HELICOBACTER PYLORI

Helicobacter pylori was considered by a previous IARC Working Group in 1994 (IARC, 1994). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

Helicobacter pylori is a highly heterogenous bacterium with a large genomic diversity. In addition, humans may sometimes harbour multiple strains, and *H. pylori* can change genotypically and phenotypically during colonization in a single host (Suerbaum & Josenhans, 2007).

1.1 Taxonomy, structure, and biology

1.1.1 Taxonomy

The presence of spiral-shaped bacteria on human gastric mucosa was first recognized nearly one hundred years ago (Pel, 1913). These bacteria were originally named *Campylobacter pylori* (*C. pylori*) (Warren, 1983).

In 1989, a new genus, *Helicobacter*, was proposed, and *C. pylori* was renamed *Helicobacter pylori* (Goodwin *et al.*, 1989). Recently (Garrity *et al.*, 2005), the genus *Helicobacter* has been included with the genus *Wolinella* in the family *Helicobacteraceae* which, with the family *Campylobacteraceae*, constitutes the *Epsilonproteobacteria*.

Over the past 20 years, 23 *Helicobacter* species have been validated, and two candidates and several strains are awaiting official classification (Table 1.1).

According to the usual site of colonization, *Helicobacter* species can be divided into gastric and enteric or enterohepatic *Helicobacter* types.

Some gastric *Helicobacter* species from animals can infect humans: *H. bizzozeroni*, *H. salomonis*, *H. felis*, *H. candidates, H. suis*. Bacausee they are extremely difficult to grow in cultures, the exact speciation is usually not done, and they are known as "*Gastrospirullum hominis*" or "*H. heilmannii*" (De Groote *et al.*, 2005).

1.1.2 Structure of the bacterium

H. pylori is a spiral or slightly curved Gram-negative rod with 2–6 characteristic unipolar flagella. The bacterium has bluntly rounded ends and measures 2.5–4.0 μm in length and 0.5–1.0 μm in width. The cell wall is smooth and may be coated with a prominent glycocalyx with a thickness of up to 40 nm (Goodwin *et al.*, 1989); it is covered with ring-like subunits with a diameter of 12–15 nm. Occasionally, the bacterium may contain bacteriophages. The flagella measure 2.5 μm in length and around 30 nm in thickness, and have a distinctive terminal bulb (Goodwin & Worsley, 1993). The bacterium

Table 1.1 Validated species of the genus *Helicobacter*

Species
Helicobacter pylori
Helicobacter acinonychis
Helicobacter aurati
Helicobacter bilis
Helicobacter bizzozeronii
Helicobacter canadensis
Helicobacter canis
Helicobacter chrolecystus
Helicobacter cinaedi
Helicobacter felis
Helicobacter fennelliae
Helicobacter ganmani
Helicobacter hepaticus
Helicobacter mesocricetorum
Helicobacter muridarum
Helicobacter mustelae
Helicobacter nemestrinae
Helicobacter pametensis
Helicobacter pullorum
Helicobacter rodentium
Helicobacter salomonis
Helicobacter trogontum
Helicobacter typhonius
Candidatus Helicobacter bovis
Candidatus Helicobacter suis

displays remarkable motility in viscous solutions, and the flagella play a central role in this motility (Hazell *et al.*, 1986; Suerbaum *et al.*, 1993).

In certain circumstances, *H. pylori* can evolve from this typical helical form to a coccoidal form. Some studies suggested that they are live organisms (Sisto *et al.*, 2000; Willén *et al.*, 2000), but others concluded that they are degenerating organisms (Kusters *et al.*, 1997).

1.1.3 Structure of the genome

The genome of three *H. pylori* strains has now been fully sequenced: strain 26695 from a patient with gastritis, strain J99 from a duodenal ulcer patient, and strain HPAG1 from a patient with chronic atrophic gastritis (Tomb *et al.*, 1997; Alm *et al.*, 1999; Oh *et al.*, 2006).

Strains 26695, J99 and HPAG1 have a circular chromosome of 1667867 base pairs (bp), 1643831 bp and 1596366 bp, respectively. HPAG1 also has a single 9369 bp plasmid, pHPAG1.

The percentage of genome-coding sequences of strains 26695, J99 and HPAG1 is around 92%, and they contain 1552 (Alm *et al.*, 1999; Boneca *et al.*, 2003), 1495 (Tomb *et al.*, 1997; Alm *et al.*, 1999), and 1536 (Oh *et al.*, 2006) predicted protein-coding genes, respectively. In these three small genomes, 1379 open reading frames (ORFs) are common to all three strains and about 10% of the genes are strain-specific (Alm *et al.*, 1999); 117 and 89 genes present in strains 26695 and J99, respectively, are absent in the other strain (Alm *et al.*, 1999); in contrast, 43 of the HPAG1 genes are either not detectable at all or incompletely represented in the 26695 and J99 genomes (Oh *et al.*, 2006).

A comparison of the three genomic sequences revealed that the genetic organization was similar in all three strains. However, it confirmed the panmictic structure of *H. pylori*, which is the result of a high mutation rate (microdiversity, i.e. high polymorphism among orthologous genes), and free recombinations (Falush *et al.*, 2003). A significant macrodiversity (presence or absence of the genes) was also observed (Raymond *et al.*, 2004). A comparative genomic analysis of isolates from 15 Caucasians (Salama *et al.*, 2000) allowed to extend the pool of strain-specific genes from 6–7% (as determined from the comparison of the first two sequenced genomes) to 18–22%. More recently, a large study was conducted on 56 *H. pylori* strains and four *H. acinonychis* strains, with whole genome microarrays. They concluded that the core genome present in all *H. pylori* isolates contains 1111 genes, with a weighted average of 27% of the genome variably present in different isolates (Gressmann *et al.*, 2005).

Besides the *cag* pathogenicity island, which is known to be a variable region, half of the

strain-specific genes are clustered in a hypervariable region, known as the 'plasticity zone' (Salama *et al.*, 2000). The group of genes containing the most variability are those that comprise genes of unknown function (44%), genes associated with DNA metabolism (most of them are restriction-modification systems 54%), outer-membrane proteins (22%), cellular processes/*cag*PAI (40%) and others (100%, including transposases) (Gressmann *et al.*, 2005).

The genomic analyses suggest that *H. pylori* strains have essentially identical metabolic potential (Table 1.2).

1.1.4 Host range

H. pylori is the *Helicobacter* species of humans. *H. pylori* isolation from several other animal species (monkey, pig, cat, dog) has been reported, but these reports were anecdotal, and these bacteria were most likely acquired from humans.

1.1.5 Target cells and tissues

The target cell of *H. pylori* is the gastric mucus-secreting cells. A low acid output leads *H. pylori* to also infect the corpus (Louw *et al.*, 1993). *H. pylori* lives mainly in the surface mucus layer and within the pits, and can adhere to mucus-secreting cells especially close to intercellular junctions (Hazell *et al.*, 1986). It is not found on intestinal-type cells in the case of intestinal metaplasia. In contrast, it has the ability to colonize metaplastic gastric cells present in the duodenum and elsewhere, for example, in the oesophagus, in Meckel's diverticulum, and in the rectum (Hill & Rode, 1998).

The main cell receptor for this adherence is the blood group antigen A, and the corresponding adhesin is named BabA. In a low proportion of the cells, *H. pylori* may be intracellular, a situation which contributes to its persistence (Dubois & Borén, 2007).

H. pylori can be present transiently in the mouth when regurgitated, and may also be found in the faeces, but it cannot survive with competing organisms (Parsonnet *et al.*, 1999).

1.1.6 Function of gene products

(a) Colonizing factors

Colonization by *H. pylori* involves an interaction between a large family of *Helicobacter* outer membrane proteins (Hop) and the gastric epithelial cells of the host. Several genes involved in determining the composition of the outer membrane are differentially regulated by a phase variation called slipped-strand repair. This phenomenon is possible due to the presence of repeated intragenic sequences, allowing replicative shifts and mismatchs, leading to changes in the status of a gene ("on/off") (Salaün *et al.*, 2004). Such proteins are the blood group antigen binding adhesion (BabA), sialic acid binding adhesion (SabA), adherence-associated lipoprotein (AlpA and AlpB), and HopZ.

Lipopolysaccharides play an important role in the interaction between Gram-negative bacteria and their host. They are potential stimulators of the immune system (Moran *et al.*, 1996). The *H. pylori* lipopolysaccharides, however, have remarkably low activity, and their synthesis may involve over 20 genes, scattered throughout the genome, unlike other bacteria in which they are grouped into a single cluster.

The expression of fucosyltransferase, an enzyme essential for the lipopolysaccharide biosynthesis pathway, is also subject to phase change, and is a key enzyme allowing *H. pylori* to mimic human Lewis antigens, which allows it to escape the host immune response (Lozniewski *et al.*, 2003).

It has been suggested that this differential regulation and the strain-specific outer-membrane-related genes may play a role in the severity of *H. pylori*-related disease, and the

Table 1.2 Classification of the genes of two *Helicobacter pylori* strains sequenced

Annotation category	No. of genes in:	
	H. pylori **J99**	*H. pylori* **26695**
Functionally classified	877	898
Aminoacid biosynthesis	44	44
Biosynthesis of cofactors etc.	60	59
Cell envelope	160	164
Cellular processes	96	113
DNA replication	23	23
DNA restriction-modification, etc.	66	68
Energy metabolism	104	104
Fatty acid and phospholipid metabolism	28	29
Purine and pyrimidine biosynthesis	34	34
Regulatory functions	32	32
Transcription	13	13
Translation	128	128
Transport and binding proteins	88	87
Conserved with no known function	275	290
***Helicobacter pylori* specific**	343	364
Total	**1495**	**1552**

From Doig *et al.* (1999)

ability of *H. pylori* to persist chronically in its host (Mahdavi *et al.*, 2002).

(i) BabA

The blood group antigen Lewis b was identified as a receptor for *H. pylori* in 1993 (Borén *et al.*, 1993). This is the dominant antigen in the gastric mucosa of secretor-positive individuals. The adhesion-recognizing Lewis b was characterized as an *H. pylori* outer-membrane protein, namely BabA (Ilver *et al.*, 1998). Another protein with almost identical amino terminal and identical carboxy terminal domains but divergent central domains, BabB, does not bind to Lewis b antigen (Aspholm-Hurtig *et al.*, 2004).

A *bab*A allele and a *bab*B allele are both present in each of the three sequenced strains, but in different locations. In the strain from which *bab* genes were initially cloned, there were two *bab*A genes but only one of them (*bab*A2) has Lewis b binding activity. According to two studies, the *bab*A gene is present in approximately 70% of *H. pylori* strains, and the *bab*B gene is present in almost them all (Colbeck *et al.*, 2006; Hennig *et al.*, 2006).

Several mechanisms have been elucidated for the regulation of BabA expression including chimera formation (Pride & Blaser, 2002) between *bab*A and *bab*B, and phase variation of *bab*A through slipped-strain mispairing (Solnick *et al.*, 2004).

To date, BabA-Lewis b is the adhesin-receptor interaction in *H. pylori* that is best characterized, and probably one of the most important (Yamaoka, 2008).

(ii) SabA

Another outer-membrane protein conferring adherence to host sialyl Lewis x was identified as sialic acid-binding adhesin (SabA) (Mahdavi *et al.*, 2002). The sialyl-Lewis x expression is induced in the gastric epithelium during persistent *H. pylori* infection, suggesting that the bacterium can trigger the host tissue to modify

the mucosal glycosylation patterns for enhanced adherence. The event could occur via induction of 3GnT5, a GlcNAc transferase essential for the biosynthesis of Lewis antigens (Marcos *et al.,* 2008). SabA could in this way contribute to the chronicity of *H. pylori* infection. SabA can also bind specifically to granulocytes and induce an oxidative burst (Unemo *et al.,* 2005).

(iii)   AlpA and AlpB

A genetic locus involved in *H. pylori* adherence to Kato cells was identified in 1999 (Odenbreit, 2005). It was named *alp*AB (adherence-associated lipoprotein A and B), and encodes two outer-membrane proteins. However, because no receptor has been identified for these proteins, their role as adhesins is unclear.

(iv) HopZ

HopZ has been described as an adhesin (Peck *et al.,* 1999) but no receptor has yet been identified for this putative adhesin.

(b)   Pathogenicity factors

(i)   cag Pathogenicity island

In many parts of the world, including Asia and most of Africa, almost all *H. pylori* strains contain an intact *cag* pathogenicity island, whereas about 30% of strains from Europe and North America lack the entire island, and are considered "*cag*-negative". However, both *cag*-positive and *cag*-negative strains can exist together in the same stomach, and the *cag* pathogenicity island can be partially deleted with the loss of type 4 secretory function (Suerbaum & Josenhans, 2007), therefore, the simple designation of *cag* status as positive or negative may not be absolute. The CagA protein encoded by the *cag*A gene within the *cag* pathogenicity island is a highly immunogenic protein that elicits serum antibody responses allowing for the detection of *cag*-positive strains by enzyme-linked immunosorbent assay (ELISA)

or Western blot analysis in serum samples for epidemiological studies.

The *cag* pathogenicity island of *H. pylori* is a DNA fragment of approximately 40 kbp which exhibits the characteristics of pathogenicity islands in general: i) a G+C% different from the rest of the chromosome (35% vs 39%), ii) two direct repeat sequences at its ends, iii) several genes linked to virulence, iv) a secretion system, and v) an insertion sequence (Censini *et al.,* 1996).

This pathogenicity island is always located between the same two genes: HP519, a gene of unknown function, and *mur*I, the glutamate racemase gene. It is integrated at the 3′ end of the glutamate racemase gene and flanked by two repeated 31 bp sequences probably derived from the duplication of the 3′ end of this gene (Akopyants *et al.,* 1998). Because this island appears to be acquired *in toto*, it may then be separated into two regions, namely *cag*I and *cag*II, by an insertion sequence (IS*605*) coding for two transposases (*tnp*A and *tnp*B) (Censini *et al.,* 1996). There are 27 potential coding sequences in the *cag* pathogenicity island (Censini *et al.,* 1996).

Not all *H. pylori* strains possess the *cag* pathogenicity island. In addition, it can be lost or gained via recombination (Kersulyte *et al.,* 1999). In addition, partial deletions have been described. Among the *cag* pathogenicity island genes, six show sequence similarity with genes coding for a secretion system in other bacteria. This is a type IV secretion system, a multi-protein complex that allows the bacterium to inject specific molecules into an eukaryotic cell (Krause *et al.,* 2000). Among such translocated molecules is the product of one of the *cag* pathogenicity island genes, CagA. This immunodominant protein of 120–145 kDa was the first *H. pylori* protein to be linked to more severe disease (Crabtree *et al.,* 1991). Phosphorylated CagA was also detected inside epithelial cells infected with *H. pylori* (Yamazaki *et al.,* 2003; Higashi *et al.,* 2005).

(ii) VacA cytotoxin

A cytotoxic activity was first reported in broth culture filtrates of *H. pylori* incubated with mammalian cells *in vitro* (Leunk *et al.*, 1988). The protein responsible for the observed effect of large intracellular vacuoles was designated vacuolating cytotoxin VacA (Cover & Blaser, 1992). It is a high-molecular weight multimeric pore-forming protein encoded by the chromosomal gene *vac*A (Cover *et al.*, 1994; Schmitt & Haas, 1994; Telford *et al.*, 1994).

As with *cag*A, no close homologues of *vac*A exist in other *Helicobacter* species nor in other bacteria or eukaryotic cells. Mature 88 kDa VacA toxin molecules are secreted as soluble proteins into the extracellular space, but can also remain localized on the surface of *H. pylori* (Ilver *et al.*, 2004). The secreted toxin can assemble into oligomeric structures (Cover *et al.*, 1997; Adrian *et al.*, 2002) for insertion into planar lipid bilayers to form anion-selective membrane channels allowing anions and urea to exit (Iwamoto *et al.*, 1999; Tombola *et al.*, 1999). The microscopic analysis of VacA oligomeric complexes has shown their dissociation into monomeric components with low vacuolating potential that can be activated by pH changes.

The secreted mature 88 kDa toxin can be cleaved in two fragments: p33 and p55 (Nguyen *et al.*, 2001). The p55 domain has a role in the binding of VacA to host cells, and the p33 domain, together with 100 amino acids of the p55 domain, is sufficient to induce intracellular vacuolation (de Bernard *et al.*, 1998).

Unlike *cag*A, *vac*A is conserved among all *H. pylori* strains, but exhibits a high level of genetic diversity. Several *vac*A alleles can be distinguished on the basis of diversity in the 5′ region, namely in the signal region, (s region) s1 and s2, and in the mid-region (m region) m1 and m2 (Atherton *et al.*, 1995). Among the different combinations, the s1m1 type produces the most active vacuolating activity in different cell lines, s1m2 produces detectable vacuolation in a limited range of cell types, s2m2 is inactive, and s2m1 does not appear to exist.

More recently, a third group of alleles has been described in the intermediary region (i) – i1 and i2 (Rhead *et al.*, 2007).

A strong association between vacA s1 and *cag* pathogenicity island has been described (Van Doorn *et al.*, 1999).

1.2 Epidemiology of infection

1.2.1 Prevalence, geographic distribution

The most common test used to determine the prevalence of infection in healthy populations is serology for *H. pylori* IgG by ELISA (Vaira *et al.*, 2002; Mueller *et al.*, 2006). Serological testing for CagA antibody is more sensitive for individuals who are infected with CagA⁺ *H. pylori*, but *H. pylori* IgG ELISA is most often used in screening. Other diagnostic tests for *H. pylori* are available but less often used in large epidemiological studies or to estimate population prevalence (Mégraud & Lehours, 2007).

H. pylori infection is common, with a global prevalence of over 50%, but with substantial country-to-country variations (Parsonnet, 1998; Suerbaum & Michetti, 2002). Prevalence rates differ by age, race/ethnicity, and socioeconomic characteristics. As a rule, rates are higher in developing countries than in developed ones; however, in several eastern European countries the prevalence of infection is high.

