Aliment Pharmacol Ther 2003; 17 (Suppl. 2): 82–88.

Review article: test and treat or test and scope for Helicobacter pylori *infection. Any change in gastric cancer prevention?*

R. M. MC LOUGHLIN, S. S. SEBASTIAN, H. J. O'CONNOR, M. BUCKLEY & C. A. O'MORAIN
Adelaide & Meath Hopsital, Tallaght, Dublin; and Trinity College, Dublin

SUMMARY

A 'test and treat' strategy is advocated for patients with dyspepsia under the age of 45 years, with endoscopy reserved for those with alarm symptoms or aged over 45 years. One of the consequences of this strategy will be a reduction in population infection rates of *Helicobacter pylori*. It is now clear that *H. pylori* is one of the prime initiators of gastric cancer with up to 70% of gastric cancers attributable to *H. pylori*. What remains unclear is if *H. pylori* reduction will lead to a reduction in gastric cancer.

INTRODUCTION

A 'test and treat' strategy was recently recommended by the European Helicobacter Pylori Study Group, as the clinical approach of choice for patients under 45 years of age with dyspepsia, in the absence of alarm symptoms or a family history of gastric cancer.[1] These guidelines imply that endoscopy can be avoided in most young patients with uncomplicated dyspepsia. A recent large study demonstrated that this approach led to a dramatic reduction in the use of endoscopy in 'test and treat' patients over a 1-year period.[2]

Gastric cancer remains a major public health issue. It is the second leading cause of cancer death world-wide[3] with approximately 1000 000 deaths per year.[4] The exact prevalence of *Helicobacter pylori* infection in gastric cancer patients is difficult to estimate because evidence of the infection can be lost with the development of gastric precancerous lesions or gastric cancer. Studies suggest that up to three-quarters of gastric cancers are attributable to *H. pylori* infection.[5] It now seems appropriate to ask whether a 'test and treat' strategy might help prevent gastric cancer. A 'test and treat' strategy for young patients with dyspepsia may result in significant reductions in population infection rates. An unexpected outcome of this strategy may be a reduction in gastric cancer rates. The impact of *H. pylori* eradication on prevention of gastric cancer is uncertain. While the link between *H. pylori* and gastric cancer development has been established the reversibility of precancerous lesions is still controversial. Studies assessing the effect of *H. pylori* eradication in gastric premalignant lesions are equivocal.

Correspondence to: Prof. C. O'Morain, Adelaide & Meath Hospital, Tallaght, Dublin 24, Ireland
E-mail: gastroenterology@amnch.ie

HELICOBACTER PYLORI AND GASTRIC CANCER

In 1994 *H. pylori* infection was classified as a definite carcinogen by the International Agency for Research on Cancer.[3] The role of *H. pylori* infection in the genesis of gastric cancer, however, is still controversial because there is a high population prevalence of infection yet less than 1% of infected subjects will develop gastric cancer.[5–11]

In 12 studies analysed by the Helicobacter and Cancer Collaborative Group involving 1228 patients with gastric cancer and over 3000 controls an overall Odd's ratio of 2.36 for the development of gastric cancer was found for those who were *H. pylori* positive. Between 65 and 80% of noncardia gastric cancer was attributable to *H. pylori* infection. This study also showed an association between the duration of infection and gastric cancer, with those known to be infected for more than

Table 1. Non-invasive screening tools for *H. pylori*

Screening for *H. pylori*	Additional screening
Urea breath test	Pepsinogen ration
H. pylori stool antigen	Antiparietal cell antibodies
Serology for *H. pylori* ELISA IgG CagA	Gastrin levels

