nm in a Biorad microplate reader (3550-uv). IgG Antibody titers were determined according to the instructions of the manufacturer using a Biorad microplote reader with analysis software. Duplicate samples were determined and titers were calculated using quadratic regression analysis and log-linear curve fitting from 4 antibody standards. Sensitivity and specificity of this ELISA for the detection of *H. pylori* carriage is 92% and 84%, respectively and has shown a very good correlation with the biopsy finding [21].

Determination of *H. pylori* - *Cag*A status was based on the presence of serum IgG and IgA using a *Cag*A *H. pylori* pizo ELISA (Medimar, Italy, Mediphos, the Netherlands). Quantification of antibody titers was identical as described for the *H. pylori* - IgG and IgA titers.

Definitions and statistics

A patient was defined as *H. pylori*-positive if one or more of the applied diagnostic methods were positive. The *Cag*A result was not used for this definition.

Statistical analysis was done with chi-square testing for contingency tables and with Student's T-test.

Results

A total of 233 patients (139 male and 94 female: mean age 55±15 years; range, 18-83 years) participated in the study. The demographic details, diagnoses and the number of available sera for *Cag*A antibody determination are noted in Table 1.

Table 1 Characteristics of the study population

Clinical diagnosis	Number total	Male (n)	Female (n)	Age(years) Mean±SD	Range	Finality *CagA* (%)
Controls (NUD)	82	39	43	51±17	18-83	81 (99%)
Oesophagitis	68	42	26	54±14	22-81	66(97%)
Grade I	9	6	3	45±10	26-60	
Grade II	19	8	11	52±15	29-78	
Grade III	3	2	1	62±10	52-72	
Grade IV	30	21	9	56±13	22-73	
Grade not known	7	5	2	60±16	34-81	
Barrett's	83	58	25	60±13	22-79	82(98%)
Total	233	139	94	55±15	18-83	229(98%)

Sixty-eight patients had reflux oesophagitis, 83 had Barrett's oesophagus, and 82 had no macroscopic abnormalities (used as control group). There were significantly more men in the 151 patients with reflux disease or Barrett's oesophagus than in the 82 NUD individuals [66% vs 48% respectively (p=0.006)], and the prevalence of *H. pylori* was lower, although this was not significant [35% vs 43% respectively (p=ns)].

The prevalence of *H. pylori* antibodies in the different groups of patients is given in table 2 and 3. Among the patients who had oesophagitis, mean Savary-Miller scores in *H. pylori*-positive patients (2.8±1.2; mean±standard deviation), and *H. pylori*-negative patients (2.9±1.2) were not significantly different. In 7 patients without *H. pylori* antibodies *H. pylori* was detected histologically in the gastric antrum, angulus or corpus. Biopsy specimens were not available in 9 patients.

Table 2 Prevalence of IgG antibodies in serum to *H.pylori*$^{+}$

Group	Number of subjects	Number *H.pylori*+$^{+}$(%)	p value *
Controls (NUD)	82	28(34%)	-
Oesophagitis	68	21(31%)	ns
Barrett's oesophagus	83	22(26%)	ns

*in relation to control group, Chi-square analysis.

Table 3 Prevalence of IgA antibodies in serum to *H.pylori*$^{+}$

Group	Number of subjects	Number *H.pylori*+$^{+}$(%)	p value *
Controls (NUD)	82	27(33%)	-
Oesophagitis	68	15(22%)	ns
Barrett's oesophagus	83	19(23%)	ns

* in relation to control group, Chi-square analysis.

*Cag*A antibodies were significantly more often present in the *H. pylori*-positive NUD group than *H.pylori*-positive patients with GORD (p=0.05). This was particularly true for the BO group in relation to the control NUD group (p=0.02) (Table 4). There was however no difference in *Cag*A antibodies between the reflux oesophagitis group and the *H. pylori*-positive control subjects.

Table 4 Prevalence of IgG antibodies to *CagA* in serum of *H.pylori*$^{+}$ patients

Group	Number of subjects	Number *CagA*$^{+}$(%)	p value *
Controls (NUD)	81	28(35%)	-
Oesophagitis	66	17(26%)	ns
Barrett's oesophagus	82	16(19%)	0,02

*in relation to control group, Chi-square analysis.

Table 5 Prevalence of IgA antibodies to *CagA* in serum of *H.pylori*$^{+}$ patients

Group	Number of subjects	Number *CagA*$^{+}$(%)	p value *
Controls (NUD)	81	19(23%)	-
Oesophagitis	66	18(27%)	ns
Barrett's oesophagus	82	23(28%)	ns

* in relation to control group, Chi-square analysis.

Among the *H. pylori*-negative patients, a positive serologic *Cag*A response was found in 17 percent. Among oesophagitis patients carrying *H. pylori*, Savary-Miller score for those with *Cag*A-positive and *Cag*A-negative strains was 2.6±1.2 and 2.9±1.1 respectively (p=ns). The presence of *CagA-positive* strains in all patients with GORD (combining reflux oesophagitis, and Barrett's oesophagus) was lower (28%) compared with NUD groups [36% (p=ns)].

Discussion

The management of GORD and BO remains a challenging problem and this is partly due to a lack of knowledge of its natural history. The relationship of GORD, BO and *H. pylori* is also complex [1]. There might also be a link between prolonged proton pump inhibition and the area of the stomach infected by *H. pylori* and the rate of progression to atrophic gastritis leading to hypochlorhydria [12-14].

Strains of *H. pylori* have been grouped into 2 broad categories: the type I strains have the ability to produce a vacuolating cytotoxin (vacA) and the *Cag*A antigen, and the type II strains lack that ability [22]. These strains differ in virulence, and the type I strains were demonstrated to be more frequently associated with duodenal ulcer disease [22], with significantly more inflammation of the gastric mucosa and with higher serum IgG levels against *H. pylori* [7]. In most duodenal ulcer patients, antral gastritis predominates but corpus gastritis often develops during maintenance therapy with acid suppressive drugs [12]. When corpus gastritis is present, hypergastrinemia does not lead to increased acid production. *H. pylori* also possesses factors capable of inhibiting parietal cells [23, 24], while host cytokines, such as TNF-alpha and IL-1ß, resulting from chronic inflammation, also inhibits parietal cell function [25]. Since the first report by Coghlan et al. in 1987 [26], a large number of studies have shown that eradication of *H. pylori* results in a dramatic reduction in the recurrence of ulcers during the subsequent 1-2 years. However, *H. pylori* – particularly the *Cag*A phenotype through gastritis and associated hypochlorhydria might protect against GORD and its complications [18]. In recent years it has become clear that a significant number of patients will develop reflux oesophagitis after apparently successful eradication [27]. The findings are consistent with the hypothesis that the declining infection rates of *H. pylori* in the general population have led to a rise in the occurrence of GORD and associated oesophageal adenocarcinoma [28], with also lower prevalence of *CagA* phenotype in patients with complicated GORD such as BO than in the rest of the population [18]. This hypothesis gives rise to the

question whether *H. pylori* (particularly *Cag*A-positive strain), if detected, should always be eradicated. Serologic testing is a sensitive method for detecting infection with *Cag*A-positive strain [29]. *Cag*A antibodies are not only a useful marker for the more virulent strains that are associated with severe gastroduodenal disease [22], but might also be helpful as an guide on decision making - whom not to try to eradicate.

Conclusion. Patients with Barrett's oesophagus have a significantly lower prevalence of *Cag*A-positive type of *H. pylori* than individuals without endoscopic abnormalities. These data suggest that colonisation with *Cag*A-positive *H. pylori* strains may protect against the development of Barrett's oesophagus.

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Chapter 6 Prolonged use of proton pump inhibitors, CagA status and the outcome of *Helicobacter pylori* gastritis.

Sunna Gudlaugsdottir[1], Herman van Dekken[2], Theo Stijnen[3], J.H.Paul Wilson[1]

1. Dept. Of Internal Medicine, University Hospital Rotterdam, The Netherlands
2. Dept. Of Pathology, University Hospital Rotterdam, The Netherlands
3. Institute of Epidemiology and Biostatistics, Erasmus University Rotterdam, The Netherlands

In press in Journal of Clinical Gastroenterology 2002

Abstract

Goals and background. To assess if prolonged use of proton pump inhibitors in patients infected with *H. pylori* has adverse effects on the gastritis.

Study. We studied 34 *H. pylori* positive individuals with reflux esophagitis, Barrett esophagus or non ulcer dyspepsia. Half of them were on maintenance treatment with proton pump inhibitors (mean; 8 years) and half were not. *H. pylori* and CagA status was tested serologically. Gastric biopsies were classified histopathologically by the updated Sydney classification.

Results. Proton pump inhibitors in *H. pylori* gastritis are associated with a significantly less antral inflammation and density of *H. pylori*, regardless of CagA status. There was a tendency to more antral atrophy in patients with the CagA strain on maintenance treatment with proton pump inhibitors ($p=0.08$), but an opposite tendency in CagA negative individuals ($p=0.08$). Intestinal metaplasia was seen more frequently in CagA positive, treated individuals ($p=0.028$)

Conclusions. These findings support the hypothesis that CagA status is important in progression to atrophy and that maintenance treatment with PPIs accelerate this progression, while reducing inflammatory infiltration.

Introduction

It has become customary for patients diagnosed as having gastroesophageal reflux disease (GERD) or Barrett's esophagus (BE) to be treated chronically with proton pump inhibitors (PPI's) (1), as maintenance of a satisfactory response of GERD depends upon effective inhibition of gastric acid production (2). However, concerns have been expressed that long-term acid inhibition in *H. pylori* positive patients may increase the risk of gastric atrophy (3). This is worrying because of the association between achlorhydria and hypochlorhydria, *H. pylori* and gastric carcinoma(4). Although the majority of patients with GERD are not infected with *H. pylori* , about one in eight is. Because we do not routinely test patients with GERD for the presence of *H. pylori* before starting with PPI treatment, we decided to assess the long-term histological effect of chronic PPI use on the gastric mucosa in our *H. pylori* positive population with reflux esophagitis, BE or non-ulcer dyspepsia. Because the CagA status of *H. pylori* appears to be the most important virulence factor we assessed the impact of the CagA status in all tested individuals.

Materials and Methods

Study population and design

Adult patients who underwent upper GI endoscopy in the University Hospital Rotterdam (Rotterdam, The Netherlands) were asked to participate in a study to look for the prevalence of *H. pylori* infection. Firstly, we reviewed endoscopic and histological data collected from patients with BE found at routine endoscopy from January 1992 until December 1996. The patients were sent a letter and were offered a repeat esophagogastroduodenoscopy and serology testing for *H. pylori*. In addition, consecutive patients referred for upper gastrointestinal endoscopy from January 1999 to July 2000 were asked to participate. Only patients with reflux esophagitis, BE or no endoscopic abnormalities were eligible for the study.