The prevalence of infection is highest in the older age groups (The EUROGAST Study Group, 1993). The rate of *H. pylori* infection has been shown to have decreased in successive birth cohorts over the past several decades in developed countries (Roosendaal *et al.*, 1997). Banatvala *et al.* (1993) screened a total of 631 serum samples collected from adults and children in 1969, 1979, and 1989, and the cohort effect on *H. pylori* positivity was estimated by Western blot based

on year of birth. The seropositivity declined by 26% (8–41%) per decade ($P < 0.008$). Eslick (2003) reported on 451 pregnant women screened for *H. pylori* infection in Australia, and found that infection rates declined from 44% in the birth cohort of 1951–60, to 29% in the birth cohort of 1961–70, to 20% in the birth cohort of 1971–80, to 9% in the birth cohort of 1981–90.

Rothenbacher *et al.* (1998) used ^{13}C–urea breath tests for population screening of approximately 1000 preschool children as part of a physician-administered school fitness test. This demonstrated its utility for determining current infection status in a relatively large population of healthy subjects.

Because of the substantial differences in the prevalence of infection over time by age group and race/ethnicity within a country, international comparisons of the overall prevalence of *H. pylori* where the populations were tested during different time periods, and different age composition or race/ethnicity or type of test performed are crude comparisons at best, and likely to be misleading (for a review, see Everhart, 2000).

The results of the EUROGAST Study Group (The EUROGAST Study Group, 1993) illustrate the importance of age-specific prevalence estimates. In Japan, the population prevalence was 61% in the 25–34 years age group, and 89% in the 55–64 years age group; in Poland the prevalence was 69% in the 25–34 years age group, and 89% in the 55–64 years age group; in Denmark the prevalence was 15% in the 25–34 years age group, and 30% in the 55–64 years age group; in the United States of America, the prevalence rate was 15% in the 25–34 years age group, and 34% in the 55–64 years age group.

Similar variations are seen within the USA between racial and ethnic groups. Hyams *et al.* (1995) conducted serological testing of 1000 military personnel aged 17–50 years. The overall prevalence of infection in the group was 25%, ranging from 18% in Caucasians to 45% in Hispanics and 46% in Blacks, with other races at 29%. More

recently Everhart *et al.* (2000) conducted a larger seroprevalence survey in the USA in which 7465 adults were tested for *H. pylori* by IgG ELISA. The overall seroprevalence was 32.5%. It was substantially higher among non-Hispanic blacks (52.7%) and Mexican-Americans (61.6%) than among non-Hispanic Caucasians (26.2%).

1.2.2 Transmission

(a) Person-to-person route

Humans are the only known significant reservoir of *H. pylori* (Oderda, 1999). Person-to-person contact is believed to be the primary route of transmission in developed countries, and is also important in developing countries. Close personal contact, particularly within the family including mother/parents to child, sibling to sibling and spouse to spouse, has been consistently demonstrated as a risk factor for transmission of infection (Dominici *et al.*, 1999; Escobar & Kawakami, 2004).

Brenner *et al.* (2006) determined current *H. pylori* infection in 670 spousal pairs by ^{13}C-Urea breath yest and monoclonal antigen immunoassay for *H. pylori* in stool. The prevalence of infection was significantly greater in women with infected partners, compared to women whose partner was not infected (34.9% vs 14.5%).

Person-to-person transmission can occur in several ways. Parsonnet *et al.* (1999) conducted a controlled clinical experimental study to determine how humans shed *H. pylori* into the environment. A total of 16 asymptomatic individuals positive for *H. pylori* were administered a cathartic and an emetic and 1/10 participating *H. pylori*-negative individuals was given an emetic. Stool and vomitus samples were collected. All vomitus specimens from *H. pylori* positive individuals grew *H. pylori* (confirmed by polymerase chain reaction (PCR)). Air was sampled during vomiting and *H. pylori* were grown from 6 of 16 samples (37.5%). Small quantities of *H. pylori* were grown in three (18.8%) and nine (56.3%)

saliva samples obtained from subjects before and after emesis, respectively. Cultures from 7/14 (50%) positive subjects had at least one positive culture and 22/101 cathartic stools (21.8%) grew *H. pylori*. Samples from negative subjects did not grow the organism on culture.

Transmission of *H. pylori* was also examined by Perry *et al.* (2006) who tested 2752 household members for *H. pylori* in serum or stool at baseline and then again 3 months later. A total of 30 new infections occurred among 1752 persons uninfected at baseline. Exposure to a household member with gastroenteritis was associated with a relative risk of 4.8 (95%CI: 1.4–17.1) for definite or probable new infection. Risk of infection was greater for exposure to vomiting (odds ratio (OR), 6.3) than to diarrhoea (OR, 3.0).

Significantly higher than expected prevalence rates of *H. pylori* infection have been observed in institutionalized adults and children (Malaty *et al.*, 1996; Böhmer *et al.*, 1997).

(b)   Oral-oral route

H. pylori DNA has been detected in the saliva of *H. pylori*-positive subjects by PCR (Namavar *et al.*, 1995; Madinier *et al.*, 1997). *H. pylori* organisms have also been successfully detected from the dental plaque of infected persons (Nguyen *et al.*, 1993). In general, isolation has not been uniformly successful, however, perhaps as a result of the transient presence of *H. pylori* in the oral cavity or poor detection capability resulting from the co-occurrence of many other bacteria in the oral cavity.

(c)   Faecal-oral route

H. pylori has been detected in faeces by culture and its DNA by PCR (Kelly *et al.*, 1994; Namavar *et al.*, 1995), although other investigators have failed to replicate this (van Zwet *et al.*, 1994). One study found detectable DNA in the faeces of 73% of known infected subjects (Gramley *et al.*, 1999). These data, together with those from Parsonnet *et al.* (1999), document the possible role of faecal shedding of *H. pylori* into the environment.

(d)   Waterborne transmission

Studies in the People's Republic of China and in Latin America found that the source of water used for consumption, bathing or swimming could possibly be associated with *H. pylori* infection (Goodman *et al.*, 1996; Zhang *et al.*, 1996). Contamination of drinking-water and sewage water has been demonstrated. Hegarty *et al.* (1999) found *H. pylori* in 60% of the samples of surface water, and 65% of the shallow ground water collected in several states in the USA. A Japanese study also reported *H. pylori* contamination of water from rivers and ponds (Sasaki *et al.*, 1999).

(e)   Iatrogenic transmission

Endoscopes used routinely in upper gastrointestinal procedures may be the source of iatrogenic infection as a result of improper disinfection between procedures (Langenberg *et al.*, 1990; Tytgat, 1995).

1.2.3 Risk factors for infection

The best established risk factor for *H. pylori* infection is low socioeconomic status, particularly during childhood when initial infection generally occurs (Malaty & Graham, 1994). Both education and income as components of socioeconomic status are inversely related to risk of infection (Replogle *et al.*, 1995). Factors closely linked to socioeconomic status that appear to contribute to this inverse relation between poverty and risk of infection include hygienic conditions, household density/crowding, and the number of young children in the household (Goodman *et al.*, 1996; Ford *et al.*, 2007).

Neither smoking nor alcohol were found to be associated with the prevalence of *H. pylori* seropositivity in the large EUROGAST study of 17 asymptomatic populations (The EUROGAST

Study Group, 1993). Because the literature is inconsistent, the most recent studies also report no significant association between *H. pylori* infection and tobacco use (Brown, 2000). Alcohol, particularly wine consumption, was found to have an inverse association with *H. pylori* infection in several studies (Brenner *et al.*, 1997, 1999a, b). Other studies have also found modest reductions in risk that were not statistically significant (Fontham *et al.*, 1995; Peach *et al.*, 1997).

1.2.4 Persistence, latency, and natural history of infection

Acquisition of *H. pylori* infection typically occurs in childhood (Malaty & Graham, 1994; Goodman *et al.*, 1996; Brown, 2000). Once infection is established, it usually lasts for life, unless treated. At present there is no vaccine available, and the treatment of infection is generally a 2-week course of triple therapy consisting of an antisecretory agent, and two antibiotics.

H. pylori antibody titre has been shown to decline over the progression of premalignant lesions, and impacts the validity of serology, particularly in retrospective studies. Kokkola *et al.* (2003) followed 47 men with advanced *H. pylori*-positive atrophic corpus gastritis by endoscopy over a 6-year period, and by serum levels of pepsinogen I and antibodies to *H. pylori* over a 10-year period. None was treated for *H. pylori* infection during the study. The mean *H. pylori* antibody titres (IgG and IgA) declined during the course of follow-up, and 11 (23%) men converted to a seronegative status, and no significant changes were observed in the grade of atrophy or intestinal metaplasia in the antrum, or in the grade of intestinal metaplasia in the corpus. Using material from a population-based case–control study, Ekström *et al.* (2001) re-evaluated the association between *H. pylori* and gastric cancer by comparing ELISA assay against *H. pylori* IgG with immunoblot against CagA antibodies to detect evidence of past *H. pylori*

infection. Among cases, the seroprevalence of *H. pylori* was around 70% by ELISA and around 90% by immunoblot; among controls, the seroprevalence was similar by the two methods (55% positive). The odds ratios relating *H. pylori* exposure to gastric cancer substantially increased when CagA antibody positivity rather than *H. pylori* IgG ELISA was used to classify past exposure.

Yoo *et al.* (2007) examined the positivity of several currently available diagnostic tests for *H. pylori* when atrophic gastritis and/or intestinal metaplasia, and presumably more advanced lesions as well, are present. The CLO test (based on urease activity), has lower sensitivity in cases of both atrophy or intestinal metaplasia. Histological identification of *H. pylori* with Giemsa stain was markedly reduced as the degree of intestinal metaplasia increased ($P < 0.01$), but was not affected in cases of atrophy only. The culture test was not affected except at the highest grade of atrophy or intestinal metaplasia, with 0% positivity.

2. Cancer in Humans

2.1 Cancer of the stomach

The previous *IARC Monograph* (IARC, 1994) reviewed results from four cohort and nine case–control studies that considered gastric carcinoma. Since its publication, results from several further cohort studies have been published. Some of these, together with the cohort studies presented in the earlier *Monograph*, were included in a pooled reanalysis (Helicobacter and Cancer Collaborative Group, 2001).

In analysing the relationship between gastric carcinoma and *H. pylori*, there is a specific bias in retrospective determination of *H. pylori* status in that precancerous subjects may undergo a loss of infection, thus producing an underestimate of prevalence in cases but not in controls (Kokkola *et al.*, 2003; Yoo *et al.*, 2007). For this

reason, relatively little weight is given to case–control studies in the assessment of the relationship between gastric carcinoma and *H. pylori*, although some are cited below as they provide specific evidence.

Since the previous *IARC Monograph*, it has also been reported that *H. pylori* appears to have a different relationship with gastric carcinoma arising in the region of the stomach distal to the cardia (non-cardia gastric carcinoma) compared with the cardia region located adjacent to the oesophageal sphincter. As a consequence, the following presentation of results, where possible, distinguishes non-cardia from cardia gastric carcinoma.

2.1.1 Non-cardia gastric carcinoma

Results are available from 17 prospective cohort studies with nested case–control designs and six further full cohort studies. Whereas the nested case–control comparisons all specify cases defined as non-cardia gastric carcinoma, for the full cohort studies, incident cancers are generally defined as gastric carcinoma without further subsite specification. [The Working Group noted that in the main, these can be assumed to be of the non-cardia.]

(a) Nested case–control analyses within cohort studies

These are summarized in Table 2.1 (available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.1.pdf). The pooled reanalysis (Helicobacter and Cancer Collaborative Group, 2001) presented results based on 762 cases of non-cardia gastric carcinoma and 2250 control subjects derived from 12 independent prospective cohort studies in nine countries (China, Finland, Iceland, Japan, Norway, Sweden, Taiwan (China), the United Kingdom, and USA). The overall matched odds ratio for the risk of non-cardia gastric carcinoma was 2.97 (95%CI: 2.34–3.77), and odds ratios for

individual studies varied from 1.52–11.1. There were no substantive differences in the odds ratios between men and women or between gastric carcinoma with intestinal or diffuse histological type. Younger cases at diagnosis had a higher odds ratio than older cases (OR, 7.10; 95%CI: 2.93–17.2, for those aged < 50 years at diagnosis).

Six of the individual studies included in the pooled reanalysis accrued more cases, and updated results have since been published (Nomura *et al.*, 2002a; Kamangar *et al.*, 2006a, 2007; Knekt *et al.*, 2006; Hansen *et al.*, 2007; Simán *et al.*, 2007). Using ELISA for *H. pylori* IgG to determine *H. pylori* infection status, odds ratios in these studies varied from 1.6–7.9, and all were statistically significant. One study (Simán *et al.*, 2007) used immunoblot against *H. pylori* or CagA to determine infection status, and reported an increase in the odds ratios from 11.1 using ELISA (Simán *et al.*, 1997) to 16.8 or 17.8 respectively, using immunoblot.

New results have been reported from four further prospective studies with nested case–control designs (Shin *et al.*, 2005; Sasazuki *et al.*, 2006; Palli *et al.*, 2007; Mitchell *et al.*, 2008). Using ELISA for IgG to determine *H. pylori* infection status, odds ratios for non-cardia gastric carcinoma varied from 1.07–5.10, and two were statistically significant (Sasazuki *et al.*, 2006; Palli *et al.*, 2007). One study (Mitchell *et al.*, 2008) also used immunoblot to determine infection status, and reported an increase in the odds ratio from 2.3 using ELISA to 10.6 using immunoblot.

[The Working Group noted that some of the variations between study results may result from variation in the sensitivity and specificity of the original ELISA assays used (Feldman *et al.*, 1995). The Working Group noted the substantial increase in estimated odds ratios in recent studies using immunoblot assays (Simán *et al.*, 2007; Mitchell *et al.*, 2008).]

In the pooled reanalysis (Helicobacter and Cancer Collaborative Group, 2001), when the results were stratified by period of follow-up, the

odds ratio for non-cardia gastric carcinoma with cases diagnosed less than 10 years after recruitment was 2.39 (95%CI: 1.82–3.12), and for those with cases diagnosed 10 or more years after recruitment, 5.93 (95%CI: 3.41–10.3). A similar relationship in the magnitude of the odds ratio with period of follow-up was reported in two of the updated studies (Nomura *et al.*, 2002a; Knekt *et al.*, 2006), but not in two others (Kamangar *et al.*, 2006a, 2007). A study from Iceland, of which preliminary results were included in the pooled reanalysis, has been reanalysed taking into account quantitative changes in antibody titre between the time of initial blood sample and the diagnosis of gastric carcinoma (Tulinius *et al.*, 2001). Repeat blood samples were available from 23/41 of the original gastric carcinoma cases, and 128 controls matched for sex, age, time, and number of repeat samples. The odds ratio for gastric carcinoma (predominantly non-cardia) was 1.16 (95%CI: 1.05–1.28) for those showing a decline in antibody titre compared with those with constant or rising levels.

(b) Cohort studies

These studies are summarized in Table 2.2 (available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.2.pdf). Three studies, two in Japan (Yamagata *et al.*, 2000; Yanaoka *et al.*, 2008) and one in China (You *et al.*, 2000) followed adult subjects undergoing health checks or general screening examinations in relation to *H. pylori* infection status. All three showed a statistically significant increased relative risk of gastric carcinoma associated with infection (in Yamagata *et al.*, 2000 only in men), with relative risks varying from 1.8–3.48.

Three further studies, two in Japan (Uemura *et al.*, 2001; Watabe *et al.*, 2005) and one in Taiwan, China (Hsu *et al.*, 2007) followed adult patients undergoing endoscopy procedures for non-malignant conditions, and found statistically significant higher rates of gastric carcinoma in *H. pylori*-positive subjects, with relative

risks [estimated by the Working Group] of 3.6 in one study (Watabe *et al.*, 2005), and infinity (no *H. pylori*-negative subjects) in the other two. None of these studies was adjusted for potential confounders.

(c) Case–control studies

In a retrospective case–control study of 234 non-cardia gastric carcinoma cases and 238 population controls in Sweden (Ekström *et al.*, 2001), the reported odds ratio when using conventional IgG ELISA to assess *H. pylori* infection status was 2.2 (95%CI: 1.4–3.6). The odds ratio increased to 21.0 (95%CI: 8.3–53.4) after exclusion from the reference group of all subjects who were ELISA-negative and CagA-positive by immunoblot [The Working Group noted that the immunoblot used was reported to be specific for CagA-positive strains of *H. pylori*.]

In a retrospective case–control study of 57 non-cardia gastric carcinoma cases and 360 controls (with colorectal cancer) in Germany (Brenner *et al.*, 2004), the reported odds ratio using an IgG ELISA to assess *H. pylori* infection status was 3.7 (95%CI: 1.7–7.9). The odds ratio increased to 18.3 (95%CI: 2.4–136.7) after exclusion from the analysis of defined groups of subjects who might have been susceptible to a misclassified serological result.

(d) Meta-analyses

Four meta-analyses of the association between gastric carcinoma and *H. pylori* infection have been published. Huang *et al.* (1998) identified 19 studies, both retrospective and prospective, including data from 2491 cases and 3959 controls. For non-cardia gastric carcinoma, the summary odds ratio was 3.08 (95%CI: 1.78–5.31) over all study designs, with evidence of significant heterogeneity. An inverse monotonic association was observed between age at diagnosis and the magnitude of the odds ratio, for non-cardia and cardia gastric carcinoma combined,

from 9.29 (95%CI: 3.43–34.04) at 20–29 years to 1.05 (95%CI: 0.73–1.52) at 70 years or older.

Danesh (1999) identified 34 retrospective and 10 nested prospective case–control studies, which included data from 3300 and 800 cases, respectively. Because of concerns about the validity of the controls, no summary estimate of the odds ratio was calculated for the retrospective studies. For the nested case–control studies, the summary odds ratio for gastric carcinoma was 2.5 (95%CI: 1.9–3.4), with no evidence of significant heterogeneity [The Working Group noted that no distinction was made between non-cardia and cardia gastric carcinoma.]

Eslick et al. (1999) identified 42 studies: eight cohort and 34 case–control designs [The Working Group noted that, unlike other meta-analyses, this included studies where the assessment of *H. pylori* status included non-serological methods.] The summary odds ratio was 2.04 (95%CI: 1.69–2.45). Cancer subsite (non-cardia vs cardia) was not a significant effect modifier. There was statistically significant heterogeneity between studies, but no evidence of publication bias.