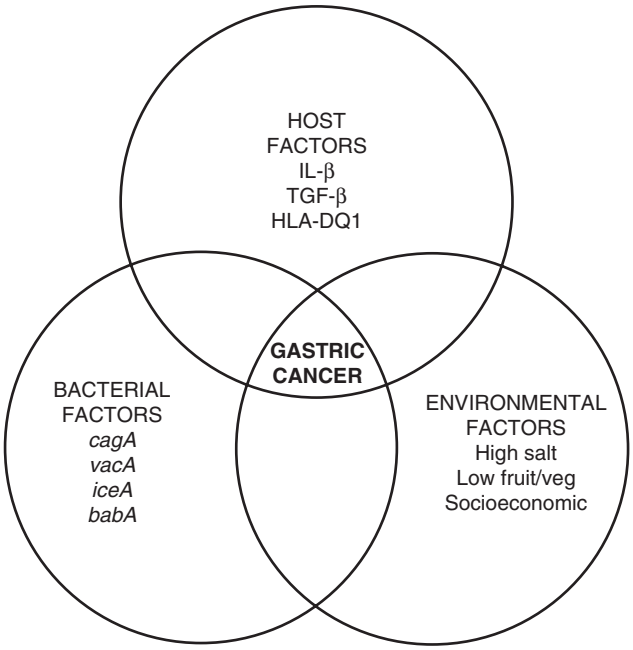

Figure 1. Pathogenesis of gastric cancer.

10 years having an Odd's ratio of 9.6 for the development of gastric cancer compared with those with a shorter duration of infection.[12] In 1994 Forman *et al.* summarized all available case studies and found an increased relative risk of 3.8 for development of gastric cancer in patients with *H. pylori* infection.[13] More recently, Uemura *et al.* in a prospective study of 1526 patients showed that the risk of gastric cancer in *H. pylori* infected patients was 5% at 10 years. Of the 1526 patients, gastric cancer developed in 36 (2.9%) of the 1246 patients with *H. pylori* and in none of the 280 who were negative for infection.[14]

Diagnostic tests including culture, immunohistochemistry, rapid urease test, urea breath test and detection of *H. pylori* in the stool all rely on the actual presence of *H. pylori*. These tests therefore may give a false negative result when *H. pylori* density in the gastric mucosa is low, as occurs in gastric atrophy, intestinal metaplasia and gastric cancer.[15, 16] Serological tests on the other hand detect evidence of both past and current infections.

PATHOGENESIS OF GASTRIC CANCER

It is hypothesized that *H. pylori* infection provokes a step-wise progression in gastric-mucosal pathology commencing with active gastritis and progressing to gastric atrophy, intestinal metaplasia, dysplasia and eventually gastric adenocarcinona.[17–19]

This pathway was initially proposed by Correa[17] before the discovery of *H. pylori* and over the past decade *H. pylori* has become established as the prime initiator. It is still not clear if there is always a sequential progression or if some stages can proceed more directly to gastric cancer.

Almost all *H. pylori* infected individuals develop chronic active gastritis that persists unless treated. Chronic gastritis is associated with excessive production of reactive oxygen metabolites and *H. pylori* infection is also associated with decreased intragastric ascorbic acid levels, a critical antioxidant.[20] *H. pylori* causes increased mucosal proliferation.[21, 22] Increased cell proliferation is associated with an increased risk of somatic mutations due to replication errors and inadequate DNA repair. Cell proliferation may also lead to selective growth advantage of mutated cells. *H. pylori* also decreases apoptosis.[23] The disturbed equilibrium of apoptosis and cell proliferation associated with *H. pylori* infection may lead to an overall increase in cellular turnover and persistence of mutated cells, which may in turn favour the development of neoplasia.

The reasons why only a small minority of patients with *H. pylori* develop gastric cancer may be related to differences in host susceptibility, environmental factors and genetic diversity of *H. pylori*.

HOST FACTORS

Subjects with a family history of gastric cancer have a 1.5–3-fold increased risk of developing gastric cancer.[24] This may be due to inherited factors. Interleukin-1beta is a potent pro-inflammatory cytokine and a powerful inhibitor of gastric acid secretion. Interleukin-1beta

polymorphisms are associated with an increased risk of hypochlorhydria and of gastric cancer.[25] Transforming growth factor beta controls cell growth, cell differentiation and migration. Increased expression of transforming growth factor beta has been demonstrated in patients with gastric cancer and in their first degree relatives.[26] The HLA-DQA1 locus is another risk factor for gastric cancer with the absence of the haplotype DQA1*0102 being associated with an increased risk of atrophic gastritis and adenocarcinoma.[27] Microsatellite instability is also reported in patients with a family history of gastric cancer.[28] The apparent increased inherited risk of gastric cancer may, however, be due to intrafamilial clustering of *H. pylori* infection, which is increased in relatives of gastric cancer patients.[29]