Patients who were seropositive for *H. pylori* and willing to undergo repeat esophagogastroduodenoscopy were divided into two groups: an index group (n=17) undergoing long-term proton pump inhibition and a control group (n=17) not taking PPIs.

The Medical Ethics committee of the University Hospital Rotterdam approved the study. Informed consent was obtained from all participating patients, before the endoscopy was performed. A standard questionnaire about current and past antisecretory medication use was noted. Patients taking antacid drugs other than PPIs such as H_2-receptor antagonists (a minority of patients) were excluded. Omeprazole 20 mg and, in one case pantoprazol 30 mg were the minimum daily doses. None of the patients in the control group had taken antisecretory medication within the previous 6 months.

A blood sample was taken on the day of the endoscopic procedure for determination of specific serum immunoglobulin G (IgG) antibodies against *H. pylori* and the CagA protein.

Definitions

Patients found at the repeat esophagogastroduodenoscopy to have reflux esophagitis, BE or no endoscopic abnormalities and who were *H. pylori* positive were eligible.

A patient was defined as *H. pylori* -positive if IgG serology for *H. pylori* was positive and CagA positive if seropositive for the CagA protein. Only one patient was known to have had attempted eradication before intake in the study but was found to be both serologically and histologically positive for *H. pylori*. Gastroesophageal reflux disease was defined as the presence of endoscopic signs of reflux oesophagitis, BE or both.

Endoscopical assessments

Endoscopy was performed using standardised procedures with the Olympus EVIS 100 video-endoscope (Olympus Optical Co., Hamburg, Germany), and findings were recorded in a standardised database. Reflux oesophagitis was scored according to the Savary-Miller system (5) as follows: grade 0, normal esophageal mucosa with no abnormalities; grade 1, erythema or

diffusely red mucosa, edema causing accentuated folds; grade 2, isolated round or linear erosions extending from the gastroesophageal junction upward in relation to the folds; grade 3, confluent erosions extending around the entire circumference or superficial ulceration; grade 4, frank ulcer or BE.

Histological assessments

At endoscopic investigation four full-depth mucosal specimens from the antrum (two prepyloric and two from the angulus region) and two from the midportion of the oxyntic mucosa were obtained for histological assessment of all eligible patients and controls. The biopsy specimens were immediately placed into separate tubes containing buffered 3.7% formaldehyde solution. After dehydration, the specimens were embedded in paraffin wax, sectioned at 4-μm thickness and stained with haematoxylin-eosin for pathological analysis. No separate staining for *H. pylori* microorganisms was done. Haematoxylin-eosin stained biopsies were graded according to the Updated Sydney classification. Detailed description of the criteria used is given elsewhere(6). Briefly, inflammation, gastritis activity, atrophy, intestinal metaplasia, and *H. pylori* colonization of the gastric mucosa are quantified using four grades: none, mild, moderate or marked (6). Inflammation was graded according to the increase in lymphocytes and plasma cells in the lamina propria. Activity of gastritis describes the occurrence and density of neutrophil granulocytes, which are known to be correlated with the degree of virulence of *H. pylori* strains. Atrophy denotes the loss of glands, whether loss of a single or many acidopeptic glands. All gastric biopsy specimens were assessed blindly by one experienced gastrointestinal pathologist (H.vD.).

Laboratory assessment

Specific serum IgG antibody levels against *H. pylori* were determined using an enzyme-linked immunosorbent assay technique (Pyloriset EIA-G III, Orion Diagnostica, Espoo, Finland). The assays were performed according to the manufacturer instructions. The absorbance of the enzyme-linked immunosorbent assay samples was quantified at 405nm in a Bio-Rad microplate reader (Bio-Rad Laboratories BV, Veenendaal, the Netherlands) (3550-uv). Immunoglobulin G antibody titers were determined according to the manufacturer instructions using a Bio-Rad microplate reader with analysis software. Duplicate samples were determined and titers were calculated using quadratic regression analysis and log-linear curve fitting from four antibody standards. Sensitivity and specificity of this enzyme-linked immunosorbent assay for the detection of *H. pylori* carriage is 92% and 84%, respectively and has shown a very good correlation with the biopsy finding (7).

Determination of *H. pylori* - CagA status was based on the presence of serum IgG antibodies using a CagA *H. pylori* p120 enzyme-linked immunosorbent assay (Mediphos, Renkum, the Netherlands) and quantified as described above.

Statistical analysis

The stratified Mann-Whitney-Wilcoxon nonparametric two-sample test was used to compare histological features and mean between the two main independent groups (PPIs versus no PPIs) of sampled data and four subgroups (CagA-negative vs CagA-positive). We controlled for age by stratifying in three age categories.

The difference in proportions of CagA positive individuals in the two groups (PPIs versus no PPIs) was assessed with the chi-square test.

A p-value < 0.05 was considered statistically significant.

Calculations were performed using SPSS 9.0 for Windows (statistical software) (SPSS Inc., Chicago,IL).

Results

Thirty-four *H. pylori* positive patients (15 men, 19 women) were included in the study and divided into two groups. The index category included those receiving PPIs and the control category included those not taking PPIs. The characteristics of the study individuals are shown in Table 1.

Table 1 Characteristics of the study individuals

	PPI	No PPI
Number of study individuals	17	17
Age (yr, mean (range)	61.8(40-78)	57.0(29-77)
Gender (M/F)	9/8	6/11
No endoscopic abnormalities	2	10
Esophagitis grade		
Grade1	1	0
Grade2	2	2
Grade3	0	0
Grade4	2	2
Barrett's esophagus	10	3
Duration of PPI* (yr)		
No use	-	17
Less than 5 years	3	-
Between 5 and 10 years	4	-
More than 10 years	10	-

F indicates female; M, male; PPI, Proton-pump inhibitor

Of the 17 patients undergoing long-term PPI, 15 had severe GERD and 2 had no endoscopic abnormalities. All patients had taken PPI daily for at least 6 months, the majority for more than 10 years. Serological findings are given in Table 2.

Table 2 Serological features

	PPI	No PPI	p-value
IgG antibodies(mean)	1,348	2,294	0.05
SD(range)	1,159 (450-4,310)	1,480 (410-5,920)	-
CagA positive	7	10	0.25•
CagA negative	10	7	

•chi-square test

The mean IgG anti-*H. pylori* concentration was significantly lower in the patients taking PPIs. The histologic features of *H. pylori* positive patients taking PPI and *H. pylori* positive patients not taking PPI are given in Tables 3, 4 and 5.

Table 3 Histologic findings in 17 patients with *H. pylori* infection not on proton pomp inhibitors (group 1) and 17 patients with *H. pylori* infection taking proton pomp inhibitors (group 2)

Variable	Group 1		Group 2		P-value
	mean	±SD	mean	±SD	
Histologic findings†					
• Corpal					
H. pylori density	2.7	1.0	2.3	1.4	0.18
Neutrophilic infiltrate	2.3	1.0	2.2	1.2	0.46
Mononuclear-cell infiltrate	2.5	0.9	2.5	1.1	0.91
Intestinal metaplasia	1.3	1.0	1.5	1.3	0.72
Glandular atrophy	1.3	1.0	1.5	1.3	0.93
• Antral					
H. pylori density	2.9	1.0	1.9	0.9	0.014
Neutrophilic infiltrate	2.5	0.8	1.7	0.5	<0.002
Mononuclear-cell infiltrate	2.5	0.6	2.5	0.7	1.0
Intestinal metaplasia	1.2	0.4	1.2	0.6	0.75
Glandular atrophy	1.1	0.3	1.2	0.5	0.44

† Histologic findings were scored as 1, absent; 2, mild; 3, moderate; 4, marked

Table 4 Histologic findings in 10 CagA positive patients with *H. pylori* infection not on proton pomp inhibitors (group 1) and 7 CagA positive patients with *H. pylori* infection taking proton pomp inhibitors (group 2)

Variable	Group 1		Group 2		P-value
	mean	±SD	mean	±SD	
Histologic findings†					
• Corpal					
H. pylori density	2.8	1.1	2.1	1.7	0.20
Neutrophilic infiltrate	2.7	1.2	2.1	1.5	0.23
Mononuclear-cell infiltrate	2.7	1.1	2.7	1.2	0.96
Intestinal metaplasia	1.5	1.3	1.6	1.5	0.82
Glandular atrophy	1.5	1.3	1.7	1.5	0.69
• Antral					
H. pylori density	2.7	1.2	1.6	0.8	0.04
Neutrophilic infiltrate	2.6	1.0	1.7	0.5	0.03
Mononuclear-cell infiltrate	2.5	0.7	2.4	0.8	0.87
Intestinal metaplasia	1.3	0.5	1.6	0.8	0.49
Glandular atrophy	1.0	0	1.4	0.8	0.08

† Histologic findings were scored as 1, absent; 2, mild; 3, moderate; 4, marked

Table 5 Histologic findings in 7 CagA negative patients with *H. pylori* infection not on proton pomp inhibitors (group 1) and 10 CagA negative patients with *H. pylori* infection taking proton pomp inhibitors (group 2)

Variable	Group 1		Group 2		P-value
	mean	±SD	mean	±SD	
Histologic findings†					
• Corpal					
H. pylori density	2.6	0.8	2.5	1.3	0.80
Neutrophilic infiltrate	2.4	0.5	2.2	1.0	0.51
Mononuclear-cell infiltrate	2.6	0.5	2.4	1.1	0.72
Intestinal metaplasia	1.0	0	1.4	1.3	0.86
Glandular atrophy	1.3	0.5	1.4	1.3	0.86
• Antral					
H. pylori density	3.1	0.9	2.2	0.9	0.06
Neutrophilic infiltrate	1.9	0.4	1.7	0.5	0.016
Mononuclear-cell infiltrate	2.1	0.4	2.5	0.7	0.95
Intestinal metaplasia	1.1	0.4	1.0	0	ns
Glandular atrophy	1.1	0.4	1.0	0	0.08

† Histologic findings were scored as 1, absent; 2, mild; 3, moderate; 4, marked

Patients using PPIs had significantly less *H. pylori,* as detected histologically in the antrum, than patients not taking PPIs. Proton pump inhibitor use was also associated with significantly less neutrophilic infiltrates in the antrum, whereas the degree of infiltration with mononuclear cells was not different. In accordance with another cross-sectional study(8), atrophy and intestinal metaplasia were rarely seen in the group as a whole (<15% for either feature). When the histologic features were analyzed separately for the CagA positive patients, use of PPI was associated histologically with higher frequency of atrophy in the antrum (Table 4), approaching significance (p=0.08). In contrast, in the CagA negative category, atrophy was less frequent in those individuals taking PPIs (Table 5) compared to those not taken PPIs. The difference was also approaching significance (p=0.08). In the PPI treated group intestinal metaplasia was significantly more frequently seen in CagA positive individuals (p=0.028)

Discussion

In this cross sectional study, all patients were seropositive for *H. pylori*. The primary aim was to examine the influence of long-term use of PPIs on histological features of the gastric mucosa. The results suggest that maintenance treatment with PPIs in *H. pylori* gastritis reduces both the antral bacterial density of *H. pylori* and the neutrophilic infiltrate (inflammatory activity), regardless of CagA status. However, individuals with CagA positive strains who take PPIs seem to run a risk of antral atrophy and intestinal metaplasia, in contrast to individuals with CagA negative strains who are taking PPIs or with CagA positive strains who are not taking PPIs.