A more recent meta-analysis focused on 16 seroprevalence studies of CagA and gastric cancer, which included a total of 2284 cases and 2770 controls from diverse geographic populations (Huang et al., 2003). Overall, ten studies provided results stratified by subsite of the tumour. Evidence of *H. pylori* infection was associated with a 2.71-fold risk of developing non-cardia gastric cancer. Because antibodies against CagA may persist longer than antibodies against other *H. pylori* components normally detectable by *H. pylori* status serology, the risk of cancer in patients who were CagA-positive but *H. pylori*-negative was also evaluated. Compared with controls who were both *H. pylori*-negative and CagA-negative, the summary odds ratio of gastric cancer (non-cardia and cardia combined) was 2.89.

(e) Impact of H. pylori CagA status

Many of the nested case–control studies identified above reported odds ratios for the risk of gastric carcinoma associated with infection with CagA-positive strains of *H. pylori* to see if disease was exclusively or predominantly associated with this genotype. In the meta-analysis by Huang et al. (2003), the analysis confined to *H. pylori*-positive cases and controls showed an additional risk of 2.01 (95%CI: 1.21–3.32) associated with CagA-positive strains.

Eight of the nested case–control studies have reported separately on results relating to CagA status (Parsonnet et al., 1997; Nomura et al., 2002a, 2005; Gwack et al., 2006; Kamangar et al., 2006a, 2007; Sasazuki et al., 2006; Palli et al., 2007; Simán et al., 2007). Five of these studies compared adjusted odds ratios for non-cardia gastric carcinoma in subjects with both CagA-positive and -negative infection status against a baseline of *H. pylori*-negative subjects. The reported odds ratios were, respectively, 5.8 vs 2.2 (Parsonnet et al., 1997), 8.93 vs 6.55 (Kamangar et al., 2006a), 6.5 vs 1.6 (Palli et al., 2007), 12.5 vs 9.5 (Sasazuki et al., 2006), and 1.58 vs 1.62 (Kamangar et al., 2007). Thus, in 4/5 studies, the odds ratio associated with CagA-positive infection was substantively greater than that for CagA-negative infection. One other study (Gwack et al., 2006), in an analysis restricted to *H. pylori*-infected individuals, reported a statistically significant increased odds ratio in relation to CagA-positive status of 3.74 (95%CI: 1.10–12.73) compared with CagA-negative status, even though the risk associated with *H. pylori per se* was not significant (Shin et al., 2005). In the other two nested case–control studies reporting on CagA-positive status (Nomura et al., 2002a; Simán et al., 2007), odds ratios were decreased in comparison with those for *H. pylori* infection alone.

(f)   Impact of H. pylori eradication

Results are available from six randomized intervention studies in which the subsequent risk of gastric carcinoma or gastric precancerous lesions has been evaluated in *H. pylori*-infected adult subjects who were randomized to receive *H. pylori* eradication therapy or placebo/no treatment (see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.3.pdf). Only one study (Wong *et al.*, 2004) was specifically designed to analyse gastric carcinoma outcomes. A total of 1630 *H. pylori* positive subjects undergoing endoscopy were followed up for a mean of 7.5 years after being randomized to eradication therapy (n = 817) or placebo (n = 813). The therapy was successful in eradicating the infection in 84% of subjects in the intervention arm. There were 7 (0.86%) and 11 (1.35%) incident cases of gastric carcinoma diagnosed in the intervention and placebo arms respectively, a non-significant difference (P = 0.33). A *post-hoc* subgroup analysis of subjects with no precancerous lesions at recruitment showed 0 (0.0%) and 6 (1.2%) incident cases in the intervention and placebo arms (P = 0.02) [The Working Group viewed the design of this study to be underpowered to assess adequately the relationship between eradication and gastric carcinoma outcomes.]

Three studies (Leung *et al.*, 2004; Mera *et al.*, 2005; You *et al.*, 2006) were designed to analyse changes in precancerous histological pathology as the primary end-point but also reported results for gastric carcinoma outcomes. These studies respectively randomized 587, 795 and 2258 *H. pylori*-positive subjects to receive eradication therapy or placebo. In the intervention and placebo arms of the three studies, during follow-up, there were four and six, three and two, and 19 and 27 incident cases of gastric carcinoma diagnosed, respectively. None of these associations was statistically significant. In terms of progression or regression of precancerous pathology compared with baseline, all three studies showed a statistically significant benefit in the intervention arms as did a further intervention study (Ley *et al.*, 2004) of 248 subjects which did not specifically report on gastric carcinoma as an outcome.

Fukase *et al.* (2008) reported a study of 544 *H. pylori*-positive patients who were all diagnosed with early gastric carcinoma, and underwent endoscopic mucosal resection and were followed up for a mean of three years after being randomized to eradication therapy (n = 272) or standard care (n = 272). There were 9 (3.3%) and 24 (8.8%) incident metachronous cases of gastric carcinoma diagnosed in the intervention and placebo arms respectively, a statistically significant difference (hazard ratio [HR], 0.35; 95%CI: 0.16–0.78). In an earlier non-randomized study (Uemura *et al.*, 1997), 132 *H. pylori* positive patients, 44–85 years of age, diagnosed with early gastric carcinoma and treated with endoscopic mucosal resection, were followed up for two years after 65 patients received eradication therapy, and 67 did not. There were no gastric carcinomas in the intervention group and six (9%) in the control group. [The Working Group viewed these two latter studies as not applicable to populations outside Japan.]

(g)   Synthesis

Since the previous *Monograph*, a substantial number of prospective observational studies, both nested case–control and cohort, had provided results supportive of an association between *H. pylori* infection and non-cardia gastric carcinoma. The magnitude of the risk is increased when more sensitive assay procedures are used and there appears to be a stronger association with CagA-positive strains of *H. pylori.* Results from randomized studies have not had sufficient power to evaluate the effect of the impact of *H. pylori* eradication on gastric carcinoma risk.

2.1.2 Cardia gastric carcinoma

Results are available from ten prospective cohort studies with nested case–control designs. These are summarized in Table 2.4 (available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.4.pdf).

(a) Nested case–control analyses within cohort studies

The pooled reanalysis (*Helicobacter and Cancer Collaborative Group, 2001*) presented results based on 274 cases of cardia gastric carcinoma and 827 control subjects derived from 12 independent prospective cohort studies in nine countries (the United Kingdom, Finland, Sweden, Norway, Iceland, USA, Taiwan (China), and Japan) analysed using a nested design. Cases were matched to controls on the basis of study, sex, age and date of blood sample collection but no further adjustment in the analysis was possible. In all studies, *H. pylori* infection status was determined by a conventional ELISA for IgG antibodies against *H. pylori*. The overall matched odds ratio for the risk of cardia gastric carcinoma was 0.99 (95%CI: 0.72–1.35). Odds ratios for individual studies varied from 0.40–1.77.

Five of the individual studies included in the pooled reanalysis accrued more cases, and updated results have since been published (Kamangar *et al.*, 2006a, 2007; Knekt *et al.*, 2006; Hansen *et al.*, 2007; Simán *et al.*, 2007). Odd ratios showed a statistically significant reduced risk (0.27 and 0.31) in two studies, no significant difference from unity in two further studies (0.82 and 1.5), and a significantly increased risk in one study (1.64).

New results were reported from four further prospective studies with nested case–control designs (Shin *et al.*, 2005; Sasazuki *et al.*, 2006; Palli *et al.*, 2007; Mitchell *et al.*, 2008). Using ELISA for IgG status to determine *H. pylori* infection status, odds ratios for cardia gastric carcinoma varied from 0.8–3.7 but none was statistically significant.

In the pooled reanalysis (*Helicobacter and Cancer Collaborative Group, 2001*) when the results were stratified by period of follow-up, the odds ratio for gastric carcinoma with cases diagnosed less than 10 years after recruitment was 1.23 (95%CI: 0.86–1.75), and for those with cases diagnosed 10 or more years after recruitment, 0.46 (95%CI: 0.23–0.90). A similar relationship in the magnitude of the odds ratio with period of follow-up was reported in one of the updated studies (Kamangar *et al.*, 2006a), but not in another (Kamangar *et al.*, 2007).

In the pooled reanalysis (*Helicobacter and Cancer Collaborative Group, 2001*), no substantive difference in the odds ratios between men (0.98; 95%CI: 0.68–1.40) and women (1.03; 95%CI: 0.55–1.92) was observed. There was, however, a difference between gastric carcinoma with intestinal (0.42; 95%CI: 0.24–0.75) and diffuse (0.93; 95%CI: 0.21–4.10) histological types. [The Working Group noted that this difference was unexplained.]

(b) Meta-analysis

Only one meta-analysis has reported specifically on the risk of cardia gastric carcinoma (Huang *et al.*, 1998). Based on the results from six studies with several study designs, the summary odds ratio was 0.93 (95%CI: 0.62–1.38), with no significant heterogeneity.

(c) Impact of H. pylori CagA status

A meta-analysis (Huang *et al.*, 2003) including results from both retrospective and prospective studies identified 16 eligible studies, ten of which provided results stratified by cardia subsite location of the tumour. The odds ratio associated with *H. pylori* infection (determined by *H. pylori* seroprevalence) was 1.13 (95%CI: 0.75–1.70); a further analysis, confined to *H. pylori*-positive cases and controls, showed a risk associated with CagA positivity of 0.70 (95%CI: 0.44–1.10).

Three nested case–control studies have reported results in which the risk of cardia gastric carcinoma in relation to CagA-positive and -negative status can be compared. Respectively, these odds ratios were 0.43 and 0.21 (Kamangar *et al.*, 2006a), 0.8 and 0.8 (Palli *et al.*, 2007), and 1.75 and 1.35 (Kamangar *et al.*, 2007). In the other nested case–control study reporting on CagA-positive status (Simán *et al.*, 2007), an increased odds ratio of 2.3 in comparison with that for *H. pylori* infection alone (OR, 1.3) was reported.

[The Working Group noted that there are substantial difficulties in the reliability of classification of cardia gastric carcinoma. Some studies may be more inclusive of distal non-cardia gastric carcinoma and other studies may be more inclusive of lower oesophageal adenocarcinoma cases, which may lead to variability of outcome between studies.]

2.2 Gastric mucosa-associated lymphoid tissue (MALT) lymphoma

Results are available from one prospective cohort study with a nested case–control design and one retrospective case–control study. These are summarized in Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.5.pdf and Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.6.pdf.

2.2.1 Nested case–control analysis within a cohort study

Parsonnet *et al.* (1994) analysed a database of 33 cases of gastric non-Hodgkin lymphoma and 132 matched controls. *H. pylori* infection status was determined by ELISA for IgG antibodies and the odds ratio for risk of gastric non-Hodgkin lymphoma was 6.3 (95%CI: 2.0–19.9).

For low-grade MALT lymphoma, the odds ratio was 2.8 (95%CI: 0.2–28.5).

2.2.2 Case–control study

A study from Spain (de Sanjosé *et al.*, 2004) compared ten cases of gastric lymphoma (four gastric MALT) with matched hospital controls. *H. pylori* infection status was determined by ELISA for IgG antibodies, the odds ratio for the risk of both gastric lymphoma and gastric MALT was infinity (all cases infected).

2.2.3 Impact of H. pylori eradication

A total of 16 uncontrolled studies (Wotherspoon *et al.*, 1993; Stolte *et al.*, 1994; Bayerdörffer *et al.*, 1995; Neubauer *et al.*, 1997; Pinotti *et al.*, 1997; Savio *et al.*, 2000; Chen *et al.*, 2001, 2005; Fischbach *et al.*, 2004; Nakamura *et al.*, 2005, 2008; Wündisch *et al.*, 2005; Hong *et al.*, 2006; El-Zahabi *et al.*, 2007; Terai *et al.*, 2008; Stathis *et al.*, 2009) reported on the effect of *H. pylori* eradication therapy on B-cell MALT gastric lymphoma regression (see Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.7.pdf). In all studies, the eradication rates were very high (in general over 94%), and were accompanied by high rates of complete remission of the MALT lymphoma (62–100%). Where assessed, remission was more strongly associated with the successfully treated patients. Subsequent relapse rates, where reported, were in the order of 10% over the 1–3 year follow-up periods. [The Working Group recognized that these results made it unlikely that ethics committees would approve randomized intervention studies on the effect of *H. pylori* eradication on MALT regression.]

2.2.4 Synthesis

Despite the small number of observational studies of B-cell lymphoma in relation to *H. pylori* infection, evidence from the eradication studies

is critically important. Treatment of patients to eradicate *H. pylori* is strongly associated with remission of low-grade lymphomas. Therefore, infection with *H. pylori* causes low-grade B-cell MALT gastric lymphoma in humans.

2.3 Cancer of the oesophagus

2.3.1 Oesophageal adenocarcinoma

Results are available from two prospective cohort studies with nested case–control designs, 15 retrospective case–control studies, and three meta-analyses.

(a)   Cohort studies

Two studies (de Martel *et al.*, 2005; Simán *et al.*, 2007) analysed a database of 51 and 12 cases of oesophageal adenocarcinoma, respectively, and reported adjusted odds ratios of 0.37 (95%CI: 0.16–0.88) and 0.46 (95%CI: 0.07–2.6) respectively (see Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.8.pdf). Analysis for CagA-positive infection status did not substantially modify these results. Both studies adjusted for smoking but only the former adjusted for body mass index [The Working Group noted that this is a potential confounder for this type of cancer.]

(b)   Case–control studies

Among the available studies, four were population-based (El-Omar *et al.*, 2003; Wu *et al.*, 2003; Ye *et al.*, 2004; Anderson *et al.*, 2008). Two studies (Ye *et al.*, 2004; Anderson *et al.*, 2008) reported significantly reduced odds ratios of 0.3 and 0.38, respectively. The other two studies (El-Omar *et al.*, 2003; Wu *et al.*, 2003) reported odds ratios that were not significantly different from unity; however, the odds ratios associated with CagA positivity decreased to 0.82 and 0.33, respectively, with the latter being statistically significant.

Three studies (Wu *et al.*, 2003; Ye *et al.*, 2004; Anderson *et al.*, 2008) adjusted for body mass index, and all of them adjusted for other potential confounders. One further hospital-based study (Früh *et al.*, 2008) that used friends and spouses as controls reported an odds ratio of 0.71 (0.95%CI: 0.4–1.0) for *H. pylori* infection, with borderline statistical significance after adjustment for confounders including body mass index.

Nine other case–control studies were based on comparisons within clinical patient groups and all reported odds ratios that were either significantly reduced or not significantly different from unity (see Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.9.pdf).

(c)   Meta-analyses

A meta-analysis (Islami & Kamangar, 2008) reviewed the results from 13 studies (2 prospective and 11 retrospective case–control studies) of oesophageal adenocarcinoma. A comparison of 840 cases with 2890 controls and an assessment of *H. pylori* infection status mainly by ELISA resulted in a summary odds ratio of 0.56 (95%CI: 0.46–0.68). There was no statistically significant heterogeneity between studies, and no evidence of publication bias. Sensitivity analyses to include only large studies or only population-based studies or similar methods for assessment of infection did not substantially modify the odds ratio. Five studies included comparisons of CagA-positive and -negative strain status against *H. pylori*-negative subjects, and for these, the summary odds ratios were 0.41 (95%CI: 0.28–0.62) and 1.08 (95%CI: 0.76–1.53), respectively.

Two further meta-analyses (Rokkas *et al.*, 2007; Zhuo *et al.*, 2008), which included fewer studies, also reported a significant decrease in risk with both *H. pylori* and CagA positivity (see Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.10.pdf).

(d)   Synthesis

The observational epidemiological studies are all consistent in showing a lack of association between *H. pylori* infection and an increased risk of oesophageal adenocarcinoma. Several of these studies as well as the meta-analyses show a statistically significant reduced risk of oesophageal cancer.

2.3.2 Oesophageal squamous cell carcinoma

Results are available from two prospective cohort studies with nested case–control designs, five retrospective case–control studies, and three meta-analyses.

(a)   Cohort studies

Two studies (Kamangar *et al.*, 2007; Simán *et al.*, 2007) analysed a database of 300 and 37 cases of oesophageal squamous cell carcinoma respectively. The adjusted odds ratios for *H. pylori* infection were 1.17 (95%CI: 0.88–1.57) and 0.56 (95%CI: 0.24–1.3), respectively. CagA infection status did not substantially modify these results (see Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.11.pdf).

(b)   Case–control studies

Four studies were population-based (El-Omar *et al.*, 2003; Wang *et al.*, 2003a; Ye *et al.*, 2004; Wu *et al.*, 2005). One of these (El Omar *et al.*, 2003) included 53 cases and reported a statistically significant increased odds ratio of 2.11; another study (Wu *et al.*, 2005) included 127 cases and reported a significantly reduced odds ratio of 0.51. The other two studies (Wang *et al.*, 2003a; Ye *et al.*, 2004) included 63 and 85 cases, respectively, and reported odds ratios not significantly different from unity. The studies all adjusted for age and sex but differed in the extent of adjustment for other confounding factors. Only one study (Wu *et al.*, 2005) adjusted for alcohol consumption. One hospital-based study (Iijima

et al., 2007) reported a non-significantly increased odds ratio of 1.40 (95%CI: 0.62–3.15 [calculated by the Working Group]) (see Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.12.pdf).

(c)   Meta-analyses

One meta-analysis (Islami & Kamangar, 2008) reviewed results from nine studies (two prospective and seven retrospective case–control studies) of oesophageal squamous cell carcinoma. A comparison of 921 cases of oesophageal squamous cell carcinoma with 2743 controls and an assessment of *H. pylori* infection status mainly by ELISA resulted in a summary odds ratio of 1.10 (95%CI: 0.78–1.55). There was statistically significant heterogeneity between studies, but no evidence of publication bias. Sensitivity analyses to include only large studies or only population-based studies or similar methods for assessment of infection did not substantially modify the risk. Four studies included comparisons of CagA-positive and -negative strain status against *H. pylori*-negative subjects: the meta-relative risks were 1.01 (95%CI: 0.80–1.27) and 1.41 (95%CI: 1.00–1.97), respectively. Two further meta-analyses (Rokkas *et al.*, 2007; Zhuo *et al.*, 2008), which included fewer studies, reported similar results (see Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.13.pdf).