BACTERIAL FACTORS

H. pylori virulence associated genes are associated with an increased risk of gastric cancer. The *Cag-A* gene increases cellular proliferation but not apoptosis,[30] and *Cag-A* positive *H. pylori* infection has been reported to carry an increased risk of neoplasia compared with *Cag-A* negative infection. Several studies have shown that *Cag-A* positive *H. pylori* strains are associated with higher degrees of acute and chronic inflammation.[31–34] Parsonnet *et al.* reported an Odd's ratio for gastric cancer development of 3.3 for *H. pylori* positive, *Cag-A* positive strains vs. 2.2 for *H. pylori* positive, *Cag-A* negative strains.[35] Interestingly Papa *et al.* showed that CagA positive infection is associated with increased production of reactive oxygen species in the gastric mucosa leading to severe oxidative DNA damage.[36] The vacA and iceA genes are associated with an increased risk of gastric cancer.[37, 38] Aside from these bacterial toxins, bacterial adherence factors such as the blood group antigen binding adhesion (*babA*) genes have recently been implicated in the development of gastric cancer.[39]

Multiple molecular and genetic alterations have been identified in gastric cancer, including activated oncogenes, growth factors and growth factor receptors.[40, 41] Inactivated tumour suppressor genes p53, APC and k-ras are seen in 30–40%, 30% and 8% of gastric cancers, respectively.[42–44] Reactivation of telomerases such that the cells do not undergo physiological senescense has been described.[45] Other abnormalities seen in gastric cancer are up-regulation of transcription factors[46] and mutations of the E-cadherin gene or hypermethylation of the E-cadherin promoter region thus blocking the expression of E-cadherin and so affecting cell adhesion.[28, 47] Microsatellite instability due to hypermethylation, rather than mutation of the mismatch repair genes,[48] has also been described in gastric cancer.

H. PYLORI ERADICATION AND GASTRIC CANCER

Although evidence for the role of *H. pylori* in gastric carcinogenesis is compelling, it is not known whether eradication of infection might effectively prevent gastric cancer. There is conflicting evidence on the effect of *H. pylori* eradication on gastric atrophy and intestinal metaplasia. Some studies of *H. pylori* eradication have shown a beneficial effect on both lesions, whereas other studies have not observed any significant improvement.

Van der Hulst *et al.* in an uncontrolled study of 155 patients followed up for 1 year after *H. pylori* eradication revealed no change in gastric atrophy or in intestinal metaplasia.[49] Forbes *et al.* followed up 54 patients for 7 years, of whom 32 had successful *H. pylori* eradication. There was no significant difference in gastric atrophy or in intestinal metaplasia between the two patient groups.[50] Annibale *et al.* successfully eradicated *H. pylori* in 25 of 32 patients. After a year there was no improvement in gastric atrophy or intestinal metaplasia.[51] In a large randomized controlled study Correa *et al.* followed up 631 patients for 6 years. Patients were randomized to eight different treatments and only 79 received *H. pylori* eradication. Intestinal metaplasia progressed at the same rate in both the placebo (23%) and the eradicated group (17%).[52]

Ohkusa *et al.* in an uncontrolled prospective trial, followed up 115 patients with dyspepsia and successful *H. pylori* eradication over 12–15 months. Glandular atrophy improved in 34 of the 38 (89%) affected patients and intestinal metaplasia improved in 21 of the 46 (61%) affected patients.[53] Sung *et al.* undertook a large scale prospective placebo-controlled trial in which 226 patients with *H. pylori* eradicated and 245 patients who remained infected with *H. pylori* were followed up for 1 year. Over that time a slight regression of intestinal metaplasia in the antrum was seen in the *H. pylori* negative group but this was not significant. Patients with persisting infection, however, had significant progression of corpus atrophy.[54] Kokkola *et al.* followed up 22 patients with *H. pylori* infection and moderate or severe corpus gastric atrophy for 7.5 years

and found no significant change in atrophy or intestinal metaplasia. *H. pylori* was then eradicated in all 22 patients and after 2.5 years follow up there was a significant improvement in both atrophy and intestinal metaplasia.[55] In a longer post-eradication follow up, Ito *et al*. in a study of 54 patients over 5 years, showed that *H. pylori* eradication led to a significant decrease in both gastric atrophy and intestinal metaplasia in the corpus and antrum.[56]

One reason for the apparent discrepancies in the impact of *H. pylori* eradication on gastric atrophy or intestinal metaplasia may be the small numbers involved in most of the studies listed and the relatively short follow-up period. Those studies showing a significant improvement in gastric preneoplastic lesions following *H. pylori* eradication had follow up for 2–5 years. The patchy distribution of both gastric atrophy and intestinal metaplasia may also jeopardize the reliability of endoscopic and biopsy-based follow-up studies.[57]