Because biopsy specimens may be falsely negative because of patchy *H. pylori* distribution in the stomach, we chose serology to define *H. pylori* status. Because our index category was using PPIs at intake, a breath test would have carried the possibility of being false negative (9). We controlled for age in a categorical stratification, as the mean age of the index category was higher.

Omeprazole is known to be bacteriostatic for *H. pylori*, and may also have antiinflammatory effects (10). The majority of our index population had been using omeprazole for a long time (mean, 8 years). It seems likely that the lower gastritis activity and density of *H. pylori* detected by histology in the index group are both because of bacteriostatic and anti-inflammatory effects of omeprazole and fewer CagA positive *H. pylori* strains in the PPI group (11). Lower antibody levels in PPI group is in agreement with less severe inflammation. The bacteriostatic and antiinflammatory effect caused by omeprazole could have caused a selection bias, with selection of patients with *H. pylori* strains resistent to PPIs. A prospective randomized study would be needed to examine that possibility. However, the main aim of present study was to gain further insight into progression of *H. pylori* gastritis and atrophy during PPI.

H. pylori has evolved lifestyles in which inflammation is necessary for its survival(12, 13), causing acute (neutrophilic) and chronic (mononuclear) inflammatory response. It possesses factors capable of inhibiting parietal cells (14, 15), and stimulates production of host cytokines, such as tumor necrosis factor-alpha and interleukin-1ß, which also inhibit parietal cell function (16). Gastritis predominantly in the corpus reduces acid output, and is thought to protect against GERD (17). However, corpus gastritis also predisposes to atrophic gastritis with presumed risk of stomach cancer (18). The vacA *s1*, CagA-positive or iceA1 strains are strongly associated with more severe gastritis, with a greater influence on the acid production (19). Mucosal inflammation predominantly in the antrum stimulates release of gastrin from the antral mucosa, which results in excessive secretion of acid by the parietal cell in the uninflamed corpus mucosa (20) which may predispose to GERD (21), possible concomitant with duodenal ulcer (22). This high acid load is associated with a slow progression to gland loss (22). A protective role against gastric malignancy for duodenal ulcer has been described (23).

Corpus gastritis has been reported to develope in *H. pylori* infected patients during maintenance therapy with acid suppressive drugs (particularly PPI treatment) and these

individuals may have an increased risk of gastric atrophy and consequently development of gastric cancer (3). The present study failed to support this shift from antrum to corpus in agreement with another cross-sectional study (8). An increase in corpus gastritis and atrophy because of use of PPIs has not been confirmed in randomised, controlled studies (24). However, it is possible that sampling error is a confounder, as atrophy can be only focal. Alternatively, the failure of find an antrum to corpus shift could be due to the selection of the index group. Patients with BE have been found to have less multifocal gastric atrophy than the control population (25). In our study most of the patients taking PPIs had BE. Barrett's esophagus and GERD are associated with less *H. pylori* infection, particularly CagA positive strains. Nearly all *H. pylori* isolates from patients with peptic ulcers, atrophic gastritis and gastric cancer are CagA positive (26, 27). In the current study, omeprazole therapy only appeared to increase the likelihood of antral atrophic gastritis in patients with CagA positive strains. Of interest is that this occured despite apparently reducing the bacterial load and acute inflammatory cells in the mucosa. The mechanism for this phenomenon remains to be elucidated. As mentioned before, corpus atrophy is thought to be related to *H. pylori* induced corpus gastritis, which impairs parietal cell function and lowers gastric acid secretion. Thus, CagA positive strains may be both harmful (increases risk of atrophy and distal cancer) and beneficial (protects against reflux oesophagitis and its sequelae) (28).

Some groups have advised testing and treating for *H. pylori* when prescribing PPIs for prolonged period. This has lead to a dilemma, as eradication of *H. pylori* has been reported to reduce the efficacy of PPIs (29) and to increase acid reflux in some groups (30). Our results suggest that, although maintenance treatment with acid suppression causes suppression of inflammatory activity of antrum gastritis and a decreased density of *H. pylori* it also causes acceleration of development of atrophic gastritis if the *H. pylori* is CagA positive. However, the underlying mechanism is unknown. The mechanism whereby CagA promotes gastric mucosal

atrophy is still not clear. Recent studies show that the CagA protein, when delivered into gastric mucosal cells from adherent bacteria, causes major changes in cell morphology. This is associated with rearrangement of the cytoskeleton (31, 32). How these changes then progress to cell loss, and how proton pump inhibition hastens the development of atrophy, is not known. We did not measure gastric acid secretion and we did not measure gastrin levels by the patients. Nevertheless, this issue might have clinical relevance and may show a link to earlier findings that some *H. pylori* positive patients undergoing maintenance therapy with acid suppressive drugs (particularly PPI treatment) have an increased risk of gastric atrophy (3), although not confirmed in randomised, controlled studies (24). The relevance of CagA needs to be studied in a prospective fashion. Routine testing for CagA positive *H. pylori* and eradication prior to starting maintenance PPI therapy for GERD should therefore be considered; however, because of the uncertainties this needs to be studied in a prospective fashion.

Acknowledgements

The authors thank Jan Francke and Felix de Rooij for the measurements of *specific H. pylori* and CagA antibodies.

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Chapter 7 General discussion and future perspectives

In this chapter I will briefly describe the most important findings and discuss the methodological issues of the conducted studies. The results will be interpreted in relation to clinical practice.

This discussion will finish with suggestions for future research on patients with Barrett's esophagus.

7.1 Introduction

In the field of Barrett's esophagus (BE), we were particularly interested in answering a number of questions concerning the surveillance for adenocarcinoma of the esophagus in individuals with Barrett's esophagus and the treatment of Barrett's esophagus:

- Who can benefit from endoscopic surveillance and what proportion of the population known to have BE can theoretically benefit from endoscopic surveillance?
- What risk factors are responsible for the increased death rate from cardiovascular disease in the BE population?
- Does the BE population have a lower prevalence of *H. pylori* infection than the general population or other patients with dyspepsia?
- What happens to the gastric mucosa in patients with *H. pylori* on maintenance treatment with PPI's?

The concept that early diagnosis of esophageal adenocarcinoma will benefit the patient (1-3), has lead to the development of endoscopic cancer surveillance programs as secondary prevention for patients with known BE. However, there is no agreement about the frequency of screening and in recent years it has been suggested that only operable patients at high risk of developing carcinoma should be screened (4). The tendency of BE patients to die at an earlier age than age and sex matched general population, mainly because of cardiovascular disease, forms a strong argument against screening all patients with BE(5), and underscores the need for

surveillance guidelines in these patients. The indications and pitfalls of endoscopic cancer surveillance of patients with BE are summarised in chapter 1.

The first clue that *H. pylori*, particularly the more pathogenic CagA-expressing form, might protect individuals against gastro-esophageal reflux disease (GERD) (including BE and adenocarcinoma of the esophagus) came with the observation that the prevalence of this infection was significantly lower in the BE population (6). This epidemiological observation could suggest that eradication treatment should not be given to BE patients infected with these particular strains,. However, prolonged use of proton pump inhibitors in patients infected with *H. pylori* has been reported to have adverse effects on the natural history of their *H. pylori* gastritis(7). Some *H. pylori* positive individuals with GERD require maintenance treatment with acid inhibitors such as PPI's because of symptoms of GERD. This is a much-debated issue with no firm conclusions, but a recent consensus report advised eradication of *H. pylori* in these patients (8).

7.2 The main findings of this thesis can be summarised as follows.

- By making use of, on the one hand, published and generally accepted risk factors for adenocarcinoma in BE, as given in table 1, as an indication for surveillance and, on the other hand, absence of these risk factors, old age or concurrent disease as reasons for exclusion from surveillance, we found that only 15.5% of patients diagnosed as having BE in our hospital would be likely to benefit from an endoscopic cancer surveillance program.
- We found that, in comparison with the general population, the BE population has a higher incidence of myocardial infarction and that the most likely risk factors for cardiovascular diseases in this group were hypertension and obesity.
- GERD patients without BE were also at increased risk of having hypertension.
- We found a significant lower prevalence of infection with the CagA *H. pylori* strain in the BE population, which suggests that CagA positive *H. pylori* protects against BE.
- The same strain appears to be responsible for the more frequent mucosal atrophy seen in the gastric antrum when *H. pylori* positive patients are on maintenance treatment with PPI's.

Table 1 Risk factors for adenocarcinoma in BE

Dysplasia, particularly high-grade dysplasia	(1, 9-13)
Caucasian men	(14-17)
Ulcer in BE	(5, 18, 19)
Stricture in BE	(4)
Longstanding reflux	(20)
Age over 55 years	(1, 5, 21)
Lenght of the BE	(4, 12, 15, 19, 22, 23)
Obesity	(24)
Tobacco	(15, 25, 26)
Alcohol	(26)
Bile / duodenal juice reflux	(27-30)

Risk factors written in *italics* were not used to include or exclude patients in the analyses described in chapter 2.

7.3 Methodological considerations and General interpretation of study results

In this thesis three types of studies are described, a retrospective cross-sectional study combined with an analysis of the literature, a cross-sectional case-control study and a cross-sectional analytical study.

At the start of the retrospective cross-sectional study we established guidelines for secondary prevention in patients known to have BE. Our first goal was to derive the risk factors for adenocarcinoma in BE patients from the literature. There appear to be subtypes of BE which do not progress or progress so slowly that even over a prolonged period they do not lead to invasive cancers(4). For example BE without dysplasia at the initial endoscopy generally does not progress and therefore is not in need of surveillance(1, 9-12). A significant proportion of patients with BE will die of other diseases before an adenocarcinoma developes in the BE and becomes a clinical problem(5). Studies aimed at identifying risk factors for adenocarcinoma in the oesophagus are limited, probably because they are hard to conduct and to analyse due to the relatively small number of cases developing cancer in any single centre. The few we found are given as references in table 1. If a factor was found to be a risk factor for adenocarcinoma developing more frequently than 1 in 200 patient-years in BE in 2 or more series, we included it in our calculation. Using the factors derived from the literature, we showed in this retrospective study that most patient without dysplasia theoretically require no endoscopic surveillance and that only a minority of patients are likely to benefit from an endoscopic surveillance program(31).