(d)   Synthesis

The Working Group concluded that there was little evidence of an association between *H. pylori* infection and the risk of oesophageal squamous cell carcinoma.

2.4 Other cancers

2.4.1 Cancer of the liver

(a)   Hepatocellular carcinoma

Results are available from 17 retrospective case–control studies, and a meta-analysis.

Two studies, based on 46 and 11 cases and using ELISA to detect IgG antibodies to *H. pylori*, showed odds ratios [calculated by the Working Group] that were significantly increased in one study (OR, 3.02; 95%CI: 1.12–8.34) ([Leone *et al.*, 2003](http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.14.pdf)), but not in the other (OR, 2.3; 95%CI: 0.15–15.1) ([Dore *et al.*, 2002](http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.14.pdf)) (see Table 2.14 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.14.pdf). No adjustment was carried out for potential confounders. All the other studies used PCR assays of liver biopsy samples from cases and controls to detect the presence of *Helicobacter* species (see Table 2.15 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.15.pdf). The primers used for the PCR assays (16s rDNA primers) were for genes associated with the *Helicobacter* genus but were not specific for *H. pylori*. In some of the studies, DNA from a subsample of positive samples was sequenced, and found to be specific for *H. pylori*. A higher proportion of positive results in 13/15 studies were observed among cases when compared to controls. Cases numbers were small in all studies, the largest having 48 cases, and studies varied in the extent to which they adjusted for potential confounding factors.

[The Working Group noted the small size of these studies, the potential problems of specificity associated with PCR assays, the use of opportunistic control series selected from patient groups, and the lack of adjustment for potential confounders.]

A meta-analysis ([Xuan *et al.*, 2008](http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.16.pdf)) reviewed results from ten studies (nine case–control and one cross-sectional) (see Table 2.16 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.16.pdf). A comparison of 242 cases of hepatocellular carcinoma with 280 hospital controls and an assessment of *H. pylori* infection status by PCR on liver biopsy samples resulted in a summary odds ratio of 13.63 (95%CI: 7.90–23.49). [The Working Group were concerned about the comparability of studies within this meta-analysis as a wide variety of control groups and methodologies were employed.]

(b) Cholangiocarcinoma

A review ([de Martel *et al.*, 2009](http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.17.pdf)) summarized results from eight studies in which PCR was used to detect the presence of *Helicobacter* species in bile or tissue biopsies from patients with biliary tract cancers and controls usually with benign biliary tract diseases (see Table 2.17 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.17.pdf). The primers used for the PCR assays were not specific for *H. pylori*. In 2/8 studies, none of the cases was reported as positive but the other six studies all showed a higher proportion of positive results in cases compared to controls. None of these studies included more than 20 cases.

[The Working Group noted the small size of these studies, the potential problems of specificity associated with PCR assays, the use of opportunistic control series selected from patient groups, and the lack of adjustment for potential confounders.]

2.4.2 Cancer of the colorectum

Results are available from two prospective cohort studies with a nested case–control design, 12 retrospective case–control studies, and one meta-analysis.

(a) Nested case–control analyses with cohort studies

Two studies ([Thorburn *et al.*, 1998](http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.18.pdf); [Limburg *et al.*, 2002](http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.18.pdf)) were based on 233 and 118 cases of colorectal cancer associated with *H. pylori* infection, and reported non-significant adjusted odds ratios of 0.9 (95%CI: 0.5–1.5) and 1.05 (95%CI: 0.63–1.74), respectively, associated with *H. pylori* infection (see Table 2.18 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.18.pdf). CagA-positive infection status

did not influence the latter result, and was not tested for in the former study.

(b)   Case–control studies

Out of 11 studies, three (Hartwich *et al.*, 2001; Machida-Montani *et al.*, 2007; Zumkeller *et al.*, 2007) were population-based (see Table 2.19 available at http://monographs.iarc.fr/ENG/ Monographs/vol100B/100B-10-Table2.19.pdf). Two of these (Hartwich *et al.*, 2001; Zumkeller *et al.*, 2007), based on 80 and 384 cases, respectively, reported statistically significant odds ratios of 3.78 and 1.41, respectively, for colorectal cancer associated with *H. pylori* infection. The third study (Machida-Montani *et al.*, 2007) included 121 cases, and reported no significant risk. CagA-positive status did not affect the observed risk. Three studies (Moss *et al.*, 1995; Fireman *et al.*, 2000; Siddheshwar *et al.*, 2001) were based within colonoscopy clinics, and included 41, 51 and 189 cases, respectively, with adjusted odds ratios for colorectal cancer associated with *H. pylori* infection reported to be between 0.74–2.43, none of which statistically significant. One other colonoscopy clinic study (Fujimori *et al.*, 2005) included 154 cases of adenocarcinomas, and reported a statistically significant odds ratio of 1.8.

Four studies were hospital-based (Penman *et al.*, 1994; Meucci *et al.*, 1997; Shmuely *et al.*, 2001; D'Onghia *et al.*, 2007), and did not adjust for any potential confounders.

(c)   Meta-analysis

A meta-analysis (Zumkeller *et al.*, 2006) reviewed results from 11 studies (two prospective and nine retrospective case–control studies) (see Table 2.20 available at http://monographs.iarc.fr/ ENG/Monographs/vol100B/100B-10-Table2.20. pdf). A total of 899 cases of colorectal cancer were compared with 1476 controls; *H. pylori* infection status was assessed by ELISA in ten studies and by urea breath test in one study. The resulting meta-relative risk was 1.4 (95%CI: 1.1–1.8). The meta-relative risk for the 2 prospective studies was 1.0 (95%CI: 0.8–1.4).

2.4.3 Cancer of the pancreas

Nilsson *et al.* (2002) analysed pancreatic biopsy specimens from patients undergoing surgery for possible pancreatic cancer to detect the presence of *Helicobacter* species and *H. pylori* by bacterial culture, PCR, and DNA sequencing. Five of six pancreatic ductal carcinomas and one malignant neuroendocrine cancer were positive for *Helicobacter* species by PCR with genus-specific primers; however, none of the five was positive for *H. pylori* by PCR with genus-specific primers. Two of the 16S rDNA PCR fragments were sequenced and compared with the GenBank database by a BLAST search (www.ncbi.nlm.nih. gov). One of those was 98% similar to the 16S rDNA of *Helicobacter* species liver 3, clustering to a phylogenetic group that includes *H. pylori*. The other was 99% similar to *H. pullorum*, and clustered to a phylogenetic group that also contains *H. bilis*.

Results are available from three informative prospective cohort studies with nested case–control designs, and one retrospective case–control study.

Two of the three prospective cohort studies (de Martel *et al.*, 2008; Lindkvist *et al.*, 2008) based on 104 and 87 cases, respectively, of pancreatic cancer associated with *H. pylori* infection reported non-significant odds ratios of 0.85 (95%CI: 0.49–1.48) and 1.25 (95%CI: 0.75–2.09), respectively. The third study (Stolzenberg-Solomon *et al.*, 2001) reported an odds ratio of 1.87 (95%CI: 1.05–3.34) for *H. pylori* seropositivity. CagA-positive infection status did not influence any of these results. All studies adjusted for age, sex, and smoking (see Table 2.21 available at http://monographs.iarc.fr/ENG/Monographs/ vol100B/100B-10-Table2.21.pdf).

The retrospective case–control study (Raderer *et al.*, 1998) included 92 cases of pancreatic

cancer. The odds ratio for the risk of pancreatic cancer associated with *H. pylori* infection was 2.1 (95%CI: 1.1–4.1) (see Table 2.22 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.22.pdf).

2.4.4 Cancer of the lung

Results are available from four retrospective case–control studies (see Table 2.23 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.23.pdf). Two retrospective case–control studies (Gocyk *et al.*, 2000; Ece *et al.*, 2005) included 50 and 43 cases of lung cancer, respectively, and showed statistically significant associations with *H. pylori* infection with odds ratios [estimated by the Working Group] of 5.06 and 13.33, respectively. The first study was not adjusted for smoking, and the second included only smokers. Two other studies (Philippou *et al.*, 2004; Najafizadeh *et al.*, 2007) included 72 and 40 cases of lung cancer, respectively, and neither showed a statistically significant association with *H. pylori* infection. [The Working Group noted that none of these four studies was adequately adjusted for smoking.]

2.4.5 Cancer of the head and neck

Results are available from four retrospective case–control studies (see Table 2.24 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.24.pdf). The studies varied slightly in their case definitions. One (Grandis *et al.*, 1997) included 21 cases of squamous cell carcinomas of the head and neck and the odds ratio for *H. pylori* infection was 0.82 (95%CI: 0.24–2.76). A second study among smokers (Aygenc *et al.*, 2001) included 26 cases of squamous cell laryngeal cancers and the odds ratio for *H. pylori* infection [estimated by the Working Group] was 3.97 (95%CI: 1.32–11.89). A third study (Rubin *et al.*, 2003) included 55 cases of squamous cell cancer of the upper aerodigestive tract (excluding oesophagus) and six cases of laryngeal severe dysplasia, and the odds ratio for *H. pylori* infection [estimated by the Working Group] for the risk of cancer/severe dysplasia was 1.86 (95%CI: 1.03–3.35). The final study (Nurgalieva *et al.*, 2005) included 119 cases of squamous cell carcinoma of the laryngopharynx, and the adjusted odds ratio for *H. pylori* infection was 1.27 (95%CI: 0.70–2.29).

2.4.6 Childhood leukaemia

One prospective cohort study (Lehtinen *et al.*, 2005) with a nested case–control design compared 341 children with acute lymphocytic leukaemia and 61 with other leukaemias with 1212 matched controls (see Table 2.25 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-10-Table2.25.pdf). *H. pylori* infection status was determined on maternal serum samples (first trimester) by ELISA for IgG and IgM antibodies. The adjusted odds ratio for risk of all leukaemias combined was 1.0 (95%CI: 0.8–1.2) for IgG antibodies. Results for IgM antibodies or specifically for acute lymphoblastic leukaemia did not differ substantially.

2.5 Cofactors

Two studies have found an effect modification between smoking, *H.pylori* infection, and gastric carcinoma (Zaridze *et al.*, 2000; Brenner *et al.*, 2002). Zaridze *et al.* (2000) reported on the relative risk of gastric cancer associated with smoking by *H. pylori* status. Among men, the odds ratio for ever smoking compared to never smoking among *H. pylori* negatives was 1.0 (95%CI: 0.5–2.1), and ever smoking compared to never smoking among *H. pylori* positives was 2.3 (95%CI: 1.1–4.7), with a *P* = 0.07 for the effect modification between smoking and *H. pylori*.

Brenner *et al.* (2002) evaluated the individual and joint association of smoking and *H. pylori*

infection as well as CagA-positive *H. pylori* infection. The adjusted relative risk of gastric cancer was 2.6 (95%CI: 1.2–5.7) for CagA-positive *H. pylori* infection in non-smokers compared to uninfected non-smokers, and CagA-positive *H. pylori*-infected smokers had a relative risk of 7.2 (95%CI: 2.2–23.6). When analyses were restricted to non-cardia gastric cancer, the corresponding estimates of relative risk were 6.1 (95%CI: 2.3–16.5) for CagA-positive non-smokers and 16.6 (95%CI: 4.3–67.2) for CagA-positive smokers. Not all studies found this effect. Machida-Montani *et al.* (2004) found gastric cancer risk associated with smoking and dietary factors to be independent of risk associated with *H.pylori* infection.

Plasma levels of vitamin C are inversely associated with gastric cancer risk for both cardia and non-cardia, diffuse, and intestinal subsites. Vitamin C plasma levels showed no effect modification with *H. pylori* infection (Jenab *et al.*, 2006). Ekström *et al.* (2000), however, found an effect modification on non-cardia gastric carcinoma risk by dietary intake of ascorbic acid, β-carotene, and α-tocopherol by *H. pylori* infection status. There was little or no association of these antioxidants in *H. pylori*-negative subjects, but 30–70% reductions in the relative risk of non-cardia gastric carcinoma in *H. pylori*-positive subjects were observed with dietary intake increments of 50 mg/day of ascorbic acid, 3.0 mg/day β-carotene or 8.0 mg/day of α-tocopherol.

A significant effect modification between *H. pylori* infection and salted, smoked foods and processed meat has been observed (Phukan *et al.*, 2006; Shikata *et al.*, 2006; Epplein *et al.*, 2008). Two studies from East Asia have correlated dietary salt intake with an increased risk of non-cardia gastric cancer over and above that attributable to *H. pylori* alone (Lee *et al.*, 2003; Shikata *et al.*, 2006).

In two recent studies, diets rich in fresh vegetables [and therefore high in antioxidants] intake were shown to be specially beneficial in reducing non-cardia gastric cancer risk among those who are *H. pylori* infected (Ekström *et al.*, 2000; Epplein *et al.*, 2008).

Ekström *et al.* (1999) found that risk of gastric cancer associated with *H. pylori* infection was independent of risk associated with specific occupational exposures.

3. Cancer in Experimental Animals

3.1 Mongolian gerbil

The first report of gastric cancer induced by *H. pylori* in an animal model was published by Watanabe *et al.* (1998). The authors infected Mongolian gerbils (*Meriones unguiculatus*) with *H. pylori* strain TN2GF4, and observed the gastric lesions after 62 weeks. Gastric adenocarcinomas were detected in 10/27 infected animals vs 0/30 controls.

The Mongolian gerbil model infected with *H. pylori* has been cited in seven other publications (Honda *et al.*, 1998; Hirayama *et al.*, 1999; Zheng *et al.*, 2004; Elfvin *et al.*, 2005; Franco *et al.*, 2005, 2008; Romero-Gallo *et al.*, 2008), and all except one (Elfvin *et al.*, 2005) reported gastric adenocarcinoma developments. They developed late in the animals' lives (62–90 weeks) except in three studies (Franco *et al.*, 2005, 2008; Romero-Gallo *et al.*, 2008) where the development was extremely rapid (8–12 weeks).

It is noteworthy that in other experiments using chemical carcinogens in Mongolian gerbils and where *H. pylori*-infected animals were used as controls, none of the controls developed gastric cancer (Sugiyama *et al.*, 1998; Tokieda *et al.*, 1999; Shimizu *et al.*, 1999; Nozaki *et al.*, 2002; Kato *et al.*, 2006) with a follow-up of 40–53 weeks, or in the study of Cao *et al.* (2007) despite a follow-up of 70 weeks.

These results indicate that the Mongolian gerbil is not the most reliable model for the development of gastric adenocarcinomas even after a long follow-up. The reason could be linked to the animal strain used. Mongolian gerbils were first bred in Japan, then exported to the USA,

and later to Europe. The genetic background of the animals may have evolved differently among the different colonies. The *H. pylori* strain used may also be the cause of these discrepant results. Two strains were essentially used (ATCC 43 504 and TN2GF4) but when Franco *et al.* (2005) used a Mongolian gerbil adapted strain (7.13) derived from the parent strain B128, they observed gastric adenocarcinomas in 59% of the animals. The high susceptibility of this strain was confirmed in two further studies by Franco *et al.* (2008) and Romero-Gallo *et al.* (2008). Another variable is the criteria used for grading the observed pathology. This point was raised by Elfvin *et al.* (2005) who published a negative result. Furthermore, in the Mongolian gerbil model, no metastasis was reported nor did any gerbil die of gastric carcinoma.

The limitation of this model led to test the impact of *H. pylori* infection in Mongolian gerbils receiving well known chemical carcinogens, e.g. *N*-methyl-*N*-Nitrosourea or *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine at different concentrations. Eight studies used such a design and in all of them, there was a synergistic effect of *H. pylori* infection on the incidence of gastric carcinomas compared to the incidence observed after treatment with the carcinogen alone.

In some studies gerbils were infected with *H. pylori* and then treated also with a chemical carcinogen to test the action of pharmacological agents such as a cyclooxygenase 2 inhibitor (etodolac) (Magari *et al.*, 2005), and an antioxidative and anti-inflammatory compound (canolol) (Cao *et al.*, 2008), both of which have a protective effect. The impact of a salty diet was also tested in two studies (Nozaki *et al.*, 2002; Kato *et al.*, 2006), and a synergy between *H. pylori* infection and a high-salt diet was observed. Romero-Gallo *et al.* (2008) and Nozaki *et al.* (2003) showed the benefit of an early eradication using clarithromycin-based triple therapy, which decreased the gastric cancer incidence.

See Table 3.1.

3.2 Mouse

3.2.1 Inbred mouse

The progression of the gastric lesions after *H. pylori* infection has also been observed in inbred mice, C57BL/6 and BALB/c. Despite a long follow-up of 80 and 100 weeks by Kim *et al.* (2003) and Wang *et al.* (2003b), respectively, no gastric adenocarcinoma occurred, only gastric lymphoma in the latter. When C57BL/6 mice crossed with 12996/SvEv mice were infected by *H. pylori* and submitted to a high-salt diet, high-grade dysplasia occurred but not adenocarcinoma (Rogers *et al.*, 2005).

In a study where C57BL/6 mice infected with *H. felis* received an eradication treatment after different time periods, Cai *et al.* (2005) observed adenocarcinomas in all untreated infected animals after 24 months, no adenocarcinomas if the treatment was given after 2 or 6 months of infection, and a decrease in the incidence of adenocarcinomas if the treatment was delayed to the 12th month.

3.2.2 Transgenic mouse

The first model (of five transgenic models) used transgenic mice deficient for TGF-β infected with *H. pylori*. Gastric adenocarcinoma or dysplasia developed in 85.7% of the mice after 36 weeks (Hahm *et al.*, 2002).