SCREENING FOR GASTRIC CANCER

Fendrik *et al*. using a decision analysis model, have shown that the cost-effectiveness of *H. pylori* screening strategies for gastric cancer depends on the cancer reduction rate. The strategy, however, remains cost-effective even at moderate rates (< 30%) of risk reduction.[58]

Studies on *H. pylori* and gastric cancer have shown Odd's ratios for increased cancer risk varying from 2.2 to 6. This variation can be attributed to differences in the subjects enrolled, the prevalence of *H. pylori* infection in the population and the method of detection used. The magnitude of Odd's ratios is affected by the background prevalence of *H. pylori*, so that where *H. pylori* is highly prevalent the Odd's ratio will be lowered although the incidence of cancer will be high.[59] In addition, the diagnostic method used influences the apparent prevalence of *H. pylori* infection and hence the Odd's ratio of *H. pylori* and gastric cancer will vary depending on the tests.[60]

SCREENING FOR *H. PYLORI*

The effectiveness of any screening programme is dependent on the accuracy and reliability of the screening tools used.

The urea breath test is considered the most accurate noninvasive method of diagnosing *H. pylori* infection. Urea breath test results, expressed as the delta value, are affected by the density of *H. pylori* infection and by the severity of atrophic gastritis. As a result urea breath test delta values in gastric cancer patients tend to be significantly lower than in patients with gastritis, duodenal ulcer or gastric ulcer.[61] In addition the urea breath test is expensive and may not be readily available for population studies.

The HpSA test detects the presence of *H. pylori* antigens in the stool, and similar to the urea breath test, the sensitivity of the HpSA test is affected by the density of *H. pylori* infection. The sensitivity and specificity of the HpSA test is at least as good as the urea breath test[62, 63] and the HpSA is less expensive than the urea breath test. One of its drawbacks is the acceptability of the test. A new stool test using monoclonal antibodies appears similar to the polyclonal HpSA.[64]

Serological detection of IgG antibody against *H. pylori* provides a reliable assessment of current or past *H. pylori* infection. *H. pylori* infection is usually lifelong therefore a positive test usually denotes active infection unless the patient has received eradication therapy. Serology testing for *H. pylori* infection is sensitive and specific, approaching 95% in some studies. It is noteworthy that Cag A antibodies persist longer after *H. pylori* eradication than surface antibodies and so studies that used Cag A antibodies, rather than *H. pylori* surface antibodies, for diagnosis have raised the Odd's ratio of *H. pylori* leading to gastric cancer development from 2.0 to 21.[5]

There are other serological tests that may prove helpful in predicting those who are at a higher risk of developing gastric cancer, including pepsinogen ratios, antiparietal cell antibodies and gastrin levels.

As atrophic gastritis becomes more extensive and severe normal gastric gland function is progressively diminished. Pepsinogen exists as two types, I and II, which are both produced by the chief and mucus neck cells in the gastric fundus. Pepsinogen II is also produced by the pyloric glands in the antrum and in the proximal duodenum. With gastritis and mild inflammation both Pepsinogen I and II are increased. With more severe atrophy Pepsinogen I decreases as the chief cells are destroyed but Pepsinogen II remains elevated. When measurement of serum Pepsinogen concentrations are used as a screening test for gastric cancer, they achieve a sensitivity of > 80% and specificity of > 70%.[65]

Anti-parietal cell antibody is well known as an auto-antibody in pernicious anaemia. Anti-parietal cell antibody is also an auto-antibody in *H. pylori* associated gastritis. The level of anti-parietal cell antibody expression is associated with the histological degree of atrophic gastritis and maybe useful in predicting those who will progress to gastric atrophy.[66]

Fundic atrophic gastritis leads to hypochlorhydria, which in turn leads to rebound hypergastrinaemia. Levels of serum gastrin have been used to screen for gastric cancer. In a recent case control study, Konturek *et al.* found elevated gastrin levels in 48% of gastric cancer patients compared with 8% of controls and found a significant correlation between the rise in serum gastrin and the rise in intragastric pH.[67]

TEST AND SCOPE

Endoscopy is a more expensive screening tool and not as well tolerated by patients. In a study of 169 patients diagnosed with gastric cancer under the age of 55 years, Gillen & Mc Coll showed that only five presented without alarm symptoms and that all five of these patients had evidence of metastasis at presentation.[68] This study suggests that, in the absence of alarm symptoms, dyspeptic symptoms in patients less than 55 years may be an appropriate age cut-off for non-invasive testing.