In the 2 case-control studies described in this thesis, BE ascertainment was based on consecutive patients diagnosed by endoscopy at the University Hospital Rotterdam. The control population was derived from 2 epidemiological studies in the general population (the Rotterdam ERGO study and the RIVM MORGEN project). The studies were performed in 2 age categories (see chapter 3 and 4). The ultimate purpose was to provide confirmation of the increased risk of

cardiovascular disease associated with reflux disease, including BE, to find clues as to the nature of the cardiovascular disease and to recognize preventable risk factors. Cross-sectional case-control studies are particularly efficient in terms of both time and costs. The comparison between diseased and non-diseased populations allows determination of features requiring further investigation. However, due to the design, case-control studies are susceptible to bias, especially when cases and controls are selected from different populations.

Selection bias. Cases of BE and GERD in our study were selected from hospital database whereas controls were selected from the general population. We were particularly interested in co-morbidity from coronary-heart disease in patients with BE. It can be postulated that co-morbidity is probably more frequent in hospital based cases than in the general population as a whole. If selection bias is present it can lead to incorrect estimates of true associations, which reduce the validity of the study. However, the cases used in this thesis were selected from endoscopic database of which many patients were outpatients or patients referred from the general practitioner making co-morbidity less likely. Also, to reduce this possible bias, we matched for age, sex, ethnicity and the area where the controls were living. Thus, since controls were chosen from the same source population from which cases were derived, it is not likely that selection bias occurred due to an ill defined sampling frame of controls. However, we cannot completely exclude another possible factor in the two case control studies. Selection bias in a case control study can occur when the response or determinants of response are different for cases and controls. Individuals not responding to invitation, or unwilling to participate in the case control study can cause a bias. The non-response rate in the Barrett's study was 48.6% compared to 33% in the Rotterdam ERGO study and 45% in the RIVM MORGEN project. Non-responders might be healthier subjects in the Barrett population, but the more unhealthy in the control group or vice versa. Response in the Barrett's population was defined as the percentage of patients who reacted to invitation and took part in the study, out of all known patients

diagnosed with BE at the University hospital Rotterdam (18-80 years) in the period January 1992 until December 1996 who were known to be alive in the year 1999. We found 212 patients, of whom 109 reacted to the invitation and took part in the study (51.4%). The reason for non-response in the Barrett's study is not known. However, as the invitation was to detect prevalence of *H. pylori* and not coronary heart disease we were convinced that the invitation did not selectively cause patients with coronary heart disease from the BE population to react and take part in the study. In the Rotterdam ERGO study the percentage of individuals 55 years of age or older, living in the suburb Omoord of Rotterdam and who took part in all parts of the study were determinant of response, the same as for the RIVM MORGEN project.

Information bias. The primary requirement for the validity of a case-control study is the ability to obtain complete and accurate information on all participants. Because both cases and controls were using somewhat different questionnaires to measure outcome in these 2 cross-sectional studies, misclassification of outcome or exposure could lead to information bias. Non-differential misclassification is a random misclassification, misclassification similar in cases and controls. We selected comparable questions from the questionnaire. Only questions with the same wording were used, so that we do not believe that this led to a significant bias. The only questions used not having the same wording were about the first degree family member in chapter 3, and these we interpreted with caution. Medication use was verified in both studies, therefore we do not believe that this aspect could have been associated with a significant bias.

Confounding. An important factor that must be considered in discussing the results is possible bias due to confounding. Confounding involves the possibility that the observed association is due to the effect of differences between study groups other than the exposure status. Important confounders in studies on the relation between potential determinants and cardiovascular risk factors are age and gender. Old age and male gender are strong risk factor for both Barrett's oesophagus and cardiovascular diseases. We controlled for the effect of age and

gender by stratification on risk factors for cardio-vascular diseases.

We performed 2 cross-sectional analytical studies (see chapter 5 and 6). In analytical studies the investigator assembles groups of individuals to determine whether the risk of a specific outcome parameter is different for individuals exposed or not exposed to a factor of interest. The factors of interest were (1) prevalence of *H. pylori* infection in the GERD population, particularly the BE population and the prevalence of CagA strain in the same groups and (2) the effect of maintenance treatment with PPI's in these groups. We used only our own cases to conduct these studies. For the studies described in chapter 5 and 6 a single laboratory technician measured by a single technique and during single session antibodies to *H. pylori* and CagA in all our cases studied during the period of this thesis. This makes a selection bias unlikely, although a selective non-response bias mentioned above can play a role in the BE population. On the other hand in chapter 6, where we compared 2 groups of all individuals serologically positive for *H. pylori* with each other with respect to exposure or not to maintenance treatment with PPI's we cannot be that certain. Information bias cannot be fully excluded as we used a standard questionnaire about medication and duration of use of a particular drug. However, we paid particulair attention to the use of acid inhibitors in all participants during interviews and when building the database. When there was any doubt on whether or not the individal had used acid inhibitors, it was re-checked. There are, however, two possible confounding factors in this study. First, there was an age difference between the groups. The mean age of the PPI group was almost 4 years older than the control group. As age by itself, especially in *H. pylori* positive individuals, prediposes to atrophy this can cause confounding bias. We tried to solve this by correcting for age-difference by stratification for age. Secondly, a possible sampling error when biopsies are taken from the gastric mucosa can cause confounding. Biopsies were taken in a standard fashion comparable to that recommended and used in other studies designed to investigate effects of various exposures on the gastric mucosa. Atrophy and

intestinal metaplasia (IM) can be focal or multifocal and the less atrophy or IM present the greater the chance of sampling error.

7.4 Closing remarks and future perspectives

7.4.1 Endoscopic cancer surveillance for subgroups of known BE patients

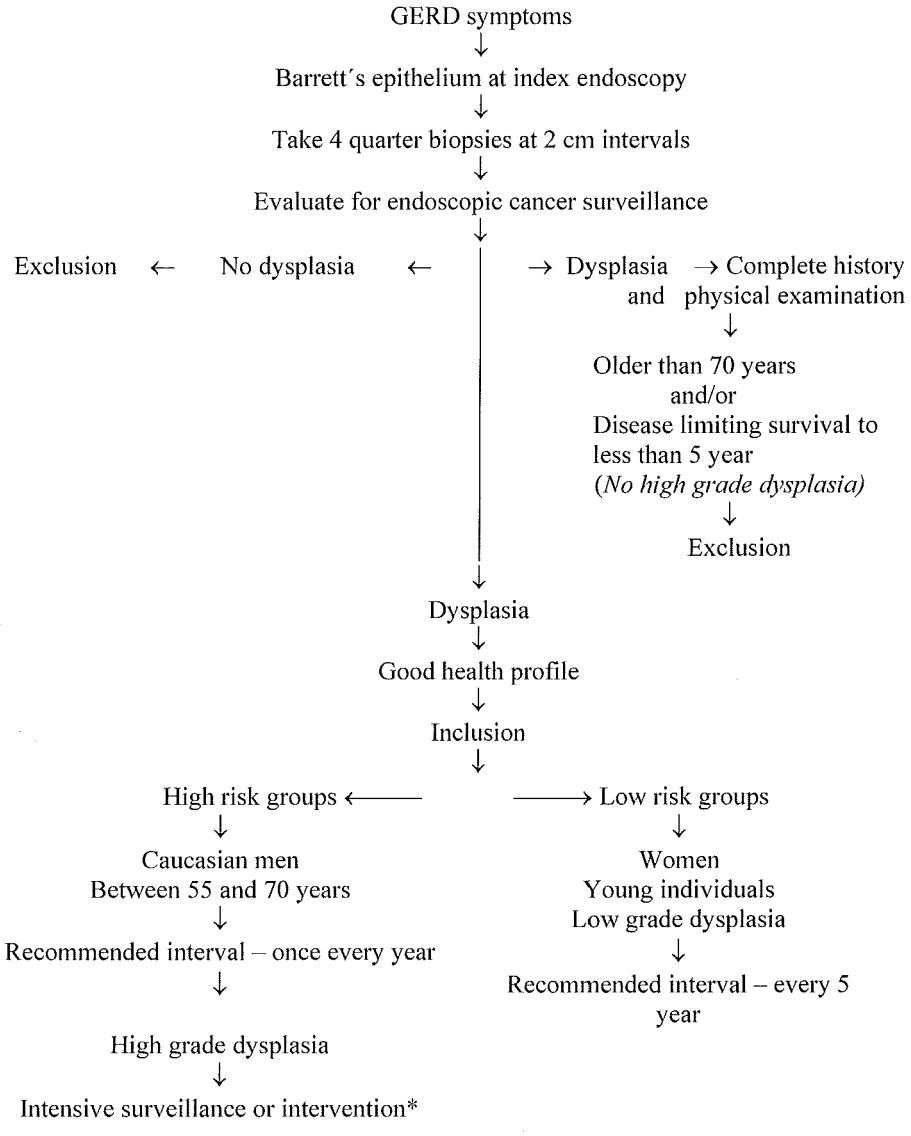
At present many endoscopists advocate endoscopic surveillance for patients known to have BE, with the intention of identifying progression in BE from metaplasia to HGD and early carcinoma before local invasion and metastasis occur (1-3). However, our own theoretical study and a recent observational study publishing final results of 10 year surveillance for BE patients failed to show a benefit for the majority of these patients (4, 31). There are many possible explanation for this failure (patients were too old, had concurrent diseases, were lost from follow-up etc.). At present there is also still discussion about the timing of treatment and whether an operation or alternative intervention is indicated when histological progression is observed. There is also uncertainty as to how treatment affects the course of the disease and the prognosis (13, 32). Ablation therapies for intestinal metaplasia and dysplasia are at present only being performed as clinical trials at special centers (33, 34). The management of high-grade dysplasia (HGD) remains controversial. Esophagectomy has been advocated if HGD or early adenocarcinoma is found incidentally or by surveillance (35, 36). Because of the risk of severe complications or mortality, esophagectomy is not an acceptable treatment if only low-grade dysplasia is present. This can be demonstrated by the course of 18 patients who were followed by surveillance and in whom an indication for esophagectomy was found because of HGD or early adenocarcinoma. Eight patients survived the operation, 3 died in the postoperative phase and 7 were in too poor a condition to undergo an operation, refused an operation or already had metastatic disease when the primary tumor was found during surveillance (1, 10, 22, 37, 38). Thus, even years of surveillance did not guarantee benefit.