The second model involves transgenic mice overexpressing gastrin (INS-GAS mice). A first study showed that infection of INS-GAS male mice with *H. pylori* strain SS1 could induce gastric adenocarcinoma in 4/6 male animals within 30 weeks (Fox *et al.*, 2003a). This finding was repeated in another study (3/7 gastric adeno-carcinoma within 28 weeks), and the protective effect of estradiol was shown (Ohtani *et al.*, 2007). In a study designed to determine the impact of *H. pylori* eradication therapy (Lee *et al.*, 2008), gastric carcinogenesis was inhibited. In another study where an H2-receptor antagonist

Table 3.1 Studies of gastric cancer in Mongolian gerbils infected by *H. pylori* by gavage with or without modifying agents

Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
62 wk Watanabe et al. (1998)	10^7 CFU *H. pylori*, TN2GF4 (M) 55, 30 (controls)	Adenocarcinoma: 10/27 cases 0/30 controls	[*P*=0.0002]	Well differentiated intestinal type cancer of the pyloric region
18 mo Honda et al. (1998)	10^9 CFU *H. pylori*, ATCC 43 504 (M) 15, 15 (controls)	Adenocarcinoma: 2/5 cases 0/5 controls	[NS]	
23 mo (average) Hirayama et al. (1999)	*H. pylori*, ATCC 43 504 (M) 56 (total), 3 (controls)	Adenocarcinoma; Carcinoids 12–18 mo: 1/16; 4/16 18–24 mo: 0/14; 3/14 >24 mo: 0/24; 11/26 Controls 0/3; 0/3	[NS]	Carcinoids were found in the fundus region of the stomach
84 wk Zheng et al. (2004)	*H. pylori*, ATCC 43 504 or *H. pylori* 161 (M, F) 1: *H. pylori* ATCC 43 504: *n*=18 2: *H. pylori* 161: *n*=18 3: Controls: *n*=10	Adenocarcinoma: 1: 1/6 (16.6%) 2: 2/11 (18.2%) 3: 0/10	[NS], Group 1 and 2 vs 3	
18 mo Elfvin et al. (2005)	1: *H. pylori*, TN2GF4: *n*=23 2: *H. pylori*, SS1: *n*=20 3: Controls: *n*=18 (M) Interim sacrifices at 3, 6 and 12 mo Group size: 3–10 animals	No adenocarcinoma observed in all 12 groups		[Age of the animals at start is described as 'sixty-seven-week-old', which could be a typo.] Discussion on the interpretation of the pathological findings to conclude adenocarcinoma: the authors conclude that, so far, adenocarcinomas have not yet been shown convincingly to develop in infected gerbils
4 wk, 8 wk or 16 wk Franco et al. (2005)	(M) Experiment 1 A. *H. pylori* B128: *n*=16 B. *H. pylori* 7.13: *n*=16 Experiment 2 C. *H. pylori* 7.13: *n*=116 D. Controls: *n*=42	Adenocarcinoma: A: 0/16 (8 wk) B: 4 wk: 2/8 (25%), 8 wk: 6/8 (75%) C: 4 wk: 17% [incidence NS], 8 wk: 59% [incidence NS], 16 wk: 59% [incidence NS] D: 0/42	[*P*<0.0001]; Group B (8 wk) vs D	*H. pylori* strains 7.13 is gerbil adapted, derived from parent strain B128 (human gastric ulcer strain). Experiment 2 is very likely to be positive at Weeks 8 and 16

Table 3.1 (continued)

Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
14–18 wk Romero-Gallo et al. (2008)	5×10^9 CFU *H. pylori* strain 7.13 1. Eradication therapy at 4 wk post infection with lansoprazole, amoxicillin and clarithromycin, orally, for 2 wk (daily). Sacrifice 8 wk after end of treatment	Adenocarcinoma: 0/8	$P=0.01$ Group 1 vs 2	Eradication treatment decreased the carcinoma incidence
	2. Controls infected for 14 wk	6/20 (33%)		
	3. Eradication therapy at 8 wk post infection with lansoprazole, amoxicillin and clarithromycin, orally, for 2 wk (daily). Sacrifice 8 wk after end of treatment	1/14 (7%)	$P=0.027$ Group 3 vs 4	
	4. Controls infected for 18 wk	5/10 (50%)		
12–52 wk Franco et al. (2008)	(M) 1. *H. pylori* 7.13 (12–16 wk, $n=18$; 24–30 wk, $n=19$; 40–52 wk, $n=9$)	Adenocarcinoma: 53% [9/17], 50% [9/18], 55% (5/9)	[$p=0.0003$], [NS], [$p=0.005$]	*cagA*, cytotoxin-associated gene *vacA*, vacuolating cytotoxin gene
	2. *H. pylori* 7.13 cagA- (12–16 wk, $n=18$; 24–30 wk, $n=20$; 40–52 wk, $n=17$)	0% (0/18), 0% (0/20), 0% (0/17)	[NS], [NS], [NS],	
	3. *H. pylori* 7.13 vacA- (12–16 wk, $n=13$; 24–30 wk, $n=9$; 40–52 wk, $n=17$)	16% (2/13), 37% [3/8], 47.5% (8/17)	[NS], [NS], [p<0.005]	
	4. Controls (12–16 wk, $n=19$; 24–30 wk, $n=5$; 40–52 wk, $n=13$)	0% (0/19), 0% (0/5), 0% (0/13)		
MNNG (in the drinking-water)				
52 wk Tokieda et al. (1999)	10^9 CFU *H. pylori*, ATCC 43 504 (M)	Adenocarcinoma:		Group 3: poorly differentiated GC Group 4: well differentiated GC
	1. Controls: $n=30$	1: 0/20		
	2. *H. pylori*: $n=25$	2: 0/14		
	3. MNNG 50 ppm orally (20 wk): $n=27$	3: 3/17 (17.6%)	$P<0.05$,	
	4. MNNG 50 ppm orally (20 wk) + *H. pylori*: $n=25$	4: 4/6 (66.7%)	Group 4 vs 3	

Table 3.1 (continued)

Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
50 wk Shimizu et al. (1999)	10^8 CFU *H. pylori*, ATCC 43 504 (M)			
		Adenocarcinoma:		
	1: MNNG 300 ppm (10 wk) followed by *H. pylori*	1: 12/27 (44%)	*P*<0.01, Group 1 vs 2	
	2: MNNG 300 ppm (10 wk) alone	2: 1/19 (5.3%)		
	3: MNNG 60 ppm (10 wk) followed by *H. pylori*	3: 6/27 (24%)	*P*<0.05, Group 3 vs 4	
	4: MNNG 60 ppm (10 wk) alone	4: 0/20		
	5: *H. pylori* followed by MNNG 100 ppm (30 wk)	5: 4/27 (14.8%)		
	6: MNNG 100 ppm (30 wk) alone	6: 3/18 (16.7%)		
	7: *H. pylori* followed by MNNG 20 ppm (30 wk)	7: 15/25 (60%)	*P*<0.001, Group 7 vs 8	
	8: MNNG 20 ppm (30 wk) alone	8: 1/19 (5%)		
	9: *H. pylori* alone	9: 0/20		
	10: Controls	10: 0/20		

MNU (in the drinking water)

Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
40 wk Sugiyama et al. (1998)	10^9 CFU *H. pylori*, ATCC 43 504 (M) Experiment 1 (18–20/group)	Adenocarcinoma:		
	A. *H. pylori* followed by MNU 10 ppm (20 wk)	A: 7/19 (36.8%)	*P*<0.01, Group A vs B	
	B. MNU 10 ppm (20 wk) alone	B: 0/18		
	C. *H. pylori* followed by MNU 3 ppm (20 wk)	C: 1/20 (5%)		
	D. MNU 3 ppm (20 wk) alone	D: 0/18		
	Experiment 2			
	E. MNU 30 ppm (6 wk) followed by *H. pylori*	E: 6/18 (33.3%)	*P*<0.05, Group E vs F	
	F. MNU 30 ppm (6 wk) alone	F: 0/18		
	G. MNU 10 ppm (10 wk) followed by *H. pylori*	G: 1/19 (5.3%)	*P*<0.005, Group 1 vs 3 NS; Group 2 vs 4	
	H. MNU 10 ppm (10 wk) alone	H: 0/20		
	I. Control: *H. pylori*	I: 0/17		

Table 3.1 (continued)

Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
50 wk Nozaki et al. (2002)	10^8 CFU *H. pylori*, ATCC 43 504 (M) - Groups 1,2,3 & 4 MNU (20 ppm) orally alternate wk for a total of 5 wk - Groups 5,6,7 & 8 Controls *H. pylori* infection at Week 11 in Groups 1 & 2, 5 & 6 and vehicle in groups 3 & 4, 7 & 8. High salt diet at Week 12 in Groups 1 & 3, 5 & 7 and control diet in Groups 2 & 4, 6 & 8	Carcinoma: 1: 9/28 (32.1%) 2: 2/17 (11.8%) 3: 0/27 4: 0/20 5: 0/11 6: 0/6 7: 0/4 8: 0/4		Synergy between *H. pylori* infection & high salt diet to promote GC
75 wk Nozaki et al. (2002)	10^8 CFU *H. pylori*, ATCC 43 504 (M) - Groups A, B, C, D, E MNU (30 ppm) orally alternate wks for a total of 5 wk - Groups A, B, C, D, F *H. pylori* infection at Week 10 - Groups A, B, C Eradication therapy at Week 5, 25 and 45 post infection with lansoprazole, amoxicillin and clarithromycin, orally - Group G not infected	Carcinoma: A: 1/15 B: 3/11 C: 13/34 D: 9/16 E: 1/16 F: 0/8 G: 0/9	$P<0.05$ vs C, $P<0.005$ vs D $P<0.05$ vs E $P<0.005$ vs E and G	*H. pylori* eradication can reduce cancer incidence when given relatively early
53 wk Magari et al. (2005)	3×10^8 CFU *H. pylori*, ATCC 43 504; MNU: 10 ppm for 24 wk (M) A. *H. pylori* + MNU B. *H. pylori* + MNU + etodolac diet (5 mg/kg/d) C. *H. pylori* + MNU + etodolac diet (10 mg/kg/d) D. *H. pylori* + MNU + etodolac diet (30 mg/kg/d) E. Control (not infected)	Adenocarcinoma: A: 4/27 (14.8%) B: 8/34 (23.5%) C: 3/34 (8.8%) D: 0/39 E: 0/16	$p<0.05$, group A and B vs D	Etodolac is a selective cyclooxygenase 2 inhibitor preventing GC induction

Table 3.1 (continued)

Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
50 wk Kato et al. (2006)	*H. pylori*, ATCC 43 504 (M) 20 groups G1–10: MNU (30 ppm) G11–20: no MNU G1–5 & G11–15: + *H. pylori* at Week 10 + increasing NaCl concentrations (0%, 2.5%, 5%, 10% in food or a gavage with diet with a saturated salt solution)	Adenocarcinoma: G1: 6/40 (15%) G2: 8/24 (33%) G3: 9/25 (36%) G4: 19/30 (63%) G5: 5/21 (24%) G8: 1/25 (4%) G6, G7, G9, G10–20: 0% (n=7–27)	P for trend <0.01 (Groups G1→G4) p<0.01 (Group G4 vs G1)	
70 wk Cao et al. (2007)	10^8 CFU *H. pylori*, ATCC 43 504 (M) 8 groups A to H A & E: inoculated at Week 0 B & F: inoculated at Week 12 C & G: inoculated at Week 18 D & H: Controls A, B, C & D received oral MNU (10 ppm) at Week 20 during 20 wk	Adenocarcinoma: A: 13/20 (65%) B: 2/10 (20%) C: 3/13 (23%) D: 0/16 E, F, G, H: 0/6	P<0.01; Group A vs D	
18 wk Cao et al. (2008)	10^8 CFU *H. pylori* strain ATCC 43 504; (M); MNU: 10 ppm; BHT: used at 0.5 ppm in the diet; Canolol: 0.1% in the diet - Experiment 1: A: *H. pylori* + Canolol + BHT B: *H. pylori* + BHT C: *H. pylori* D: Canolol + BHT E: BHT F: Control - Experiment 2: G: *H. pylori* + MNU + Canolol + BHT H: *H. pylori* + MNU + BHT I: *H. pylori* + MNU + Control diet J: Control + Canolol + BHT	Adenocarcinoma: A to F: 0/58 G: 6/40 (15%) H: 13/33 (39.4%) I: 15/36 (41.7%) J: 0/5	P=0.031 (Group G vs H) P=0.011 (Group G vs I)	Canolol, an antioxidative and anti inflammatory compound, prevents GC induction. BHT is an antioxidant additive No MNU-only treated group

ATCC, American type culture collection; BHT, butylated hydroxytoluene; CFU, colony forming units; d, day or days; F, female; GC, gastric cancer; *H. pylori, Helicobacter pylori*; M, male; MNNG, *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine; MNU, *N*-methyl-*N*-nitrosourea; mo, month or months; NS, not significant; vs, versus; wk, week or weeks

(loxtidine) and a CCk-2-receptor antagonist were given for 6 months (Takaishi *et al.*, 2005), gastric carcinogenesis was also inhibited in *H. felis*-infected animals. [The Working Group noted that no tumour incidences were provided.] Again, in the Lee *et al.* (2008) study, an early eradication (8 weeks) almost prevented gastric cancer development.

The third model used transgenic p27 deficient mice infected with *H. pylori* strain SS1. Infection and p27-deficiency were synergistic in gastric cancer development (Kuzushita *et al.*, 2005).

The fourth model used Trefoil factor family 2 (TFF2)-deficient mice, with a B6129Sv strain background, infected with *H. pylori* strain SS1. Gastric adenocarcinomas were observed 19 months after infection (Fox *et al.*, 2007).

The fifth model used transgenic mice over-expressing IL-1β. The two lines of mice built infected with *H. felis* developed gastric adenocarcinomas but at a low incidence (Tu *et al.*, 2008).

3.2.3 Mouse models of gastric MALT lymphoma

Mouse models have been used as models of gastric MALT lymphomas. Gastric lymphomas histologically similar to the low-grade lymphoma observed in humans have been observed in mice infected for about 2 years with *Helicobacter* species, including *H. pylori and H. felis*. Enno *et al.* (1995) infected BALB/c mice with *H. felis*, and observed lymphoepithelial lesions (gastric lymphomas) in 25% of the mice after 22–26 months. Such lesions were observed in both BALB/c and C57BL/6 mice infected with *H. pylori* in the study by Wang *et al.* (2003b) (see above), and in BALB/c mice infected with *H. felis* (Sutton *et al.*, 2004). However, the best model corresponds to neonatal thymectomized mice because all animals infected by *H. pylori* developed these lesions within 12 months (Fukui *et al.*, 2004).

See Table 3.2.

4. Other Relevant Data

It had been well established much before the discovery of *Helicobacter pylori* in 1983 that gastric cancers usually arose in a chronically inflamed stomach. Since the recognition of the role of *H. pylori* infection as the dominant cause of chronic gastritis, affecting approximately half of the world's population, considerable evidence has accumulated that the nature of the chronic inflammatory process driven by *H. pylori* is of critical importance in gastric carcinogenesis.

H. pylori-related gastric carcinogenesis is a slow process, typically developing over 4–6 decades, and accompanied by specific histological changes (Correa *et al.*, 1975). The 'intestinal' subtype of gastric adenocarcinoma develops through a preneoplastic sequence from chronic superficial gastritis through atrophic gastritis, intestinal metaplasia, and dysplasia. The 'diffuse' subtype is also usually preceded by many years of chronic *H. pylori*-associated gastritis, although the molecular pathways and histological changes involved in progression to cancer are less fully characterized (Peek & Blaser, 2002).

Investigating the mechanisms responsible for gastric carcinogenesis through studies *in vivo* necessitates investigating simultaneously the effects of the bacterium together with the associated intense neutrophilic and mononuclear inflammatory response, which always accompanies *H. pylori* infection. In contrast, examining direct effects of the bacterium on gastric epithelial cells is only possible in co-culture experiments *in vitro* that are subject to numerous artefacts including the almost universal use of cancer-derived gastric epithelial lines, and the lack of the normal stroma, substrate and cell-cell interactions that exist *in vivo*.

Table 3.2 Studies of gastric cancer in mice infected by *H. pylori* by gavage

Strain Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
Inbred mice				
C57BL/6 80 wk Kim et al. (2003)	10^6 CFU *H. pylori*, SS1 Gender NR *H. pylori*: n=25 Controls: n=35	No gastric tumours observed		
C57BL/6 & BALB/c 23 mo Wang et al. (2003b)	*H. pylori*, 119p *H. pylori*, G50 *H. pylori*, SS1 Gender NR	Gastric lymphoma		
	C57BL/6 *H. pylori*: n=9 (total) Controls: n=4	C57BL/6 *H. pylori* 119p: 3/4 *H. pylori* G50: 3/3 *H. pylori* SS1: 0/2 controls: 0/4		
	BALB/c *H. pylori*: n=9 (total) Controls: n=4	BALB/c *H. pylori* 119p : 2/4 *H. pylori* SS1 : 0/5 controls : 0/4		
C57BL/6 24 mo Cai et al. (2005)	10^7 CFU *H. felis* (M) *H. felis* eradication therapy* after 2 , 6 & 12 mo * made of tetracycline, metronidazole & bismuth subsalicylate orally for 14 d Controls: no eradication Number of animals per group NR	Adenocarcinoma when eradication of infection after 2 mo: 0%; 6 mo: 0%; 12 mo: 30% Adenocarcinoma when no eradication: 100%		
C57BL/6 × 12 996/SvEv 15 mo Rogers et al. (2005)	10^8 CFU *H. pylori*, SS1 (M, F) (gender distribution NR) 4 groups: 1. 0.25% salt diet 2. 7.5% salt diet 3. 0.25% salt diet + *H. pylori* 4. 7.5% salt diet + *H. pylori* Total n=62	Increased incidence of high-grade dysplasia (indefinite dysplasia or atypical hyperplasia) in Groups 3 & 4. No adenocarcinoma		High-salt diet switch Th1 to a Th2 immune response. Th1: *H. pylori*-specific IgG2c; Th2: *H. pylori*-specific IgG1.