Across Europe there is a wide variation in the national incidence of gastric cancer (per 100 000) with Portugal (31.9), Austria (21.6) and Italy (20.7) having the highest incidence and the lowest incidence in Denmark (8.9), France (10.3) and Sweden (10.6).[69] In countries with a high prevalence of *H. pylori* infection where the incidence of gastric cancer is also high it may be necessary to recommend endoscopy at a younger age as suggested by Dzuba *et al.* who proposed screening with endoscopy in those over 30 years of age in Russia.[70]

One of the benefits of endoscopy is that it allows detection of precancerous lesions and also permits continued surveillance thereafter. Uemura *et al.* showed that among patients infected with *H. pylori*, those with severe gastric atrophy, intestinal metaplasia and corpus predominant gastritis were at the highest risk of developing gastric cancer.[14] Whiting *et al.* have recently shown, in a study of 1753 patients attending for open access endoscopy where 166 patients were subsequently selected to undergo annual endoscopic surveillance, that the risk of malignancy was 11% in those patients who had atrophic gastritis or intestinal metaplasia at their initial endoscopy. Furthermore annual endoscopic surveillance allows the detection of most new cancers at an early stage with improvement in the 5-year survival from 10% to 50%.[71]

RECOMMENDATIONS

Current European guidelines suggest that in areas of low prevalence of *H. pylori* infection, and in the absence of alarm symptoms or a family history of gastric cancer, a 'test and treat' approach is suitable for patients aged < 45 years. In areas of high prevalence of *H. pylori* the age cut-off for endoscopy may need to be reduced to minimize the risk of missing early gastric cancer.

H. pylori infection is a major public health issue and gastric cancer remains an important disease with a high mortality once diagnosed. Widespread population screening and eradication of *H. pylori* may have the potential to reduce the incidence of gastric cancer but further large scale studies are warranted to answer this question. Targeted screening and eradication of *H. pylori* infection, apart from alleviation of dyspepsia may have other beneficial effects and should be promoted as an important public health issue.

REFERENCES

1 Malfertheiner P, Megraud F, O'Morain C, and the European Helicobacter pylori Study Group. Current concepts in the management of *Helicobacter pylori* infection – The Maastricht 2–2000 Consensus Report. Aliment Pharmacol Ther 2002; 16: 167–80.

2 McColl KEL, Murray LS, Gillen D, *et al.* A randomized trial of endoscopy with testing for *Helicobacter pylori* compared with non-invasive *H. pylori* testing alone in the management of dyspepsia. Br Med J 2002; 324: 999–1002.

3 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Helicobacter pylori*. In: Schistosomes, Liver Flukes and *Helicobacter pylori*: Views and Expert Opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon: IARC, 1994: 177–240.

4 Schandl L, Malfertheiner P, Ebert MP. Prevention of gastric cancer by *Helicobacter pylori* eradication? Results from clinical intervention studies. Dig Dis 2002; 20(1): 18–22.

5 Ekstrom AM, Held M, Hansson L, Engstrand L, Nyren O. *Helicobacter pylori* in gastric cancer established by CagA immunoblot as a marker of past infection. Gastroenterology 2001; 121: 784–91.

6 Kuipers EJ, Garcia-Casanova M, Pena AS, *et al. Helicobacter pylori* serology in patients with gastric carcinoma. Scand J Gastroenterol 1993; 28: 433–7.

7 Estevens J, Fidalgo P, Tendeiro T, *et al.* Anti-*Helicobacter pylori* antibodies prevalence and gastric adenocarcinoma in Portugal: report of a case-control study. Eur J Cancer Prev 1993; 2: 377–80.

8 Muszynski J, Dzierzanowska D, Sieminska J, Bogdanska M, Vogt E, Ehrmann A. Is *Helicobacter pylori* infection a real risk factor for gastric carcinoma? Scand J Gastroenterol 1995; 30: 647–52.

9 Rudi J, Muller M, von Herbay A, *et al.* Lack of association of *Helicobacter pylori* seroprevalence and gastric cancer in a population with low gastric cancer incidence. Scand J Gastroenterol 1995; 30: 958–63.