Furthermore it has recently been argued that an operation may not be indicated in HGD until invasion is observed (32). Two studies offered their patients an alternative option for HGD in the form of an intensive follow-up program instead of esophagectomy (32, 39). The results of these

studies provided meaningful information about the natural course of HGD. Both studies used a systematic biopsy protocol and intensive follow-up and only when invasive cancer was found were the patients referred for operation. Leven *et al* published results of follow-up of 70 patients with high-grade dysplasia or early carcinoma (39). Invasive cancer was found within 2 months from the start of follow-up in 12 patients and in another 15 patients after a mean of 1.1 year. The remaining 58 patients were followed for a mean period of 2.5 years. In most of them (n=27) the high-grade dysplasia persisted, but in 16 patients regression of dysplasia was observed. The other study was very recently published. Schnell *et al* came to the conclusion that HGD without cancer in BE follows a relatively benign course in majority of patients (32). They followed 79 HGD patient without evidence of cancer when diagnosed. Cancer did not develop in 63 HGD patients during the whole follow-up, but 12 developed cancer (16%) during a mean 7.3-years surveillance period. Eleven of 12 patients did well after operation or ablation.

At present most patients who are diagnosed as having adenocarcinoma of the esophagus were not previously known to have BE. This means that we are probably putting too much effort and money in to screening the small target group known to have BE for adenocarcinoma, without there being a general agreement or accepted guidelines for screening of these patients to make the surveillance more effective. It is probably good sense to offer surveillance only to patients with a good health profile and high risk of developing BE carcinoma. Time, effort and finance could be reallocated to start looking at preventive measures for the 95% of patients who now present with symptomatic adenocarcinoma by gaining insights into how we could detect these patients at an earlier stage. The guidelines developed by us are given in figure 1. It is our hope that by presenting this work-up protocol that surveillance programs for BE patients will be more cost-effective.

Figure 1 - A work-up protocol (guidelines) for patients with BE



*Intensive surveillance is once every three months. Intervention means either esophagectomy or ablation.
Very long segment BE (longer than 6 cm) should be treated with caution and it is probably important to check twice for presence of dysplasia before exclusion

7.4.2 Population screening for subgroups in the general population

Recently, population screening limited to patients considered to have a high risk for BE and associated adenocarcinoma has been considered (40). This might be the next step in approaching the problem of the rising incidence of adenocarcinoma in the esophagus in the Western countries.

Adenocarcinoma in BE has been gaining importance as a health problem in the developed countries (14, 41). All major health problems are a reason to consider population screening. However, although 95% of BE patients in the general population are at present undiscovered, as yet BE does not fulfill all recommended criteria for population screening according to the '*Principles of early disease detection*' as defined by World Health Organization (WHO)(42). The ability to treat the condition adequately when discovered is the most important criterion for screening (42). At present BE patients are treated with acid inhibition or antireflux surgery if they have reflux symptoms (43-45). These therapies have little or no effect on the BE itself nor on the development of adenocarcinoma. It would be great step forward if BE could be ablated with minimally invasive treatment before adenocarcinoma has developed. Some ablative therapies (photodynamic therapy, thermal techniques and endoscopic mucosal resection) have been reported to be promising and are currently being evaluated for this purpose (33). Until these therapies have been fully approved, screening of the general population for BE will not be acceptable.

There are however fewer arguments against trying to find subgroups in the adult population who are at highest risk of developing adenocarcinoma in the future but who at present are not endoscopically identified as a risk group. Here are a few suggestions:

1) ***Population screening for Caucasian men aged 55-70 years of age.*** The overall cancer risk in patients with BE is lower than previously estimated and most recent larger studies with longer follow-up have tended to report rates of 0.5%/year or lower (46). As Caucasian men over 60 years old are the major risk group for adenocarcinoma in BE, there is evidence in favour of starting population-based screening of Caucasian men between the ages of 55 to70 years (see table 2)

Table 2 Caucasian men at ages between 55 and 70 years are particularly at risk of BE. The same age range holds true for adenocarcinoma of the esophagus.

- In most studies the majority of patients with BE are Caucasian men (women:men ratio range between 1:3 and 1:8)
- In most studies the greater majority of patients with adenocarcinoma in the esophagus are Caucasian men(14-17)
- The mean age at which BE was diagnosed was 63 years, although with very broad age-range(21)
- The mean age at which adenocarcinoma in BE was diagnosed was 64 years (range30-89) (21)
- The mean age at which adenocarcinoma was diagnosed at the University Hospital Rotterdam in BE was 67 years (range 52-81 years)(5)

2) ***Primary prevention in the form of instruction.*** Another possibility could be primary prevention in form of prophylactic instruction on a population basis about reflux symptoms and possible consequences. Population based studies on reflux symptoms have shown that the prevalence of reflux complaint in the general population is high. About half of the western population suffers from heartburn at least once a year (47), about 20% of the white population of the USA experiences heartburn weekly (48-51). Symptoms of reflux are considered to be a fairly accurate indicator for GERD (52), although only a small minority consults a physician. It has been suggested that as adenocarcinoma of the esophagus does not invariably develop from BE (53) and as a history of GERD symptoms seems to be a risk factor for adenocarcinoma, it might be advisable to give prophylactic treatment and offer endoscopic screening to patients with symptomatic reflux (20). However, this would lead to an immense workload for the endoscopy units, as at present we see only small fraction of the risk group. GERD is diagnosed in 10% of all upper gastrointestinal endoscopies performed, BE patients represent less than 1% and patients with adenocarcinoma of the esophagus less than 0.1%. These last two groups are currently the targets of research. Information for the public regarding GERD symptoms and its possible consequences might bring a patient at risk of developing adenocarcinoma under medical attention sooner. However such a public information program should only be undertaken if sufficient endoscopic facilities can be provided. In addition it should be pointed out that not all patients with adenocarcinoma of the esophagus give a clear history of GERD-related complaints (see for example Menke-Pluymers and Bytzer)(15, 47). An index endoscopy might be used to select the particular patient for inclusion or exclusion in endoscopic cancer surveillance in the same way as shown for known BE above. If endoscopic cancer surveillance is done only in selective risk groups in both the BE population and the GERD population as a whole, workload might be reduced to feasible proportions.

3) ***Not eradicating Helicobacter pylori infection, particularly the CagA positive strain, in GERD patients, as primary prevention.*** The influence of *H. pylori* infection on GERD has in recent years received great attention. Clustering of observations demonstrates that the greater the extent to which corpus gastritis is present in infected individuals, the greater the protective effect against GERD is likely to be (54). This is related to how well the gastritis lowers the acid load. Nearly all isolates from patients with peptic ulcers, atrophic gastritis and gastric cancer are CagA positive (55). However, patients with duodenal ulcer disease do not have low acid output(56), while patients with gastric atrophy do(57). There is evidence that CagA phenotype of *H. pylori* has a protective role against the development of BE (6, 58) and esophageal adenocarcinoma. It has been shown that PPI's are more effective in the presence of *H. pylori* (59). Based on these findings it can be postulated that we should not eradicate *H. pylori*, particularly if it is CagA positive. On the other hand, concern has been voiced that treating reflux symptoms with PPI's might worsen *H. pylori* gastritis (7) and although this hypothesis is not proven (60) a current consensus advises eradication of *H. pylori* infection in all positive individuals who are to be put on a maintenance treatment with PPI's (8). This leads to a dilemma which is not yet fully solved. At present we do not have enough evidence to not eradicate the *H. pylori* infection, even though the patient might benefit by less GERD complaints and be protected on the long-run against the complications of GERD. At present it is probably better to follow the recommendations of the Maasticht consensus and advise eradication of *H. pylori* if maintenance treatment with PPI's is to be given to *H. pylori* positive individuals. Our results in chapter 5 support the hypothesis that CagA positive *H. pylori* gastritis protects against BE development, but our data also support that concept the CagA phenotype might lead to atrophy developing more rapidly when the patient is on maintenance treatment with PPI's (see chapter 6).

7.5 Targets for future research on BE include

1. ***Finding biological markers that identify patients at higher risk of progressing to cancer.*** A better understanding of the pathophysiology of Barrett's adenocarcinoma based on expression of novel biomarkers and use of such biomarkers in examination of biopsies or endoscopic examination may help to identify patients at increased risk for malignant transformation. If the genetic modifications, which lead to adenocarcinoma, are clarified in the future this may provide an approach to the prevention of adenocarcinoma. A major problem in current practice is the large interobserver variation in classifiying dysplasia as low-grade, high-grade or carcinoma -in-situ. New biomarkers may prove useful in reducing this variation.
2. ***Defining appropriate surveillance intervals and appropriate risk groups.*** At present there is little agreement about the ideal frequency of endoscopic cancer surveillance in patients with BE nor about who would benefit from such a program. Surveillance for everyone with BE is not cost effective and in most cases surveillance would not provide health benefits. Clinical aspects and histological features can now be used to define patients with BE who are likely to benefit from endoscopic cancer surveillance, as has been discussed in this thesis. The development of biomarkers of early stages of carcinogenesis in combination with surveillance has the potential to allow identification of patients at high risk of neoplastic change. Large numbers of patients need to be followed prospectively to learn more about the natural history of BE and especially the rate at which the disease progresses through the various histological stages towards adenocarcinoma.
3. ***Defining the cancer risk and the appropriate management of patients with short segment Barrett's esophagus.*** Even though short segment BE is very common and possible precursor of every cardia carcinoma, the exact cancer risk is not known. Short segment of BE is not

seen as an indication for endoscopic cancer surveillance. However, if we are to find a way to lower the incidence of adenocarcinoma of the esophagus and cardia we need to discover the cancer risk of patients with short segment BE and define strategies for prevention, treatment and surveillance.

4. ***Understanding the natural history of dysplasia and comparing alternatives for the management of high-grade dysplasia.*** The question whether the presence of any degree of dysplasia is an indication for close clinical follow-up regardless of the extent of BE needs to be answered. Is there a form of dysplasia that does not progress and how can we recognise it? In this regard high-grade dysplasia is very important, particularly with respect to treatment strategy. When is it safe to wait, when can we use ablative technic and when do we need to operate?
5. ***Studying whether ablation can delay or prevent progression to dysplasia and adenocarcinoma.*** We have to continue to develop various ablation therapies in Barrett's patients to approved standards to be able to use one or more of these techniques in clinical practice.

These questions can only be answered by large scale observational studies and well-designed, controlled interventional trials which compare different strategies.