Table 3.2 (continued)

Strain Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
TGF-β deficient mice				
pS2-dnRII derived from FVB/N strain (wild-type) 36 wk Hahm et al. (2002)	10^9 CFU *H. pylori*, 43 504 (M, F) 1. TGF-β-deficient mice (infected): $n=48$ 2. wild-type (infected): $n=48$ 3. TGF-β-deficient mice (non infected): $n=38$	Dysplasia or carcinoma: 6/7 (85.7%) 0/6 No lesion		
INS-GAS mice				
7 mo Fox et al. (2003a)	10^8 CFU *H. pylori*, SS1 (M/F) $n=20$ (total)	Carcinoma: 4/6 males; 0/6 females; 0/8 male and female controls		Only males developed gastric adenocarcinomas
28 wk Ohtani et al. (2007)	10^8 CFU *H. pylori* strain SS1 (M, F) 1. Males: $n=29$ 2. Ovariectomized females: $n=35$ 3. Intact females: $n=29$ 4. Estradiol-treated* ovariectomized females: $n=16$ Part of each group was infected or not. Sacrifice occurred at Weeks 16 & 28 post-infection *Subcutaneous placement of a time-release estradiol pellet 16 wk post-infection	Adenocarcinoma: A. 3/7 (42%) infected males B. 1/10 (10%) infected ovariectomized females C. 0/7 infected intact females D. 0/8 E$_2$ treated ovariectomized females (infected) F. 0% non infected males and females		Protective effect of estradiol
28 wk Lee et al. (2008)	10^9CFU *H. pylori*, SS1 (M) 1. Infected and untreated 2. Eradication therapy* at 8 wk post-infection 3. Eradication therapy* at 12 wk post-infection 4. Eradication therapy* at 22 wk post-infection 5. Non infected * with omeprazole, metronidazole and clarithromycin in 0.2 mL orally, for 7 d	Adenocarcinoma: 1. 10/10 (100%) 2. 1/11 (9%) 3. 8/9 (89%) 4. 6/12 (50%) 5. 0/7	[$P<0.0001$], Group 1 vs 5 [$P<0.05$], Group 1 vs 2 [$P<0.05$], Group 1 vs 4	Protective effect of eradication to the greatest extent when given early

Table 3.2 (continued)

Strain Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
p27-deficient mice				
17 mo Kuzushita et al. (2005) C57BL/6 (p27-deficient) C57BL/6 (wild-type)	10^9 CFU *H. pylori*, SS1 (M, F) Sacrifice at 15, 30, 45, 60 and 75 wk post-inoculation	Gastric carcinoma or dysplasia		
	1. wild-type + *H. pylori*	0/40, carcinoma		Incidence for carcinoma (vs dysplasia) in Group 2 can not be ascertained from data provided
	2. p27$^{-/-}$ + *H. pylori*	1/10 (30 wk), 1/6 (45 wk), 5/6 (60 wk), 2/6 (75 wk)	$P<0.05$ (60 wk vs Group 1), $P<0.05$ (75 wk vs Group 4)	
	3. Wild-type (controls)	0/9, carcinoma		
	4. p27$^{-/-}$ (controls) 25–50 animals/group	0/10, carcinoma		
TFF2-deficient mice				
19 mo Fox et al. (2007) TFF2$^{-/-}$ C57BL/6 X Sv129 C57BL/6 X Sv129 (wild-type)	10^8 CFU *H. pylori*, SS1 (M, F) 1. TFF2-deficient (infected): 20 2. TFF2-deficient (not infected): 10 3. Wild-type (infected): 20 4. Wild-type (not infected): 10	Gastric intraepithelial neoplasia 2/10 (20%) 0% 1/20 (10%) 0%		
IL-1β transgenic mice				
12 mo Tu et al. (2008)	10^8 CFU *H. felis*, ATCC 49179 (M) 1. Infected mice overexpressing human IL-1β (line 19) 2. Infected mice overexpressing human IL-1β (line 42) 3. Infected control mice 4. Uninfected line 42	Carcinomas: 1/12 (8.4%) 1/10 (10%) 0% 0%		

Table 3.2 (continued)

Strain Duration Reference	Dosing regimen, strain Gender Animals/group at start	Incidence of tumours	Significance	Comments
MALT lymphoma mice models				
26 mo Enno et al. (1995) BALB/c	10^9 CFU *H.felis*, ATCC 49179 (F) 1. Infected a. Sacrifice 0–19 mo: 167 b. Sacrifice 22–26 mo: 80 2. Controls (uninfected) a. Sacrifice 0–19 mo: 95 b. Sacrifice 22–26 mo: 48	Lymphoepithelial lesions (gastric lymphoma) 1a: 0/167 1b: 20/80 (25%) [$P<0.0001$] 2a: 0/95 2b: 0/48		Lesions are B-cell lymphoid infiltrates
22 mo Sutton et al. (2004) BALB/c	10^8 CFU *H. felis*, CS1 (F) A. Untreated (control): n=17 B. Infected: n=15 C. Immunised + infected. - *H. felis* positive: n=4 - *H. felis* negative: n=15	MALT lymphoma 1/17 13/15 4/4 5/15	[$P<0.0001$], Group B vs A [$P<0.0001$], Group C positive vs A [NS], Group C negative vs A	
12 mo Fukui et al. (2004) BALB/c	10^8 CFU *H. pylori*, TN2GF4 (M, F) Sacrifice at 2, 4, 6 and 12 mo 1. Non-thymectomized mice uninfected (Control): 40 2. Non-thymectomized mice infected: 40 3. Neonatal thymectomized (3 d) mice (nTx) uninfected: 40 4. Neonatal thymectomized (3 d) mice (nTx) infected: 40	Lymphoepithelial lesions (gastric lymphoma) 0/40 0/40 0/40 2 mo: 6/10 4 mo: 8/10 6 mo: 9/10 12 mo: 10/10		

ATCC, American Type Culture Collection; CFU, colony forming units; d, day or days; F, female; GC, gastric cancer; *H. pylori, Helicobacter pylori*; IL-1β, interleukin-1β; M, male; MALT, mucosa-associated lymphoid tissue; mo, month or months; TFF2, trefoilfactor family 2; vs, versus; wk, week or weeks

4.1 Data supporting the carcinogenicity of *H. pylori*

4.1.1 Genotoxicity linked to H.pylori infection

The intense gastric inflammatory infiltrate (gastritis) that accompanies gastric colonization by *H. pylori* in humans (or by related *Helicobacter* species in animal models) can generate potentially genotoxic reactive oxygen and nitrogen species from the inflammatory cells themselves, and from adjacent gastric epithelial cells (Macarthur et al., 2004; Ding et al., 2007).

H. pylori is not directly genotoxic *in vitro*, and evidence for genotoxicity related to *H. pylori* and/or the associated inflammatory response *in vivo* is relatively limited. An increased frequency of micronuclei in the peripheral blood lymphocytes of *H. pylori*-infected patients (Suárez et al., 2007), more DNA strand breaks as shown by the comet assay (Ladeira et al., 2004), increased gastric mucosal DNA adduct (8-hydroxy-2′-deoxyguanosine) formation (Farinati et al., 1998), and an increased mutation frequency in the gastric mucosa of *H. pylori*- or *felis*-infected transgenic mutation reporter mice (Touati et al., 2003; Jenks et al., 2003) have all been reported to occur relatively early during *Helicobacter* infection, before gastric cancer development.

Increased expression of activation-induced cytidine deaminase (AID), a DNA- and RNA-editing enzyme, was reported in *H. pylori*-infected human gastric biopsies, and was noted to decrease following *H. pylori* eradication. When human gastric adenocarcinoma epithelial cells were infected *in vitro* with *H. pylori*, the resulting AID overexpression occurred in parallel with the accumulation of mutations in *p53*, but much less frequently in *β-catenin* and *c-myc* genes; this supports a relatively specific role for AID in the generation of *p53* mutation by *H. pylori* (Matsumoto et al., 2007).

4.1.2 Changes in gene expression

Several reports have demonstrated that *H. pylori* alters the expression of specific oncogenes and tumour-suppressor genes implicated in gastric carcinogenesis. For example *H. pylori* infection promotes the nuclear translocation of β-catenin, thereby activating downstream β-catenin-responsive genes including cyclin D (Franco et al., 2005), upregulates the p53 homologue p73 in gastric cells to promote apoptosis (Wei et al., 2008), and decreases expression of the cell-cycle inhibitory protein p27 (Eguchi et al., 2003) that is known to be lost in aggressive gastric cancers.

Hypermethylation of several genes has been found in *H. pylori*-associated chronic gastritis, including *E-cadherin* and *p14*, that are of potential importance mechanistically in gastric carcinogenesis. Methylation of the *E-cadherin* gene has been reported to reverse with the eradication of *H. pylori*. *In vitro*, *H. pylori* and the reactive oxygen species or nitric oxide released during the chronic inflammatory process may be responsible for gene methylation (Hmadcha et al., 1999; Tamura, 2004; Chan et al., 2006; Maekita et al., 2006; Nardone et al., 2007; Tahara et al., 2007).

4.1.3 Altered cell turnover

It is well established that in human and experimental animal infections, *H. pylori* is associated with increased numbers of both apoptotic and proliferating gastric epithelial cells (Shirin et al., 2001). Increased cell turnover has long been linked to a risk of carcinogenesis, based on the increased chance of mutations arising under conditions of accelerated DNA replication (Preston-Martin et al., 1990). In contrast to the stimulation of apoptosis in association with *H. pylori* infection, some have reported that *H. pylori* may have anti-apoptotic effects (Peek et al., 1997; Mimuro et al., 2007), which could directly promote aberrant tissue growth and perhaps gastric neoplasia.

The development of an acquired resistance to *H. pylori*-induced gastric epithelial apoptosis has been associated with decreased expression of p27 *in vitro* (Shirin *et al.*, 2000), and downregulation of Fas-mediated signalling pathways *in vivo* (Houghton *et al.*, 2000). However, there is no evidence that the balance between programmed cell death and cell proliferation is any different in subjects who are at higher risk for cancer compared with the *H. pylori*-infected population in general (Moss *et al.*, 1999). [The Working Group noted that most studies addressing postulated mechanisms of carcinogenicity *in vivo* have compared only *H. pylori*-infected patients with uninfected patients (or the same patients before and after *H. pylori* eradication), but have not compared the minority of subjects who develop gastric cancer with the majority who do not.]

4.1.4 Changes in gastric acid secretion

While some persons infected by *H. pylori* develop duodenal ulcers related to depletion of somatostatin secretion and increased gastrin and gastric acid secretion (Calam, 1995), in some others, there is a marked decrease of acid secretion from the loss of or damage to the acid-secreting parietal cells. This state of hypochlorhydria typically occurs in patients progressing towards the 'intestinal' type of gastric cancer, where the loss of acid secretion can promote intragastric colonization of non-*Helicobacter* bacteria, and the formation of luminal *N*-nitrosamines with some genotoxic potential (Sanduleanu *et al.*, 2001).

4.1.5 Inflammation and bone-marrow derived stem cells

An especially intense inflammatory response to *H. pylori* is thought to induce greater gastric epithelial cell damage, faster cell turnover, and the eventual emergence of gastric epithelial cells carrying cancer-prone mutations (Moss & Blaser, 2005). An alternative view of the detrimental effects of the infiltrating inflammatory cells in the gastric mucosa is that of Houghton *et al.* (2004), who provided evidence in *H. felis*-infected mice that the bone-marrow-derived haematopoietic stem cells recruited to the gastric mucosa by *H. felis* can repopulate this mucosa, and progress through metaplasia and dysplasia to intraepithelial cancer. Whether this occurs during human gastric carcinogenesis remains untested thus far.

4.2 Host immune system and genetic susceptibility

Some of the genetic factors underpinning the pathophysiology of the loss of normal gastric secretory function and severe inflammation in gastric carcinogenesis have been uncovered in recent years. Based upon evidence that interleukin-1β (IL-1β) is both a potent gastric acid secretion inhibitor and a pro-inflammatory gastric cytokine, El-Omar *et al.* (2000, 2001) documented the association of pro-inflammatory single nucleotide polymorphisms (SNPs) in both the *IL-1β* gene and the *IL-1RN* gene that encode the endogenous IL-1 receptor antagonist in association with hypochlorhydria and gastric atrophy in first-degree relatives of gastric cancer patients in a Scottish population. They also showed that pro-inflammatory *IL-1β* and *IL-1RN* SNPs were associated with a 2–3-fold increase in gastric cancer risk in a case–control study from Poland. Figueiredo *et al.* (2002) evaluated simultaneously *H. pylori vacA* and *cagA* genotypes together with *IL-1 β* and the *IL-1RN* genotypes of a large group of Portuguese shipyard workers with chronic gastritis and gastric cancer patients. They obtained risk ratios for gastric cancer among *H. pylori*-infected patients that differed markedly, based upon a combination of these four genes.

Moderate associations between SNPs in other genes encoding cytokines or genes involved in the initiation and maintenance of inflammation

have also been reported that include genes that encode tumour necrosis factor α (TNF-α), IL-10, IL-8, and toll-like receptor 4 (Amieva & El-Omar, 2008). Furthermore, increased non-cardia gastric cancer risk in *H. pylori*-infected subjects has also been related to polymorphisms in IL-1β, IL-1RN, TNF-α and IL-10 in subjects from a multicentre case–control study in the US population (El-Omar *et al.*, 2003) but not, in that same study, to cardia gastric cancer or oesophageal adenocarcinoma risk. Thus, these SNPs appear to be relatively specific to increased distal gastric cancer risk following *H. pylori* infection.

There remains considerable debate regarding the reproducibility of many of these findings, reflecting perhaps differences in the populations studied, and the relationship of the cases to the controls in individual studies (Perri *et al.*, 2005; Starzyńska *et al.*, 2006). Most studies are relatively small and evaluate only a few SNPs simultaneously, without adjustment for other potential confounding variables such as *H. pylori* genotype or other SNPs. Recent meta-analyses suggest that the influence of *IL-1β* and *IL-1RN* SNPs on gastric cancer risk is relatively weak, and/or confined to Caucasians (Camargo *et al.*, 2006; Kamangar *et al.*, 2006b), whereas the relationship between non-cardia gastric cancer and two specific *TNF-α* SNPs (especially the –308AA SNP) is more consistent, though again mainly in Western populations (Gorouhi *et al.*, 2008; Zhang *et al.*, 2008). [The Working Group noted that larger and more extensive studies are necessary to determine the importance of individual SNPs in gastric cancer risk in different populations, and in understanding how they may modulate the risk of cancer following *H. pylori* infection.]

4.3 Factors associated with gastric carcinogenesis

4.3.1 H. pylori virulence factors

(a) cag Pathogenicity island

As reviewed in Section 2, although CagA-positive strains confer an increased risk of gastric carcinogenesis, CagA-positive infections are also associated with the development of duodenal ulcer disease, which is itself inversely related to gastric cancer risk (Hansson *et al.*, 1996; Nomura *et al.*, 2002b). This suggests that factors other than just the presence or absence of CagA may be important in gastric carcinogenesis. In regions such as south-eastern Asia, where almost all strains are CagA-positive, structural variations in tyrosine phosphorylation sites in the *C*-terminal domain of the CagA protein have been identified. These variations within regions encoded by the five amino acids sequence Glu-Pro-Ile-Tyr-Ala (EPIYA) serve as sites of CagA phosphorylation by gastric epithelial Src kinases. Four types of EPIYA motifs have been described (A through D), but the number of repeats of the EPIYA-C sequence in particular correlates with increased CagA phosphorylation, and a more marked phenotypic effect on infected gastric epithelial cells *in vitro*. EPIYA sequences differ markedly between east Asian strains (where gastric cancer is most prevalent), and western European/North American strains (Yamaoka *et al.*, 1998; Basso *et al.*, 2008). In a multivariate analysis of 203 Italian *H. pylori*-infected patients, 53 of whom had gastric cancer, the number of repeats of the EPIYA-C motif was associated with the prevalence of both gastric cancer and its histological precursor, intestinal metaplasia (Basso *et al.*, 2008). Similar associations of EPIYA motifs with gastric cancer have been described in smaller studies from east Asia (Yamaoka *et al.*, 1998).

(b) Evidence of carcinogenic effect of cag genes in animal models

CagA-positive strains of *H. pylori* are associated with more vigorous gastric inflammatory responses. Several genes within the *cag* pathogenicity island, though not *cagA*, may facilitate colonization (Marchetti & Rappuoli, 2002). Two studies have highlighted the importance of an intact *cag* pathogenicity island in the induction of gastric cancer in rodent species. In the gerbil model infected by *H. pylori* strain 7.13, an isogenic mutant lacking the *cagA* gene failed to produce gastric cancer whereas cancers were seen in over 50% of the gerbils infected by wild-type or *vacA*-negative strains. There was also much less inflammation with the *cagA* knockout strain (Franco *et al.*, 2008). Deletion of *cagE*, which is known to be important in the functionality of the type 4 secretory system, delayed, but did not prevent, gastric cancer in the INS-GAS mouse model (Fox *et al.*, 2003b).

The only direct evidence of oncogenicity of the CagA protein *in vivo* is in transgenic mice overexpressing a virulent form of the *cagA* gene (Ohnishi *et al.*, 2008). About 10% of such mice developed hyperplastic polyps and about 1% gastric or small intestinal cancer after 72 weeks, whether the CagA protein was targeted specifically to parietal cells in the stomach or expressed ubiquitously in all cells. Unexpectedly, transgenic CagA expression did not induce gastric inflammation, and leukaemias were also observed in some of the mice. The latter is consistent with the known effect of CagA on activating SHP-2 tyrosine phosphatase, an event that is also involved in leukaemogenesis.

In contrast to the paucity of data regarding the carcinogenic effects of *cag*-encoded proteins in animal models, there is a very extensive literature describing the cellular and molecular consequences of CagA translocation by the type 4 secretory system that is encoded by multiple genes within the *cag* pathogenicity island (reviewed in Buret *et al.*, 2005; Backert & Selbach, 2008; Wen & Moss, 2009). Following adherence of *H. pylori* to gastric epithelial cells, the CagL protein on the cag pilus interacts with the $\alpha_5\beta_1$ host cell integrin to initiate CagA translocation. Translocated CagA is then phosphorylated by host cell Src kinases at EPIYA tyrosine phosphorylation sites to promote downstream signalling, resulting in reorganization of the actin cytoskeleton, and enhanced cellular motility (thus giving rise to the so-called "humming bird" phenotype in cultured cells). Activation of the transcription factor NF-κB by CagA leads to mitogenic signalling through mitogen-activated protein (MAP) kinase pathways, and also to pro-inflammatory gene activation. Some other cellular events activated by CagA translocation are not dependent on CagA phosphorylation. These events include the disruption of tight and adherent junctions between adjacent gastric epithelial cells through interactions with occludin, zonulin-1, junctional adhesion molecules, claudins, E-cadherin, and β-catenin. β-Catenin translocation to the nucleus promotes further mitogenic gene expression. One of the hallmark epithelial consequences of *cag*-positive infections is secretion of the pro-inflammatory chemokine IL-8, but it is currently unclear whether this is dependent on CagA translocation or by some other *cag*-island dependent stimulus. The muramyldypeptide component of *H. pylori*'s cell wall, peptidoglycan, is also translocated to gastric epithelial cells by type 4 secretion, where it can interact with the intracellular NOD1 protein, a component of the innate immune response to pathogen-associated molecular patterns of bacteria. NOD1-binding also stimulates NF-κB-dependent signalling.