10 Kato S, Onda M, Matsukura N, *et al.* Genetic polymorhisms of the cancer related gene and *Helicobacter pylori* infection in Japanese gastric cancer patients. Cancer 1996; 77: 1654–61.

11 Parsonnet J. *Helicobacter pylori* infection and gastric cancer. Gastroenterol Clin North Am 1993; 22: 89–104.

12 Helicobacter and Cancer Collaborative Group. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. Gut 2001; 49: 347–53.

13 Forman D, Webb P, Parsonnet J. *H. pylori* and gastric cancer. Lancet 1994; 343: 243–4.

14 Uemura N, Okamoto S, Yamamoto S, *et al. Helicobacter pylori* infection and the development of gastric cancer. NEJM 2001; 345: 784–9.

15 Tabata H, Fuchigami T, Kobayashi H, *et al. Helicobacter pylori* and mucosal atrophy in patients with gastric cancer: a special study regarding the methods for detecting *Helicobacter pylori*. Dig Dis Sci 1999; 44: 2027–34.

16 Chen X, Haruma K, Kamada T, *et al.* A low 13C urea breath test value is associated with increased risk of gastric cancer. J Gastroenterol 2001; 36: 601–5.

17 Correa P. Human gastric carcinogenesis. a multistep and multifactorial process – First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 1992; 52: 6735–40.

18 Craanen ME, Dekker W, Blok P, Ferwerda J, Tytgat GNJ. Intestinal metaplasia and *Helicobacter pylori*; an endoscopic bioptic study of the gastric antrum. Gut 1992; 33: 16–20.

19 Kuipers EJ, Uyterlinde AM, Pena AS, *et al.* Long term sequelae of *Helicobacter* gastritis. Lancet 1995; 345: 1525–8.

20 Banerjee S, Hawksby C, Miller S, Dahill S, Beattie AD, McColl K. Effect of helicobacter and its eradication on gastric juice ascorbic acid. Gut 1994; 35: 317–22.

21 Cahill RJ, Xia H, Kilgallen C, Beattie S, Hamilton H, O'Morain C. Effect of eradication of H. pylori infection on gastric epithelial cell proliferation. Dig Dis Sci 1995; 40: 1627–31.

22 Lynch DAF, Mapstone NP, Clarke AMT, *et al.* Cell proliferation in *Helicobacter pylori* associated gastritis and the effect of eradication therapy. Gut 1995; 36: 346–50.

23 Moss SF, Calam J, Agarwal B, Wang S, Holt PR. Induction of gastric epithelial apoptosis by *Helicobacter pylori*. Gut 1996; 38: 498–501.

24 Huang JQ, Sridhar S, Chen Y, *et al.* Meta-analysis of the relationship between *Helicobacter pylori* seropositivity and gastric cancer. Gastroenterology 1998; 114: 1169–79.

25 El-Omar EM, Orein K, Murray LS, *et al.* Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature 2000; 404: 398–402.

26 Ebert M, Yu J, Miehlke S, *et al.* Expression of transforming growth factor beta 1 in gastric cancer and in the gastric mucosa of first degree relatives of patients with gastric cancer. Br J Cancer 2000; 82: 1795–800.

27 Azuma T, Ito S, Sato F, *et al.* The role of the HLA-DQA1 gene in resistance to atrophic gastritis and gastric adenocarcinoma induced by *Helicobacter pylori* infection. Cancer 1998; 82: 1013–8.

28 Keller G, Vogelsang H, Becker I, *et al.* Diffuse type gastric and lobular breast carcinoma in a familial gastric cancer patient with en E-cadherin germline mutation. Am J Pathol 1999; 155: 3337–42.

29 Brenner H, Bode G, Boeing H. *Helicobacter pylori* infection among offspring of patients with stomach cancer. Gastroenterology 2000; 118: 31–5.

30 Peek RM, Moss SF, Tham KT, *et al. Helicobacter pylori* cag A strains and dissociation of gastric epithelial cell proliferation from apoptosis. J Natl Cancer Inst 1997; 89: 863–8.

31 Crabtree JE, Covacci A, Farmery SM, *et al. Helicobacter pylori* induced interleukin-8 expression in gastric epithelial cells is associated with Cag A positive phenotype. J Clin Pathol 1995; 48: 41–5.

32 Huang J, O'Toole PW, Doig P, Trust TJ. Stimulation of interleukin-8 production in epithelial cell lines by *Helicobacter pylori*. Imfect Immun 1995; 63: 1732–8.