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Chapter 8 Summary – Samenvatting

8.1 Summary

The clinical research reported in this thesis was performed from September 1997 until August 1999. The research was based both on older theories and on recently published findings and concepts, which can be outlined as following:

1. The incidence of adenocarcinomas of the esophagus and gastric cardia has been rising steadily since 1970. This rising incidence rate is an important stimulus for investigation into the causes of these poorly understood types of cancer.
2. The only known risk factor for adenocarcinoma in the esophagus is Barrett's esophagus with biopsy proven intestinal metaplasia.
3. Many centers have advocated long-term endoscopic and histologic follow-up (surveillance) programs for patients with Barrett's esophagus, with the aim of detecting high grade dysplasia or cancer at a curable stage.
4. So far, observational and follow-up studies have reported disappointing results for surveillance. Most adenocarcinomas in the esophagus are diagnosed in patients not known to have Barrett's epithelium and 50% of patients known to have Barrett's epithelium die from an unrelated medical disorder at an earlier than expected for an age- and sex-matched normal population. The most likely reason for death has been reported to be cardiovascular disease with pulmonary causes in second place.
5. Reflux of acid from the stomach into the esophagus is presumed to be the most important factor in the pathogenesis of Barrett's epithelium.
6. Acid inhibitors are the most widely used treatment for gastroesophageal reflux disease and Barrett's esophagus. Since 1985 proton pomp inhibitors have been on the market, and have proven efficacy in controlling symptoms and healing esophagitis.
7. Since 1995 concerns have been expressed that the use of proton pump inhibitors in individuals infected with *Helicobacter pylori* can speed up atrophy of the gastric mucosa

and possible increase the chance of gastric malignancy. A consensus report advised the eradication of *Helicobacter pylori* in infected individuals if they were to be given proton pump inhibitors as a maintenance treatment .

Chapter 1

In chapter 1 an overview is given of publications on Barrett's oesophagus, its causes and complications beginning with a brief historical survey and the most likely reasons for its popularity as a field of investigation. The present day definition of Barrett's disease, its induction and rate of development and factors which play a role in the pathogenesis of complicated and uncomplicated reflux disease are reviewed. The association between Barrett's disease and adenocarcinoma of the esophagus and what is known of the natural history of Barrett's disease is described.

The interaction between Helicobacter pylori and gastroesophageal reflux disease is summarised. The prevalence of Helicobacter pylori in this specific subgroup of the population, the importance of the virulence factors of the Helicobacter pylori for effects on the gastric mucosa and the influence of Helicobacter pylori on gastric acid production are reviewed. Concerns about atrophy in Helicobacter pylori gastritis under maintenance treatment with proton pump inhibitors are emphasised. Finally, arguments for and against endoscopic cancer surveillance in Barrett's population are discussed. With regard to surveillance it is important to see the patient as a whole, particularly at the initial visit, as this is generally agreed to be the best moment to weigh the risk of esophageal cancer against the likelihood of having other diseases which impair survival. The observation that the Barrett's population has a mean age of death which is lower than that of an age and sex matched normal population is mentioned, with cardiovascular diseases as the most frequent cause of death. This chapter ends with a summary of the aims of this doctoral thesis.

The main aim of the thesis was:

To obtain a better insight into recognising those Barrett's patients who are particularly at risk of developing esophageal adenocarcinoma and identification of those Barrett's patient particularly at risk of having or getting cardiovascular disease.

Further elucidation of the interaction of Helicobacter pylori with gastroesophageal reflux disease, especially Barrett's esophagus, was also one of the aims of the thesis. This included studying the prevalence of Helicobacter pylori infection and the risk of maintenance treatment with proton pump inhibitors in specific subgroups.

Chapter 2

The proportion of healthy Barrett's patients, who because of strong risk factors for adenocarcinoma in the esophagus in the near future would benefit from endoscopic cancer surveillance, as a proportion of the total population at present diagnosed as having Barrett esophagus, was determined. The literature on factors for or against endoscopic cancer surveillance is reviewed; the factors include factors appear to protect against adenocarcinoma in the esophagus, factors overriding that protection and necessitating endoscopic surveillance and other factors like illness, frailness or old age which are strong arguments against effective endoscopic cancer surveillance. Each risk factor was evaluated with respect to the incidence-risk of developing adenocarcinoma in the esophagus if that factor was present. If at least one cancer occurs in 200 patients with that factor followed for one year, then patients with that factor were classified a potentially deserving surveillance. If the risk was lower then it was regarded as being too small or the patient was to old or to frail to benefit from surveillance, then they were classified as unlikely to benefit from a cancer surveillance program. We found that, of the patients known to have Barrett esophagus in the University Hospital Rotterdam, only 15.5% patients evaluated in this fashion would benefit from endoscopic cancer surveillance. If every

patient with Barrett's esophagus were to be included in a surveillance program, then the workload would be too large for the health services and in most cases a burden rather than a benefit for the patient. Guidelines are given in this chapter for the selection of patients with Barrett's esophagus who are likely to benefit from endoscopic cancer surveillance.

Chapter 3

A cohort of patients with Barrett's esophagus aged 55-80 years were compared with sex and age matching normal population with respect to the prevalence of myocardial infarction and related risk factors (smoking, hypertension, treatment for hypertension, family history of cardiovascular diseases in a first degree relative, measurement of blood pressure and serum cholesterol spectrum).

The results show that the Barrett's population with upper gastrointestinal complaints are more likely to have a history of myocardial infarction and hypertension and are more often treated for hypertension than the normal population. Obesity was more frequently seen in the Barrett's population, which may in part explain the predisposition to hypertension. No difference was found in the history of smoking or present smoking habits between the groups. A new carefully designed prospective study is needed to confirm these results. If the results are true, it implies that these factors should be taken into account when designing prospective studies or selecting patients for surveillance programs.

Chapter 4

Three groups were investigated in the age category 20 – 59.9 years; Barrett's patients, patients with endoscopically confirmed reflux esophagitis and patients with normal gastroscopic findings. Each group was compared to the age and sex matched normal population with respect to risk factors for coronary heart disease (smoking, history of hypertension and treatment for hypertension; blood pressure and serum cholesterol spectra were measured).

The results shows that patients diagnosed because of upper GI complaints with Barrett's disease or reflux esophagitis are more likely to have hypertension, be treated for hypertension and to have higher cholesterol than the normal population. This was not seen in the category with a normal gastroscopy. There was no difference in the history of smoking or present smoking habits between the groups. A new carefully designed prospective study is again needed to confirm these results. If the results are true it implies that these factors should be taken into account when designing prospective studies or selecting patients in this age category for surveillance.

Chapter 5

Two study cohorts (Barrett's patients and patients with endoscopically proven reflux esophagitis) were compared to a reference population with normal endoscopical features. The total group numbered 224 individuals. A blood sample was taken from everyone to measure IgG antibodies against Helicobacter pylori and the cytotoxin-associated protein A (CagA).

The results show that patients with endoscopically confirmed reflux esophagitis or Barrett's esophagus have a lower prevalence of Helicobacter pylori compared to patients without endoscopic abnormalities. Patients with Barrett's esophagus have a significantly lower prevalence of colonisation with CagA Helicobacter pylori strain than the reference population.

The results support the hypothesis that CagA positive Helicobacter pylori strains can protect against Barrett's mucosa forming in the esophagus.

Chapter 6

Seventeen Helicobacter pylori positive patients on maintenance treatment with proton pump inhibitors (mean; 8 years) were compared with 17 Helicobacter pylori positive patients not on these medications. All patients underwent gastroscopy with histological sampling from the stomach (antrum, angulus, corpus) for classification of gastritis by means of the updated Sidney classification. The endoscopic diagnosis made in the patients were one of the following: Barrett's esophagus, reflux esophagitis or without endoscopic abnormalities.

The results demonstrated that proton pump acid inhibitors are associated with significantly lower gastritis activity in the gastric antrum and lower density of Helicobacter pylori regardless of the CagA status. However, atrophy was more often detected in the gastric antrum of CagA positive individuals on maintenance treatment with proton pump inhibitors. Intestinal metaplasia was seen significantly more often in CagA positive individuals on maintenance treatment with proton pump inhibitors.

The results support the hypothesis that maintenance treatment with proton pump inhibitors in CagA positive individuals hastens the development of atrophy in the antrum. An opposite effect was observed in CagA negative individuals. No difference was seen in the gastric corpus between the groups.

Chapter 7

Conclusions.

Recommendations are made for subsequent studies. Five broad areas of investigation are proposed:

1. Studies to find new, predictive biomarkers for progression towards a carcinoma. Dysplasia, which is a histological finding, has proven to be too subjective and variable a parameter for use in individuals.
2. Studies to determine the ideal interval for surveillance endoscopy, and to improve the clinical criteria to select patients who have an increased risk of developing a carcinoma.
3. Studies to define the risk of short-segment Barrett's esophagus.
4. Investigation of the natural history of dysplasia, and, in combination with these studies, investigation of different strategies for high grade dysplasia.
5. Studies to answer the question whether ablation therapy (removal or destruction of Barrett's mucosa) is capable of reducing the rate of progression to, or eliminating the risk of carcinoma.

It is clear that all these proposals for further studies will require both large numbers of patients and many years of follow-up.

8.2 Samenvatting

In september 1997 werd begonnen met het onderzoek naar enkele klinische aspecten van Barrett oesophagus, beschreven in dit proefschrift. Barrett oesophagus is een aandoening van de distale slokdarm, waarbij het normaal aanwezig plaveiselepitheel is vervangen door metaplastisch cilinderepitheel. Het onderzoek is gebaseerd op concepten uit zowel oudere als recente publicaties over deze aandoening. Deze concepten kunnen als volgt worden samengevat:

1. De incidentie van adenocarcinomen van slokdarm en cardiagebied van de maag neemt sinds 1970 duidelijk toe in de Westerse landen. Deze toename in incidentie heeft geleid tot een stijgend aantal publicaties over klinisch epidemiologisch onderzoek en pathogenetisch onderzoek naar de oorzaken van deze carcinomen.
2. De enig bekende risico factor voor een adenocarcinoom van de slokdarm is het Barrett slijmvlies met intestinale metaplasie.
3. Vele centra bevelen aan levenslange endoscopisch en histologisch controle voor patiënten met Barrett slokdarm, om vroegtijdig hooggradig dysplasie of resectabele kanker op te sporen.
4. Na-controle van patiënten met Barrett slokdarm heeft echter tot dusver onvoldoende steun geleverd voor het invoeren van surveillance programma's. De meeste adenocarcinomen van de slokdarm worden gediagnosticeerd bij patiënten die niet bekend zijn met Barrett slijmvlies en 50% van patiënten die wel bekend zijn met Barrett slijmvlies sterven op een jonger dan verwachte leeftijd aan een oorzaak niet gerelateerd aan Barrett slijmvlies. De voornaamste doodsoorzaak bij patiënten bekend met Barrett slijmvlies is hart- en vaatziekten, gevolgd door longziekten.
5. Reflux van maaginhoud wordt verondersteld de belangrijkste factor te zijn in het ontstaan van Barrett slijmvlies.