(c) VacA

In many studies in Western populations, peptic ulcer disease has been strongly associated with the *vacA* genotype (particularly s1m1), while in some of these studies the s1m1 genotype has been linked to gastric cancer (Miehlke *et al.*,

2000). East Asian strains are almost universally s1m1, and are not associated with any particular clinical outcome. The recent reports of *vacA* i region polymorphism where the i1 type was associated with gastric cancer in Iranian ([Rhead et al., 2007](#)) and Italian ([Basso et al., 2008](#)) populations are worthy of further corroboration by other groups. However, as for *cagA*, the *vacA* i region polymorphism may not correlate with gastric cancer risk in east Asia, where very few strains are of the i2 type ([Ogiwara et al., 2008](#)).

(d) Evidence of carcinogenic effect of vacA in animal models

VacA deletion does not alter the inflammatory or carcinogenic effects of *H. pylori* in the gerbil model ([Franco et al., 2008](#)). Multiple biological effects of VacA have been demonstrated *in vitro*, including the induction of apoptosis in epithelial cells, and the inhibition of T-cell activation and proliferation that may allow for *H. pylori* persistence, but the relevance of these observations to gastric carcinogenesis remains obscure ([Takeshima et al., 2009](#); [Matsumoto et al., 2011](#)).

(e) BabA and SabA

Some studies have demonstrated an association between the *babA2* genotype and gastric cancer ([Yu et al., 2002](#)) though this association may be confounded by the frequent co-association of *babA2* with *vacA* s1m1 and *cagA* positivity. Although the induction of *SabA* expression in *H. pylori* strains has been associated with gastric epithelial cell adhesion ([Marcos et al., 2008](#)), no good evidence points to a more direct role of SabA in carcinogenesis.

4.3.2 Cofactors and co-infections

Effects of dietary salt on inflammation and proliferation have been observed in some animal studies, but the data from these is not consistent ([Rogers et al., 2005](#)).

H. pylori induces a predominantly Th1 immune response which is more typical of intracellular bacteria rather than extracellular organisms that produce typically a Th2 response. Because gastric cancer is thought to result from a Th1 pro-inflammatory immune response, it has been postulated that concurrent parasitic infection (which is more likely to induce a Th2 immune response) may modify the gastric inflammation and carcinogenic effects of *H. pylori*. Such a hypothesis is supported by *H. felis*-induced gastric atrophy in mice with concurrent intestinal nematode infection ([Fox et al., 2000](#)). Although gastric cancer was not evaluated in this model, this hypothesis may perhaps explain the low rate of *H. pylori*-associated cancer despite high *H. pylori* infection rate in areas of the world where parasitic infection is common ([Whary et al., 2005](#)).

4.4 Mechanisms of lymphomagenesis

4.4.1 Host immune system and genetic susceptibility in humans

Several different host polymorphisms associated with gastric lymphoma have been reported. These include the 49 G/G polymorphism in *CTLA4*, coding for a receptor on CD4-positive T cells, which inhibits T-cell functioning on ligand binding. This polymorphism was associated with a 6-fold higher risk of developing MALT lymphoma after *H. pylori* infection in a study from Taiwan, China ([Cheng et al., 2006](#)). Association of the R702W mutation in the *NOD2/CARD15* gene was demonstrated in a study in German/Austrian patients with a 2.4-fold risk of gastric lymphoma development ([Rosenstiel et al., 2006](#)). Susceptible polymorphisms for gastric lymphoma have also been reported at certain human leukocyte antigen (HLA) loci in a small Japanese cohort ([Kawahara et al., 2005](#)), and within the *TNF-α* gene (moderate effects at distinct loci, which were different for low- and

high-grade lymphoma) (Hellmig *et al.*, 2005a), and in the toll-like receptor TLR4 in German/Austrian patients (Hellmig *et al.*, 2005b). Each of these findings requires independent corroboration in other populations, and the understanding of additional factors that may predispose certain individuals or populations to gastric lymphoma following *H. pylori* exposure remains poor.

4.4.2 H. pylori virulence factors

Unlike the large literature regarding the importance of certain *H. pylori* factors in association with gastric cancer, the data for gastric lymphoma are inconsistent, and generally not supportive of any specific association.

4.4.3 Molecular mechanisms

The normal human gastric stomach contains few or no inflammatory cells. On infection by *H. pylori* or other *Helicobacter* species, such as *H. heilmanii*, an active infiltration of acute and chronic inflammatory cells (including B-cell lymphoid follicles) results. This so-called MALT lymphoma is the precursor of a low-grade lymphoma of B cells, gastric MALT lymphoma, originating in B cells of the marginal zone of the secondary follicles that are generated in the inflammatory response to *H. pylori* (Du & Isaccson, 2002). Hussell *et al.* (1993) demonstrated that in the early stages of MALT, lymphoma B-cell proliferation was dependent on both *H. pylori* antigens, and tumour-infiltrating T cells.

Most cases of MALT lymphoma are clonal, and will respond to *H. pylori* eradication. However, approximately 20% of MALT lymphomas are not responsive to eradication therapy, and it is thought that this is because they acquire further mutations, in particular the *API2-MALT1* fusion gene that results from a translocation of [t(11;18)(q21;q21)]. Three other relatively uncommon translocations [t(1;14)(p22;q32), t(14;18)(q32;q21), and t(3;14)(p13;q32)] are also associated with gastric MALT lymphoma. Three of the four above translocations lead to the activation of NF-κB, a transcription factor important in inhibiting programmed cell death (Sagaert *et al.*, 2007). Other mutations in gastric MALT lymphoma include *TP53*, *c-MYC* (approximately 20% of cases each), and epigenetic events such as gene promoter hypermethylation of *p16* (Isaacson, 1999; Huang *et al.*, 2004).

[The Working Group noted that how *H. pylori* and/or the associated inflammatory response promote downstream mutations that result in subsequent *H. pylori*-independent growth and high-grade disease that may be refractory to removing the offending antigen has not been defined. Whether high-grade lymphomas that are refractory to *H. pylori* eradication arise through the same pathways that lead *H. pylori* to promote low-grade lymphomagenesis is also unclear and worthy of further investigation. Little is known of possible environmental cofactors in the predisposition to *H. pylori*-induced gastric lymphomagenesis.]

4.5 Synthesis

Multiple lines of evidence point to a central role for the chronic gastric inflammatory response and resulting oxidative stress in *H. pylori*-associated gastric carcinogenesis. This leads to altered cellular turnover accompanied by changes in gene expression, methylation, and mutation. The nature and extent of the inflammatory response, and the subsequent effects of the inflammatory environment on gastric epithelial cells are associated with three interrelated factors: 1) host-determined modulation of inflammatory responses, 2) specific *H. pylori* virulence factors, including CagA, and 3) altered gastric secretory function.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of chronic infection with *Helicobacter pylori.* Chronic infection with *Helicobacter pylori* causes non-cardia gastric carcinoma and low-grade B-cell MALT gastric lymphoma.

For oesophageal adenocarcinoma, there is *evidence suggesting lack of carcinogenicity* of chronic infection with *Helicobacter pylori* in humans.

There is *sufficient evidence* in experimental animals for the carcinogenicity of infection with *Helicobacter pylori*.

Chronic infection with *Helicobacter pylori* is *carcinogenic to humans (Group 1).*

References

Adrian M, Cover TL, Dubochet J, Heuser JE (2002). Multiple oligomeric states of the Helicobacter pylori vacuolating toxin demonstrated by cryo-electron microscopy. *J Mol Biol*, 318: 121–133. doi:10.1016/S0022-2836(02)00047-5 PMID:12054773

Akopyants NS, Clifton SW, Kersulyte D *et al.* (1998). Analyses of the cag pathogenicity island of Helicobacter pylori. *Mol Microbiol*, 28: 37–53. doi:10.1046/j.1365-2958.1998.00770.x PMID:9593295

Alm RA, Ling LS, Moir DT *et al.* (1999). Genomic-sequence comparison of two unrelated isolates of the human gastric pathogen Helicobacter pylori. *Nature*, 397: 176–180. doi:10.1038/16495 PMID:9923682

Amieva MR & El-Omar EM (2008). Host-bacterial interactions in Helicobacter pylori infection. *Gastroenterology*, 134: 306–323. doi:10.1053/j.gastro.2007.11.009 PMID:18166359

Anderson LA, Murphy SJ, Johnston BT *et al.* (2008). Relationship between Helicobacter pylori infection and gastric atrophy and the stages of the oesophageal inflammation, metaplasia, adenocarcinoma sequence: results from the FINBAR case-control study. *Gut*, 57: 734–739. doi:10.1136/gut.2007.132662 PMID:18025067

Aspholm-Hurtig M, Dailide G, Lahmann M *et al.* (2004). Functional adaptation of BabA, the H. pylori ABO blood group antigen binding adhesin. *Science*, 305: 519–522. doi:10.1126/science.1098801 PMID:15273394

Atherton JC, Cao P, Peek RM Jr *et al.* (1995). Mosaicism in vacuolating cytotoxin alleles of Helicobacter pylori. Association of specific vacA types with cytotoxin production and peptic ulceration. *J Biol Chem*, 270: 17771–17777. PMID:7629077

Aygenc E, Selcuk A, Celikkanat S *et al.* (2001). The role of Helicobacter pylori infection in the cause of squamous cell carcinoma of the larynx. *Otolaryngol Head Neck Surg*, 125: 520–521. PMID:11700453

Backert S & Selbach M (2008). Role of type IV secretion in Helicobacter pylori pathogenesis. *Cell Microbiol*, 10: 1573–1581. doi:10.1111/j.1462-5822.2008.01156.x PMID:18410539

Banatvala N, Mayo K, Megraud F *et al.* (1993). The cohort effect and Helicobacter pylori. *J Infect Dis*, 168: 219–221. doi:10.1093/infdis/168.1.219 PMID:8515114

Basso D, Zambon CF, Letley DP *et al.* (2008). Clinical relevance of Helicobacter pylori cagA and vacA gene polymorphisms. *Gastroenterology*, 135: 91–99. doi:10.1053/j.gastro.2008.03.041 PMID:18474244

Bayerdörffer E, Neubauer A, Rudolph B *et al.*MALT Lymphoma Study Group (1995). Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type after cure of Helicobacter pylori infection. *Lancet*, 345: 1591–1594. doi:10.1016/S0140-6736(95)90113-2 PMID:7783535

Böhmer CJ, Klinkenberg-Knol EC, Kuipers EJ *et al.* (1997). The prevalence of Helicobacter pylori infection among inhabitants and healthy employees of institutes for the intellectually disabled. *Am J Gastroenterol*, 92: 1000–1004. PMID:9177519

Boneca IG, de Reuse H, Epinat JC *et al.* (2003). A revised annotation and comparative analysis of Helicobacter pylori genomes. *Nucleic Acids Res*, 31: 1704–1714. doi:10.1093/nar/gkg250 PMID:12626712

Borén T, Falk P, Roth KA *et al.* (1993). Attachment of Helicobacter pylori to human gastric epithelium mediated by blood group antigens. *Science*, 262: 1892–1895. doi:10.1126/science.8018146 PMID:8018146

Brenner H, Arndt V, Bode G *et al.* (2002). Risk of gastric cancer among smokers infected with Helicobacter pylori. *Int J Cancer*, 98: 446–449. doi:10.1002/ijc.10201 PMID:11920598

Brenner H, Arndt V, Stegmaier C *et al.* (2004). Is Helicobacter pylori infection a necessary condition for noncardia gastric cancer? *Am J Epidemiol*, 159: 252–258. doi:10.1093/aje/kwh039 PMID:14742285

Brenner H, Berg G, Lappus N *et al.* (1999a). Alcohol consumption and Helicobacter pylori infection: results from the German National Health and Nutrition Survey. *Epidemiology*, 10: 214–218. doi:10.1097/00001648-199905000-00004 PMID:10230827

Brenner H, Rothenbacher D, Bode G, Adler G (1997). Relation of smoking and alcohol and coffee consumption to active Helicobacter pylori infection: cross sectional study. *BMJ*, 315: 1489–1492. PMID:9420488

Brenner H, Rothenbacher D, Bode G, Adler G (1999b). Inverse graded relation between alcohol consumption and active infection with Helicobacter pylori. *Am J Epidemiol*, 149: 571–576. PMID:10084247

Brenner H, Weyermann M, Rothenbacher D (2006). Clustering of Helicobacter pylori infection in couples: differences between high- and low-prevalence population groups. *Ann Epidemiol*, 16: 516–520. doi:10.1016/j.annepidem.2005.09.009 PMID:16388968

Brown LM (2000). Helicobacter pylori: epidemiology and routes of transmission. *Epidemiol Rev*, 22: 283–297. PMID:11218379

Buret AG, Fedwick JP, Flynn AN (2005). Host epithelial interactions with Helicobacter pylori: a role for disrupted gastric barrier function in the clinical outcome of infection? *Can J Gastroenterol*, 19: 543–552. PMID:16151546

Cai X, Carlson J, Stoicov C *et al.* (2005). Helicobacter felis eradication restores normal architecture and inhibits gastric cancer progression in C57BL/6 mice. *Gastroenterology*, 128: 1937–1952. doi:10.1053/j.gastro.2005.02.066 PMID:15940628

Calam J (1995). The somatostatin-gastrin link of Helicobacter pylori infection. *Ann Med*, 27: 569–573. doi:10.3109/07853899509002471 PMID:8541034

Camargo MC, Mera R, Correa P *et al.* (2006). Interleukin-1beta and interleukin-1 receptor antagonist gene polymorphisms and gastric cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 15: 1674–1687. doi:10.1158/1055-9965.EPI-06-0189 PMID:16985030

Cao X, Tsukamoto T, Nozaki K *et al.* (2007). Severity of gastritis determines glandular stomach carcinogenesis in Helicobacter pylori-infected Mongolian gerbils. *Cancer Sci*, 98: 478–483. doi:10.1111/j.1349-7006.2007.00416.x PMID:17284248

Cao X, Tsukamoto T, Seki T *et al.* (2008). 4-Vinyl-2,6-dimethoxyphenol (canolol) suppresses oxidative stress and gastric carcinogenesis in Helicobacter pylori-infected carcinogen-treated Mongolian gerbils. *Int J Cancer*, 122: 1445–1454. doi:10.1002/ijc.23245 PMID:18059022

Censini S, Lange C, Xiang Z *et al.* (1996). cag, a pathogenicity island of Helicobacter pylori, encodes type I-specific and disease-associated virulence factors. *Proc Natl Acad Sci U S A*, 93: 14648–14653. doi:10.1073/pnas.93.25.14648 PMID:8962108

Chan AO, Peng JZ, Lam SK *et al.* (2006). Eradication of Helicobacter pylori infection reverses E-cadherin promoter hypermethylation. *Gut*, 55: 463–468. doi:10.1136/gut.2005.077776 PMID:16428266

Chen LT, Lin JT, Shyu RY *et al.* (2001). Prospective study of Helicobacter pylori eradication therapy in stage I(E) high-grade mucosa-associated lymphoid tissue lymphoma of the stomach. *J Clin Oncol*, 19: 4245–4251. PMID:11709568

Chen LT, Lin JT, Tai JJ *et al.* (2005). Long-term results of anti-Helicobacter pylori therapy in early-stage gastric high-grade transformed MALT lymphoma. *J Natl Cancer Inst*, 97: 1345–1353. doi:10.1093/jnci/dji277 PMID:16174856

Cheng TY, Lin JT, Chen LT *et al.* (2006). Association of T-cell regulatory gene polymorphisms with susceptibility to gastric mucosa-associated lymphoid tissue lymphoma. *J Clin Oncol*, 24: 3483–3489. doi:10.1200/JCO.2005.05.5434 PMID:16849765

Colbeck JC, Hansen LM, Fong JM, Solnick JV (2006). Genotypic profile of the outer membrane proteins BabA and BabB in clinical isolates of Helicobacter pylori. *Infect Immun*, 74: 4375–4378. doi:10.1128/IAI.00485-06 PMID:16790815

Correa P, Haenszel W, Cuello C *et al.* (1975). A model for gastric cancer epidemiology. *Lancet*, 306: 58–60. doi:10.1016/S0140-6736(75)90498-5 PMID:49653

Cover TL & Blaser MJ (1992). Purification and characterization of the vacuolating toxin from Helicobacter pylori. *J Biol Chem*, 267: 10570–10575. PMID:1587837

Cover TL, Hanson PI, Heuser JE (1997). Acid-induced dissociation of VacA, the Helicobacter pylori vacuolating cytotoxin, reveals its pattern of assembly. *J Cell Biol*, 138: 759–769. doi:10.1083/jcb.138.4.759 PMID:9265644

Cover TL, Tummuru MK, Cao P *et al.* (1994). Divergence of genetic sequences for the vacuolating cytotoxin among Helicobacter pylori strains. *J Biol Chem*, 269: 10566–10573. PMID:8144644

Crabtree JE, Taylor JD, Wyatt JI *et al.* (1991). Mucosal IgA recognition of Helicobacter pylori 120 kDa protein, peptic ulceration, and gastric pathology. *Lancet*, 338: 332–335. doi:10.1016/0140-6736(91)90477-7 PMID:1677696

D'Onghia V, Leoncini R, Carli R *et al.* (2007). Circulating gastrin and ghrelin levels in patients with colorectal cancer: correlation with tumour stage, Helicobacter pylori infection and BMI. *Biomed Pharmacother*, 61: 137–141. doi:10.1016/j.biopha.2006.08.007 PMID:17258885