33 Sharma SA, Tummuru MK, Miller GG, Blaser MJ. Interleukin-8 response of gastric epithelial cell lines to *Helicobacter pylori* stimulation in vitro. Infect Immun 1995; 63: 1681–7.

34 Blaser MJ. *Helicobacter pylori* phenotypes associated with peptic ulceration. Scand J Gastroenterol Suppl 1994; 205: 1–5.

35 Parsonnet J, Friedman GD, Orentreich N, Vogelman H. Risk for gastric cancer in people with Cag A positive or Cag A negative *Helicobacter pylori* infection. Gut 1997; 40: 297–301.

36 Papa A, Danese S, Sgambato A, *et al.* Role of *Helicobacter pylori* CagA + infection in determining oxidative DNA damage in gastric mucosa. Scand J Gastroenterol 2002; 37: 409–13.

37 Miehlke S, Yu J, Schuppler M, *et al. Helicobacter pylori* vacA, iceA and cagA status and pattern of gastritis inpatients with malignant and benign gastroduodenal disease. Am J Gastroenterol 2001; 96(4): 1008–13.

38 Louw JA, Kidd MS, Kummer AF, Taylor K, Kotze U, Hanslo D. The relationship between *Helicobacter pylori* infection, the virulence genotypes of the infecting strain and gastric cancer in the African setting. Helicobacter 2001; 6(4): 268–73.

39 Yu J, Leung WK, Go MYYY, *et al.* Relationship between *Helicobacter pylori* babA2 status with gastric epithelial cell turnover and premalignant gastric lesions. Gut 2002; 51: 480–4.

40 Hara T, Ooi A, Kobayashi M, *et al.* Amplification of c-myc, k-sam and c-met in gastric cancers: detection by fluorescence in situ hybridization. Lab Invest 1998; 78: 1143–53.