6. Tegenwoordig zijn remmers van zuurproductie de meest gebruikte medicamenteuze behandeling voor gastro-oesofageale reflux en Barrett slijmvlies. Na de introductie van protonpomp remmers in 1985 is deze groep van geneesmiddelen zeer populair geworden, voornamelijk omdat zij zeer effectief zijn gebleken in het bestrijden van klachten en in het genezen van de oesophagitis.
7. Na een eerste publicatie in 1995, maakt men zorgen dat langdurige behandeling met protonpomp remmers, bij patiënten met Helicobacter pylori infecties, het ontwikkelen van atrofie en dysplasie van het maagslijmvlies kan bevorderen. Atrofie en dysplasie gaan gepaard met een toegenomen kans op het ontstaan van een maagcarcinoom. Een consensus rapport heeft geadviseerd Helicobacter pylori infecties te behandelen bij alle patiënten die gedurende langere tijd protonpomp remmers zullen gaan gebruiken.

Hoofdstuk 1

In hoofdstuk 1 wordt de literatuur over de oorzaken en complicaties van Barrett slijmvlies samengevat. Onder andere wordt ingegaan op de definities van Barrett slokdarm, de ontstaan van Barrett slijmvlies en factoren betrokken bij de pathogenese van zowel gecompliceerde en ongecompliceerde reflux ziekten. Het verband tussen Barrett slokdarm en adenocarcinoom wordt beschreven.

De interacties tussen Helicobacter pylori en gastro-oesofageale reflux ziekten worden samengevat, met aandacht voor de prevalentie van Helicobacter pylori in patiënten met gastro-oesofageale reflux of Barrett slokdarm. Het belang van virulentiekenmerken van Helicobacter pylori op secretie van maagzuur wordt benadrukt. De zorgen over een versneld progressie naar atrofie bij patiënten met Helicobacter pylori gastritis, tijdens een onderhoudsbehandeling met protonpomp remmers worden besproken.

De argumenten voor en tegen endoscopische surveillance op kanker in patiënten met Barrett slokdarm worden toegelicht. Het lijkt belangrijk alle aspecten van de gezondheid van de patiënt te evalueren tijdens het eerste bezoek, omdat dit waarschijnlijk het beste moment is om het risico van het ontstaan van slokdarmkanker af te wegen tegen de kans op andere ziekten die de gezondheid of levensverwachting kunnen beïnvloeden. De bevinding, dat personen met Barrett slokdarm een kortere levensverwachting hebben dan personen uit de bevolking met dezelfde leeftijd en geslacht, wordt genoemd. Hart- en vaatziekte blijkt de meest frequente doodsoorzaak te zijn.

Samenvatting van de doelstelling van het proefschrift:

Doel van het onderzoek was:

- Het identificeren van risicofactoren voor, en beschermingsfactoren tegen, ontwikkeling van een adenocarcinoom in BE.
- Het opstellen van praktische richtlijnen voor selectie van patiënten met BE die eventueel in aanmerking zouden kunnen komen voor surveillance.
- Het opsporen van risicofactoren bij patiënten met BE, die een verklaring zouden kunnen leveren voor de oversterfte aan hart-en vaatziekten bij deze patiënten.
- Om de prevalentie van risicofactoren voor hart-en vaatziekten bij patiënten met BE te vergelijken met die bij patiënten met andere vormen van GERD of bovenbuikklachten.
- Om de interacties tussen Helicobacter pylori en GERD te exploreren en de volgende vragen te beantwoorden:
    - Is de prevalentie van Helicobacter pylori infectie bij patiënten met BE of andere vormen van GERD anders dan bij patiënten met non-ulcer dyspepsie?
    - Is er een verschil in prevalentie van de virulente vorm (CagA positieve) van Helicobacter pylori tussen patiënten met verschillende oorzaken van bovenbuikklachten?

- Wat zijn de lange termijn effecten van proton-pomp remmers op het maagslijmvlies bij patiënten met een Helicobacter pylori infectie, en heeft de CagA status van de bacterie invloed op deze effecten?

Hoofdstuk 2

Hoofdstuk 2 beschrijft een evaluatie van het percentage patiënten met Barrett slokdarm, die waarschijnlijk baat zullen hebben van endoscopische kanker surveillance. De literatuur over factoren, die van invloed zouden kunnen zijn op een voorstel voor surveillance, wordt eerst samengevat. Er zijn factoren geïdentificeerd die gepaard gaan met een verminderde kans op adenocarcinoom van de slokdarm, factoren die gepaard gaan met een verhoogd risico (en dus mogelijk een indicatie zouden kunnen vormen voor endoscopische surveillance) en niet aan Barrett slokdarm gerelateerde, waaronder andere ziekten of hoge leeftijd, die een argument zijn tegen endoscopische kanker surveillance. De verschillende risico factoren zijn geëvalueerd als relatief risico voor het krijgen van adenocarcinoom van de slokdarm. Als het risico groter was dan één carcinoom per 200 patiënten gedurende 1 jaar follow-up, werd de patiënt geclassificeerd als potentieel kandidaat voor surveillance. Als het risico kleiner was, of de patiënt een verminderde levensverwachting had wegens een andere ziekte, werd de kans op een gunstig effect van endoscopische kanker surveillance onwaarschijnlijk geacht. Slechts 15,5% van 335 patiënten met een Barrett slokdarm in het Academisch Ziekenhuis Rotterdam, op deze wijze geëvalueerd, zouden theoretisch baat kunnen hebben van endoscopische kanker surveillance. Eenvoudige richtlijnen worden gegeven voor het selecteren van patiënten met Barrett slokdarm, die waarschijnlijk baat van endoscopische kanker surveillance zouden hebben.

Hoofdstuk 3

De prevalentie van myocardinfarct en verwante risico factoren (roken, hypertensie, anamnese van hart- en vaatziekte bij een eerste graad familielid) zijn geïnventariseerd en bloeddruk- en serum cholesterol metingen zijn verricht bij een groep patiënten met Barrett slokdarm met een leeftijd tussen 55 en 80 jaar, en zijn vergeleken met personen uit de normale bevolking met dezelfde leeftijd en geslacht. De resultaten van het onderzoek laten zien dat de oudere bevolking met Barrett slokdarm, gediagnosticeerd tijdens endoscopisch onderzoek wegens klachten van de bovenste tractus digestivus, hebben vaker een myocardinfarct en een hoge bloeddruk, of zijn vaker behandeld voor hypertensie, dan de controle bevolking.

Vetzucht werd vaker gezien in de Barrett groep. Mogelijk speelt vetzucht een rol bij het ontstaan van de hoge bloeddruk. Er waren geen verschillen in rookgewoontes of een anamnese van roken tussen de groepen.

Een prospectief onderzoek dient verricht te worden om deze resultaten te bevestigen. Indien de resultaten bevestigd worden, dan moeten deze factoren in overweging genomen worden bij het ontwikkelen van prospectieve studies van Barrett slokdarm of bij het selecteren van patiënten voor surveillance.

Hoofdstuk 4

Drie groepen zijn onderzocht in de leeftijdscategorie 20 tot 59,9 jaar: patiënten met Barrett slokdarm, patiënten met een endoscopisch bevestigd reflux oesophagitis en patiënten met bovenbuik klachten en normale bevindingen bij gastroscopie. Het aanwezig zijn van risico factoren voor coronaire hartziekten (roken, hypertensie en behandeling voor hypertensie, bloeddruk en serum cholesterol metingen) bij deze drie groepen werd vergeleken met de normale bevolking van dezelfde leeftijd en geslacht. Patiënten met bovenste tractus digestivus klachten en Barrett slokdarm of reflux oesophagitis hebben vaker een hoge bloeddruk of worden behandeld voor een hypertensie, en hebben ook gemiddeld een hogere serum cholesterol dan de normale bevolking. Deze veranderingen werden niet gevonden bij patiënten met bovenste tractus digestivus klachten zonder afwijkingen bij gastroscopie. Er was geen significant verschil in huidige of voorafgaande rookgewoontes tussen de groepen. Een nieuwe prospectieve studie is wenselijk om deze resultaten te bevestigen. Indien bevestigd, dient men ook rekening te houden met deze factoren bij het opzetten van prospectieve studies met patiënten met Barrett slokdarm en bij de selectie van patiënten voor surveillance.

Hoofdstuk 5

Twee groepen - patiënten met Barrett slokdarm en patiënten met endoscopisch bewezen reflux oesophagitis - zijn vergeleken met een groep personen met normale endoscopische bevindingen. In totaal zijn 224 personen onderzocht. Bloed werd afgenomen ten behoeve van de bepaling van IGG antistoffen tegen Helicobacter pylori en tegen cytotoxine geassocieerde proteïne A (CagA). Patiënten met endoscopisch bewezen reflux oesophagitis of Barrett slokdarm hadden een lager prevalentie voor Helicobacter pylori dan patiënten zonder endoscopische afwijkingen. Patiënten met Barrett slokdarm hadden ook een significant lage prevalentie van CagA-positieve

Helicobacter pylori dan de vergelijkingsgroep. Deze resultaten ondersteunen de hypothese dat infectie met CagA-positieve Helicobacter pylori bescherming biedt tegen het ontwikkelen van Barrett slijmvlies in de slokdarm.

Hoofdstuk 6

Zeventien Helicobacter pylori positieve patiënten tijdens behandeling met de protonpomp remmers (gemiddelde duur van de behandeling 8 jaar) zijn vergeleken met 17 Helicobacter pylori positieve patiënten die deze middelen niet gebruikten. Alle patiënten hebben een gastroscopie ondergaan met biopsie van antrum angelus en corpus van de maag ten behoeve van histologische classificatie volgens een herziene Sydney classificatie systeem. De gestelde endoscopische diagnoses waren: Barrett slokdarm, reflux oesophagitis of geen afwijkingen. Bij gebruik van protonpomp remmers neemt zowel de ontstekingsactiviteit in het antrum als de densiteit van Helicobacter pylori af, ongeacht CagA status. Atrofie werd vaker gevonden in het antrum van CagA positieve personen tijdens langdurig protonpomp remmer behandeling dan bij andere personen. Intestinale metaplasie werd significant vaker gezien bij CagA positieve individuen tijdens een onderhoudsbehandeling met protonpomp remmers. Deze bevindingen ondersteunen de hypothese dat onderhoudsbehandeling met protonpomp remmers in CagA positieve personen het ontwikkelen van atrofie in het antrum versnelt. Een tegenovergesteld effect werd gevonden in CagA negatieve individuen. Er zijn geen verschillen gevonden in maag corpus slijmvlies tussen de verschillende groepen.