41 Park JB, Rhim JS, Park SC, *et al.* Amplification, overexpression and rearrangement of the c-erbB2 protooncogene in primary human stomach carcinomas. Cancer Res 1989; 49: 6605–9.
42 Ranzani GN, Luinetti O, Padovan LS, *et al.* p53 gene mutations and protein nuclear accumulation are early events in intestinal type gastric cancer but late events in diffuse type. Cancer Epidemiol Biomark Prev 1995; 4: 223–31.
43 Hsieh LL, Huang YC. Loss of heterozygosity of APC/MCC gene in differentiated and undifferentiated gastric carcinoma in Taiwan. Cancer Lett 1995; 96: 169–74.
44 Hiyama T, Haruma K, Kitadai Y, *et al.* K-ras mutation in *Helicobacter pylori*-associated chronic gastritis in patients with and without gastric cancer. Int J Cancer 2002; 97: 409–13.
45 Kakeji Y, Maehara Y, Koga T, *et al.* Gastric cancer with high telomerase activity shows rapid development and invasiveness. Oncol Rep 2001; 8: 107–10.
46 Sepulveda AR, Tao H, Carloni E, Sepulveda J, *et al.* Screening of gene expression profiles in gastric epithelial cells induced by *Helicobacter pylori* using microarray analysis. Aliment Pharmacol Ther 2002; 16: 145–57.
47 Tamura G, Yin J, Wang S, *et al.* E-cadherin gene promoter hypermethylation in primary human gastric carcinomas. J Natl Cancer Inst 2000; 92: 569–73.
48 Leung SY, Yuen ST, Chung LP, *et al.* hMLH1 promoter methylation and lack of hMLH1 expression in sporadic gastric carcinomas with high-frequency microsatellite instability. Cancer Res 1999; 59: 159–64.
49 Van der Hulst RWM, van der Ende A, Dekker FW, *et al.* Effect of *Helicobacter pylori* eradication on gastritis in relation to cagA: a prospective 1-year follow up study. Gastroenterology 1997; 113: 25–30.
50 Forbes GM, Warren JR, Glaser ME, Cullen DJE, Marshall BJ, *et al.* Long-term follow-up of gastric histology after *H. pylori* eradication. J Gastroenterol Hepatol 1996; 11: 670–3.
51 Annibale B, Aprile MR, D'ambra G, *et al.* Cure of *Helicobacter pylori* infection in atrophic body gastritis patients does not improve mucosal atrophy but reduces hypergastrinaemia and its related effects on body ECL-cell hyperplasia. Aliment Pharmacol Ther 2000; 14: 625–34.
52 Correa P, Fontham ETH, Bravo JC, *et al.* Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter therapy. J Natl Cancer Inst 2000; 92: 1881–8.
53 Ohkusa T, Fujike K, Takashimizu I, *et al.* Improvement in atrophic gastritis and intestinal metaplasia in patients in whom *Helicobacter pylori* was eradicated. Ann Intern Med 2001; 134: 380–6.
54 Sung JJY, Lin SR, Ching JYL, *et al.* Atrophy and intestinal metaplasia one year after cure of *H. pylori* infection: a prospective, randomized study. Gastroenterology 2000; 119: 7–14.
55 Kokkola A, Sipponen P, Rautelin H, *et al.* The effect of *Helicobacter pylori* eradication on the natural course of atrophic gastritis with dysplasia. Aliment Pharmacol Ther 2002; 16: 515–20.
56 Ito M, Haruma K, Kamada T, *et al. Helicobacter pylori* eradication therapy improves atrophic gastritis and intestinal metaplasia: a 5-year prospective study of patients with atrophic gastritis. Aliment Pharmacol Ther 2002; 16: 1449–56.
57 Genta RM. Atrophy, metaplasia and dysplasia: are they reversible? Ital J Gastroenterol Hepatol 1998; 30: 324–5(S).
58 Fendrick AM, Chernew ME, Hirth RA, Bloom BS, Bandekar RR, Scheiman JM. Clinical and economic effects of population-based *Helicobacter pylori* screening to prevent gastric cancer. Arch Intern Med 1999; 159: 2483–4.
59 Kituchi S, Wada O, Nakajima T, *et al.* Association between gastric cancer and *H. pylori* with reference to age. Gut 1995; 37(S1): A8(Abstract).
60 Enroth H, Kraaz W, Rohan T, Nyren O, Engstrand L. Does the method of *Helicobacter pylori* detection influence the association with gastric cancer risk. Scand J Gastroenterol 2002; 37: 884–90.
61 Ohara S, Kato M, Asaka M, Totota T. Studies of 13C-urea breath test for diagnosis of *Helicobactor pylori* infection in Japan. J Gastroenterol 1998; 33: 6–13.
62 The European HpSA Study Group. Diagnosis of *Helicobacter pylori* with a new non-invasive antigen-based assay. Lancet 1999; 354: 30–3.
63 Vaira D, Vakil N, Menegatti M, *et al.* The stool antigen test for detection of *Helicobacter pylori* after eradication therapy. Ann Intern Med 2002; 136: 280–7.
64 Dore MP, Wengler G, Tadeu V, *et al.* A novel monoclonal antibody test to detect *H. pylori* antigens in human stool. Gut 2002; 51(S11): A108. (Abstract)
65 Kitahara F, Kobayashi K, Sato K, *et al.* Accuracy of screening for gastric cancer using serum pepsinogen concentration. Gut 1999; 44(5): 693–7.
66 Ito M, Haruma K, Kaya S, *et al.* Role of anti-parietal cell antibody in *Helicobacter pylori* associated agrophic gastritis: evaluation in a country of high prevalence of atrophic gastritis. Scand J Gastroenterol 2001; 3: 287–93.
67 Konturek SJ, Starzynska T, Konturek P, *et al. Helicobacter pylori* and CagA status, serum gastrin, interleukin-8 and gastric acid secretion in gastric cancer. Scand J Gastroenterol 2002; 37: 891–8.
68 Gillen D, McColl KEL. Does concern about missing malignancy justify endoscopy in uncomplicated dyspepsia in patients aged less than 55? Am J Gastroenterol 1999; 94(8): 2329–30.
69 Black RJ, Bray F, Ferlay J, Parkin DM. Cancer incidence and mortality in the European Union. Cancer registry data and estimates of national incidence for 1990. Eur J Cancer 1997; 33: 1075–107.
70 Dzuba LP, Domareva IV, Ganskaya ZJ, *et al.* The use of test and treat strategy in country with high prevalence of *H. pylori* infection. Gut 2002; 51(S11): A109. (Abstract).
71 Whiting JL, Sigurdsson A, Rowlands DC, Hallissey MT, Fielding JWL. The long term results of endoscopic surveillance of premalignant gastric lesions. Gut 2002; 50: 378–81.