Hoofdstuk 7

In dit hoofdstuk worden de resultaten samengevat. Methodologische problemen, deels inherent aan vergelijkend klinisch onderzoek waarbij gebruik wordt gemaakt van bestaande bevolkingsgegevens, worden besproken. In de toekomst dienen een aantal prospectieve studies

verricht te worden over risicofactoren voor carcinogenese bij Barrett slokdarm en refluxziekte, en over de voor- en nadelen van surveillance. Thans zijn onvoldoende theoretische en empirische gegevens beschikbaar om surveillance bij patiënten met Barrett slokdarm als regel aan te bevelen. In afwachting van prospectief onderzoek en ontwikkelingen op het gebied van minder invasieve therapie, worden een aantal aanbevelingen gedaan wie wel en wie niet baat zou kunnen hebben van surveillance. Omdat slechts een minderheid van personen met een Barrettslokdarm als zodanig bekend is, is het duidelijk dat surveillance een zeer gering effect zal hebben op

Conclusies

Een aantal aanbevelingen worden gedaan voor vervolgonderzoek naar:

A De klinische epidemiologie en determinanten van hart en vaatziekte en kanker bij patiënten met GERD en BE.

B Minder invasieve en meer effectieve behandelingen voor zowel slokdarmcarcinoom als BE

C Voor haart- en vaatziekten bij patiënten met BE te vergelijken met die bij patiënten met andere vormen van GERD of bovenbuikklachten

Chapter 9 Addendum

9.1 Dankwoord

'Qui e nue nucleum esse vult, frangit nucem' (Diegene die de inhoud van de walnoot wil eten breekt de schaal). De buitenkant van de walnoot is hard en bitter maar de inhoud smaakt heerlijk. Iemand die het geluk zoekt moet eerst door moeilijkheden want zonder deze geen geluk. Om het doel te bereiken komt een bitter begin, het vervolg is makkelijk, en het einde heerlijk. Deze wijsheid van de 16e-eeuwse Erasmus van Rotterdam is wel verouderd maar nog goed van toepassing.

Om te beginnen wil ik het personeel van het Zuiderziekenhuis te Rotterdam (Medisch Centrum Rijnmond Zuid – locatie zuider) bedanken. Alle collega's en verpleegkundigen die mij zo fantastisch hebben ontvangen toen ik , met mijn zeer beperkte taalkennis, aldaar met mijn opleiding tot interniste begon. Mijn collega's van de arts assistenen groep in opleiding wilde ik bedanken voor hun prettige samenwerking, vaak gezellig borrelen en vriendschap. Mijn opleider Dr. A Berghout en andere internisten voor hun begeleiding en steun. Met name wil ik Dr. PL Batenburg bedanken voor zijn begeleiding met het doen van endoscopiën en later zijn advies en steun in het kader van mijn vervolgopleiding als gastroenteroloog.

Dit proefschrift is tot stand gekomen dankzij veel mensen. Ik wil iedereen bedanken die op enigerlei wijze een bijdrage heeft geleverd aan de totstandkoming van dit proefschrift. Alhoewel de samenwerking tussen de afdeling Interne Geneeskunde en afdeling Maag- Darm en Leverziekten soms is tegengevallen, is de hele research-periode voor mij zeer leerzaam geweest en in die zin, zeer waardevol.

Met name wil ik bedanken:

Alle onderzochte patiënten en behandelende specialisten voor hun medewerking.

Prof. JHP Wilson , mijn promotor en initiatiefnemer van het uitvoeren van dit onderzoek, voor de mogelijkheid om met wetenschappelijk onderzoek te starten, het vertrouwen en de vrijheid die ik heb gekregen bij het verrichten daarvan. Je gaf me volop de gelegenheid mijn eigen weg te gaan, iets wat ik vooral achteraf als zeer waardevol beschouw.

Marja Bendik, mijn trial-coordinator. Beste Marja, bedankt voor het vele werk en inspanning voor dit onderzoek. De momenten tijdens schrijven van de vele patientenbrieven en organisatorische brieven voor dit onderzoek waren vaak zeer gezellig.

Het personeel van de MDL centrale wil ik zeer bedanken voor de prettige samenwerking. De verpleging aldaar die me zo lief heeft opgevangen.

Dr. M van Blankenstein voor zijn enthousiaste interesse en input in het onderzoek, begeleiding van deel daarvan en bijdrage die tot goede ideeën leidde.

Jan Dees voor de mogelijkheid om de vele gastroscopieën te kunnen verrichten bij deelnemende patienten en vaak praktische steun bij het uitvoeren van het onderzoek.

Prof. Dr. EJ Kuipers en Prof. Dr. SW Schalm voor de stimulatie aan het eind en voor de gelegenheid dit promotieonderzoek af te kunnen ronden.

Dr. FWM de Rooij en J Franken, voor alle bepalingen die verricht zijn op Lab Interne II: Beste Felix en Jan, hartelijk dank voor jullie inzet.

Prof. Dr. T Stijnen, bedank ik de statistische ondersteuning en voor de hulp bij verwerking van de verschillende onderzoeken.

Dr. Jacqueline C Witteman en Frank van Rooij voor data-verwerking en belangrijk medewerking als co-auteurs van Hoofdstuk 3

Monique Verscheuren voor het leveren van controle data en medewerking als co-auteur van Hoofdstuk 4

Het personeel van de afdeling pathologie, met name Dr H van Dekken, dank ik voor de waardevolle beoordeling van biopten.

Alle medewerkers van de afdeling 4 Noord, voor de prettige samenwerking en de goede sfeer die bij dit werk onontbeerlijk zijn geweest.

Kamergenoten RA Feelders en C Lebrun: Beste Richard, samen hebben wij de spanning rond de opleiding tot internist meegemaakt. Bedankt voor je collegialiteit en vaak praktische, waardevolle adviezen. Beste Corinne, bedankt voor je gezelligheid. Ik waardeer zeer je getoonde intresse in het doen van wetenschappelijk onderzoek en algemeen in het vak geneeskunde.

Richard Feelders en Vigfus Sigurdsson voor hun steun als paranimf.

Medische studenten; Els Janssen, Addy Romme en Mark A Hofstetter wil ik bedanken voor hun bijdrage, die in het kader van afstudeerprojekten aan de Erasmus Universitieit Rotterdam ook aan dit onderzoek hebben meegewerkt.

De leden van de promotiecommissie, Prof. Dr. EJ Kuipers, Prof Dr. BHCh Stricker en Prof Dr. HW Tilanus voor de beoordeling van het manuscript.

Tot slot wil ik de voor mij belangrijkste mensen bedanken. Snorri, jouw steun en liefde blijven van onschatbare waarde voor mij. Altijd heb je veel belangstelling getond en wist mij te stimuleren, en mijn ambities te leren relativeren. Svanlaug en Stefan, bedankt voor jullie blijdschap, steun, liefde en geduld tijdens gehele opleiding en voorbereiding voor dit proefschrift.

Alle gezellige mensen die bij gelegenheid bereid zijn geweest van niet-medische gedachten te wisselen en te filosoferen over het leven.

9.2 About the author

Sunna Gudlaugsdottir was born on Augustus 17th 1962 in Reykjavik, Iceland. She attended secondary school at Fjolbrautarskolinn Breidholti in Reykjavik and graduated in 1981. In 1981 she started at the University of Iceland in Reykjavík for a short while at the Faculty of Nursing.

In 1982 she started her Medical Study at the University of Iceland. She graduated from medical school in 1989, after which she worked as a resident in different departments (General Surgery, Obstetrics, Internal Medicine, Casualty and Emergency Dept., Clinical Oncology, Psychiatry and Pediatrics) at the Reykjavik City Hospital and the University Hospital of Iceland from Augustus 1st 1989 until July 1st 1992. During this period she performed a research project in the Department of Clinical Oncology (Dr. H. Sigurdsson, University hospital of Iceland) on flow cytometry and breast cancer.

She worked as a senior resident at Reykjavík City Hospital, Dept of Internal Medicine from Oktober 1st 1992 until Augustus 1st 1993.

In Augustus 1993 she started her specialty training in Internal Medicine at the Zuiderziekenhuis Rotterdam, The Netherlands (Dr. A Berghout) and subsequently at the University Hospital Rotterdam, The Netherlands (Prof. Dr. M.A.D.H. Schalekamp and Prof. J.H.P.Wilson). She has been registered as a specialist in internal medicine in Iceland since April 17th 1997 and since September 1st 1999 as specialist in internal medicine in The Netherlands.

In September 1997 she started the work described in this thesis in the Department of Internal Medicine and Gastroenterology & Hepatology of the Erasmus Medical Centre in Rotterdam (Prof. J.H.P.Wilson).

From September 1st1998 until September 1st 2001 she was in specialty training for Gastroenterology & Hepatology in the department of Gastroenterology & Hepatology University hospital Rotterdam, The Netherlands (Prof. Dr S.W. Schalm and Prof. Dr. E.J. Kuipers). On July 18th 2001 she was registered as Internist/Gastroenterologist in Iceland and on September 1st 2001 she was registered as Internist/Gastroenterologist in The Netherlands.

Since September 2001 she has been working as a specialist in Internal Medicine and as a Gastroenterologist at the Akranes hospital, Iceland and she will be starting at The Specialist Medical Centre ''Læknasetrið'' in Reykjavík – Mjódd in September 1st 2002.

9.3 List of abbreviations used in this thesis

BE	Barrett's esophagus
BO	Barrett's oesophagus
GERD	Gastroesophageal reflux disease
GORD	Gastrooesophageal reflux disease
IM	Intestinal Metaplasia
HGD	high grade dysplasia
LGD	low grade dysplasia
LES	Lower esophageal sphincter
H. pylori	*Helicobacter pylori*
CagA	Cytotoxin-assoiate gene
VacA	Vacuolating cytotoxin A
ACE inhibitors	angiotensin converting enzyme inhibitors
PPI	proton pump inhibitors
NUD	nonulcer dyspepsia
WHO	World Health Organization
IgG	Serum immunoglobulin G antibodies
TNF-alpha	Tumor necrosis factor-alpha
IL-8	Interleukin-8
EGD	esophagogastroduodenoscopy
OGD	oesophagogastroduodenoscopy
ECS	endoscopic cancer surveillance
CHD	cardiovascular risk factors
CVD	cardiovascular disease
MI	myocardial infarction
BMI	body mass index
HDL	high density lipoprotein
SBP	systolic blood pressure
DBP	diastolic blood pressure