Danesh J (1999). Helicobacter pylori infection and gastric cancer: systematic review of the epidemiological studies. *Aliment Pharmacol Ther*, 13: 851–856. doi:10.1046/j.1365-2036.1999.00546.x PMID:10383517

de Bernard M, Burroni D, Papini E *et al.* (1998). Identification of the Helicobacter pylori VacA toxin domain active in the cell cytosol. *Infect Immun*, 66: 6014–6016. PMID:9826387

De Groote D, Van Doorn LJ, Van den Bulck K *et al.* (2005). Detection of non-pylori Helicobacter species in "Helicobacter heilmannii"-infected humans. *Helicobacter*, 10: 398–406. doi:10.1111/j.1523-5378.2005.00347.x PMID:16181350

de Martel C, Llosa AE, Farr SM *et al.* (2005). Helicobacter pylori infection and the risk of development of

esophageal adenocarcinoma. *J Infect Dis*, 191: 761–767. doi:10.1086/427659 PMID:15688293

de Martel C, Llosa AE, Friedman GD *et al.* (2008). Helicobacter pylori infection and development of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*, 17: 1188–1194. doi:10.1158/1055-9965.EPI-08-0185 PMID:18483341

de Martel C, Plummer M, Parsonnet J *et al.* (2009). Helicobacter species in cancers of the gallbladder and extrahepatic biliary tract. *Br J Cancer*, 100: 194–199. doi:10.1038/sj.bjc.6604780 PMID:19034278

de Sanjosé S, Dickie A, Alvaro T *et al.* (2004). Helicobacter pylori and malignant lymphoma in Spain. *Cancer Epidemiol Biomarkers Prev*, 13: 944–948. PMID:15184250

Ding SZ, Minohara Y, Fan XJ *et al.* (2007). Helicobacter pylori infection induces oxidative stress and programmed cell death in human gastric epithelial cells. *Infect Immun*, 75: 4030–4039. doi:10.1128/IAI.00172-07 PMID:17562777

Doig P, de Jonge BL, Alm RA *et al.* (1999). Helicobacter pylori physiology predicted from genomic comparison of two strains. *Microbiol Mol Biol Rev*, 63: 675–707. PMID:10477312

Dominici P, Bellentani S, Di Biase AR *et al.* (1999). Familial clustering of Helicobacter pylori infection: population based study. *BMJ*, 319: 537–540. PMID:10463891

Dore MP, Realdi G, Mura D *et al.* (2002). Helicobacter infection in patients with HCV-related chronic hepatitis, cirrhosis, and hepatocellular carcinoma. *Dig Dis Sci*, 47: 1638–1643. doi:10.1023/A:1015848009444 PMID:12141829

Du MQ & Isaccson PG (2002). Gastric MALT lymphoma: from aetiology to treatment. *Lancet Oncol*, 3: 97–104. doi:10.1016/S1470-2045(02)00651-4 PMID:11902529

Dubois A & Borén T (2007). Helicobacter pylori is invasive and it may be a facultative intracellular organism. *Cell Microbiol*, 9: 1108–1116. doi:10.1111/j.1462-5822.2007.00921.x PMID:17388791

Ece F, F Hatabay N, Erdal N *et al.* (2005). Does Helicobacter pylori infection play a role in lung cancer? *Respir Med*, 99: 1258–1262. doi:10.1016/j.rmed.2005.02.038 PMID:16140226

Eguchi H, Herschenhous N, Kuzushita N, Moss SF (2003). Helicobacter pylori increases proteasome-mediated degradation of p27(kip1) in gastric epithelial cells. *Cancer Res*, 63: 4739–4746. PMID:12907657

Ekström AM, Eriksson M, Hansson LE *et al.* (1999). Occupational exposures and risk of gastric cancer in a population-based case-control study. *Cancer Res*, 59: 5932–5937. PMID:10606238

Ekström AM, Held M, Hansson LE *et al.* (2001). Helicobacter pylori in gastric cancer established by CagA immunoblot as a marker of past infection. *Gastroenterology*, 121: 784–791. doi:10.1053/gast.2001.27999 PMID:11606491

Ekström AM, Serafini M, Nyrén O *et al.* (2000). Dietary antioxidant intake and the risk of cardia cancer and noncardia cancer of the intestinal and diffuse types: a population-based case-control study in Sweden. *Int J Cancer*, 87: 133–140. doi:10.1002/1097-0215(20000701)87:1<133::AID-IJC20>3.0.CO;2-E PMID:10861464

El-Omar EM, Carrington M, Chow WH *et al.* (2000). Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature*, 404: 398–402. doi:10.1038/35006081 PMID:10746728

El-Omar EM, Carrington M, Chow WH *et al.* (2001). The role of interleukin-1 polymorphisms in the pathogenesis of gastric cancer. *Nature*, 412: 99 doi:10.1038/35083631 PMID:11808612

El-Omar EM, Rabkin CS, Gammon MD *et al.* (2003). Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. *Gastroenterology*, 124: 1193–1201. doi:10.1016/S0016-5085(03)00157-4 PMID:12730860

El-Zahabi LM, Jamali FR, El-Hajj II *et al.* (2007). The value of EUS in predicting the response of gastric mucosa-associated lymphoid tissue lymphoma to Helicobacter pylori eradication. *Gastrointest Endosc*, 65: 89–96. doi:10.1016/j.gie.2006.05.009 PMID:17185085

Elfvin A, Bölin I, Von Bothmer C *et al.* (2005). Helicobacter pylori induces gastritis and intestinal metaplasia but no gastric adenocarcinoma in Mongolian gerbils. *Scand J Gastroenterol*, 40: 1313–1320. doi:10.1080/00365520510023611 PMID:16334441

Enno A, O'Rourke JL, Howlett CR *et al.* (1995). MALToma-like lesions in the murine gastric mucosa after long-term infection with Helicobacter felis. A mouse model of Helicobacter pylori-induced gastric lymphoma. *Am J Pathol*, 147: 217–222. PMID:7604881

Epplein M, Nomura AM, Hankin JH *et al.* (2008). Association of Helicobacter pylori infection and diet on the risk of gastric cancer: a case-control study in Hawaii. *Cancer Causes Control*, 19: 869–877. doi:10.1007/s10552-008-9149-2 PMID:18369531

Escobar ML & Kawakami E (2004). Evidence of mother-child transmission of Helicobacter pylori infection. *Arq Gastroenterol*, 41: 239–244. doi:10.1590/S0004-28032004000400008 PMID:15806268

Eslick GD (2003). Pregnant women and the Helicobacter pylori generation effect. *Helicobacter*, 8: 643 doi:10.1111/j.1523-5378.2003.00188.x PMID:14632679

Eslick GD, Lim LL, Byles JE *et al.* (1999). Association of Helicobacter pylori infection with gastric carcinoma: a meta-analysis. *Am J Gastroenterol*, 94: 2373–2379. doi:10.1111/j.1572-0241.1999.01360.x PMID:10483994

Everhart JE (2000). Recent developments in the epidemiology of Helicobacter pylori. *Gastroenterol Clin North Am*, 29: 559–578. doi:10.1016/S0889-8553(05)70130-8 PMID:11030073

Everhart JE, Kruszon-Moran D, Perez-Perez GI *et al.* (2000). Seroprevalence and ethnic differences in Helicobacter pylori infection among adults in the United States. *J Infect Dis*, 181: 1359–1363. doi:10.1086/315384 PMID:10762567

Falush D, Wirth T, Linz B *et al.* (2003). Traces of human migrations in Helicobacter pylori populations. *Science*, 299: 1582–1585. doi:10.1126/science.1080857 PMID:12624269

Farinati F, Cardin R, Degan P *et al.* (1998). Oxidative DNA damage accumulation in gastric carcinogenesis. *Gut*, 42: 351–356. doi:10.1136/gut.42.3.351 PMID:9577340

Feldman RA, Deeks JJ, Evans SJ (1995). Multi-laboratory comparison of eight commercially available Helicobacter pylori serology kits. Helicobacter pylori Serology Study Group. *Eur J Clin Microbiol Infect Dis*, 14: 428–433. doi:10.1007/BF02114899 PMID:7556232

Figueiredo C, Machado JC, Pharoah P *et al.* (2002). Helicobacter pylori and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. *J Natl Cancer Inst*, 94: 1680–1687. PMID:12441323

Fireman Z, Trost L, Kopelman Y *et al.* (2000). Helicobacter pylori: seroprevalence and colorectal cancer. *Isr Med Assoc J*, 2: 6–9. PMID:10892362

Fischbach W, Goebeler-Kolve ME, Dragosics B *et al.* (2004). Long term outcome of patients with gastric marginal zone B cell lymphoma of mucosa associated lymphoid tissue (MALT) following exclusive Helicobacter pylori eradication therapy: experience from a large prospective series. *Gut*, 53: 34–37. doi:10.1136/gut.53.1.34 PMID:14684573

Fontham ET, Ruiz B, Perez A *et al.* (1995). Determinants of Helicobacter pylori infection and chronic gastritis. *Am J Gastroenterol*, 90: 1094–1101. PMID:7611204

Ford AC, Forman D, Bailey AG *et al.* (2007). Effect of sibling number in the household and birth order on prevalence of Helicobacter pylori: a cross-sectional study. *Int J Epidemiol*, 36: 1327–1333. doi:10.1093/ije/dym201 PMID:17905807

Fox JG, Beck P, Dangler CA *et al.* (2000). Concurrent enteric helminth infection modulates inflammation and gastric immune responses and reduces helicobacter-induced gastric atrophy. *Nat Med*, 6: 536–542. doi:10.1038/75015 PMID:10802709

Fox JG, Rogers AB, Ihrig M *et al.* (2003a). Helicobacter pylori-associated gastric cancer in INS-GAS mice is gender specific. *Cancer Res*, 63: 942–950. PMID:12615707

Fox JG, Rogers AB, Whary MT *et al.* (2007). Accelerated progression of gastritis to dysplasia in the pyloric antrum of TFF2 -/- C57BL6 x Sv129 Helicobacter pylori-infected mice. *Am J Pathol*, 171: 1520–1528. doi:10.2353/ajpath.2007.070249 PMID:17982128

Fox JG, Wang TC, Rogers AB *et al.* (2003b). Host and microbial constituents influence Helicobacter pylori-induced cancer in a murine model of hypergastrinemia. *Gastroenterology*, 124: 1879–1890. doi:10.1016/S0016-5085(03)00406-2 PMID:12806621

Franco AT, Israel DA, Washington MK *et al.* (2005). Activation of beta-catenin by carcinogenic Helicobacter pylori. *Proc Natl Acad Sci U S A*, 102: 10646–10651. doi:10.1073/pnas.0504927102 PMID:16027366

Franco AT, Johnston E, Krishna U *et al.* (2008). Regulation of gastric carcinogenesis by Helicobacter pylori virulence factors. *Cancer Res*, 68: 379–387. doi:10.1158/0008-5472.CAN-07-0824 PMID:18199531

Früh M, Zhou W, Zhai R *et al.* (2008). Polymorphisms of inflammatory and metalloproteinase genes, Helicobacter pylori infection and the risk of oesophageal adenocarcinoma. *Br J Cancer*, 98: 689–692. doi:10.1038/sj.bjc.6604234 PMID:18253117

Fujimori S, Kishida T, Kobayashi T *et al.* (2005). Helicobacter pylori infection increases the risk of colorectal adenoma and adenocarcinoma, especially in women. *J Gastroenterol*, 40: 887–893. doi:10.1007/s00535-005-1649-1 PMID:16211345

Fukase K, Kato M, Kikuchi S *et al.* Japan Gast Study Group (2008). Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet*, 372: 392–397. doi:10.1016/S0140-6736(08)61159-9 PMID:18675689

Fukui T, Okazaki K, Tamaki H *et al.* (2004). Immunogenetic analysis of gastric MALT lymphoma-like lesions induced by Helicobacter pylori infection in neonatally thymectomized mice. *Lab Invest*, 84: 485–492. doi:10.1038/labinvest.3700056 PMID:14968120

Garrity GM, Bell JA, Lilburn T (2005) Class V. Epsilonproteobacteria *fam. nov.* In: Garrity GM (ed) 2nd ed. *Bergey's Manual of Systematic Bacteriology*. New York, USA: Williams & Wilkins, 1145–94.

Gocyk W, Nikliński T, Olechnowicz H *et al.* (2000). Helicobacter pylori, gastrin and cyclooxygenase-2 in lung cancer. *Med Sci Monit*, 6: 1085–1092. PMID:11208460

Goodman KJ, Correa P, Tenganá Aux HJ *et al.* (1996). Helicobacter pylori infection in the Colombian Andes: a population-based study of transmission pathways. *Am J Epidemiol*, 144: 290–299. PMID:8686698

Goodwin CS, Armstrong JA, Chilvers T *et al.* (1989). Transfer of Campylobacter pylori and Campylobacter mustelae to Helicobacter gen. nov. as Helicobacter pylori comb. nov. and Helicobacter mustelae comb. nov., Respectively. *Int J Syst Bacteriol*, 39: 397–405. doi:10.1099/00207713-39-4-397

Goodwin CS & Worsley BW (1993). Microbiology of Helicobacter pylori. *Gastroenterol Clin North Am*, 22: 5–19. PMID:8449570

Gorouhi F, Islami F, Bahrami H, Kamangar F (2008). Tumour-necrosis factor-A polymorphisms and gastric

cancer risk: a meta-analysis. *Br J Cancer*, 98: 1443–1451. doi:10.1038/sj.bjc.6604277 PMID:18319718

Gramley WA, Asghar A, Frierson HF Jr, Powell SM (1999). Detection of Helicobacter pylori DNA in fecal samples from infected individuals. *J Clin Microbiol*, 37: 2236–2240. PMID:10364591

Grandis JR, Perez-Perez GI, Yu VL *et al.* (1997). Lack of serologic evidence for Helicobacter pylori infection in head and neck cancer. *Head Neck*, 19: 216–218. doi:10.1002/(SICI)1097-0347(199705)19:3<216::AID-HED9>3.0.CO;2-5 PMID:9142522

Gressmann H, Linz B, Ghai R *et al.* (2005). Gain and loss of multiple genes during the evolution of Helicobacter pylori. *PLoS Genet*, 1: e43 doi:10.1371/journal.pgen.0010043 PMID:16217547

Gwack J, Shin A, Kim CS *et al.* (2006). CagA-producing Helicobacter pylori and increased risk of gastric cancer: a nested case-control study in Korea. *Br J Cancer*, 95: 639–641. doi:10.1038/sj.bjc.6603309 PMID:16909137

Hahm KB, Lee KM, Kim YB *et al.* (2002). Conditional loss of TGF-beta signalling leads to increased susceptibility to gastrointestinal carcinogenesis in mice. *Aliment Pharmacol Ther*, 16: Suppl 2115–127. doi:10.1046/j.1365-2036.16.s2.3.x PMID:11966532

Hansen S, Vollset SE, Derakhshan MH *et al.* (2007). Two distinct aetiologies of cardia cancer; evidence from premorbid serological markers of gastric atrophy and Helicobacter pylori status. *Gut*, 56: 918–925. doi:10.1136/gut.2006.114504 PMID:17317788

Hansson LE, Nyrén O, Hsing AW *et al.* (1996). The risk of stomach cancer in patients with gastric or duodenal ulcer disease. *N Engl J Med*, 335: 242–249. doi:10.1056/NEJM199607253350404 PMID:8657240

Hartwich A, Konturek SJ, Pierzchalski P *et al.* (2001). Helicobacter pylori infection, gastrin, cyclooxygenase-2, and apoptosis in colorectal cancer. *Int J Colorectal Dis*, 16: 202–210. doi:10.1007/s003840100288 PMID:11515678

Hazell SL, Lee A, Brady L, Hennessy W (1986). Campylobacter pyloridis and gastritis: association with intercellular spaces and adaptation to an environment of mucus as important factors in colonization of the gastric epithelium. *J Infect Dis*, 153: 658–663. doi:10.1093/infdis/153.4.658 PMID:3950447

Hegarty JP, Dowd MT, Baker KH (1999). Occurrence of Helicobacter pylori in surface water in the United States. *J Appl Microbiol*, 87: 697–701. doi:10.1046/j.1365-2672.1999.00912.x PMID:10594710

Helicobacter and Cancer Collaborative Group (2001). Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut*, 49: 347–353. doi:10.1136/gut.49.3.347 PMID:11511555

Hellmig S, Fischbach W, Goebeler-Kolve ME *et al.* (2005a). A functional promotor polymorphism of TNF-alpha is associated with primary gastric B-Cell lymphoma. *Am J Gastroenterol*, 100: 2644–2649. doi:10.1111/j.1572-0241.2005.00338.x PMID:16393214

Hellmig S, Fischbach W, Goebeler-Kolve ME *et al.* (2005b). Association study of a functional Toll-like receptor 4 polymorphism with susceptibility to gastric mucosa-associated lymphoid tissue lymphoma. *Leuk Lymphoma*, 46: 869–872. doi:10.1080/1042819050086451 PMID:16019531

Hennig EE, Allen JM, Cover TL (2006). Multiple chromosomal loci for the babA gene in Helicobacter pylori. *Infect Immun*, 74: 3046–3051. doi:10.1128/IAI.74.5.3046-3051.2006 PMID:16622249

Higashi H, Yokoyama K, Fujii Y *et al.* (2005). EPIYA motif is a membrane-targeting signal of Helicobacter pylori virulence factor CagA in mammalian cells. *J Biol Chem*, 280: 23130–23137. doi:10.1074/jbc.M503583200 PMID:15831497

Hill P & Rode J (1998). Helicobacter pylori in ectopic gastric mucosa in Meckel's diverticulum. *Pathology*, 30: 7–9. doi:10.1080/00313029800169585 PMID:9534200

Hirayama F, Takagi S, Iwao E *et al.* (1999). Development of poorly differentiated adenocarcinoma and carcinoid due to long-term Helicobacter pylori colonization in Mongolian gerbils. *J Gastroenterol*, 34: 450–454. doi:10.1007/s005350050295 PMID:10452676

Hmadcha A, Bedoya FJ, Sobrino F, Pintado E (1999). Methylation-dependent gene silencing induced by interleukin 1beta via nitric oxide production. *J Exp Med*, 190: 1595–1604. doi:10.1084/jem.190.11.1595 PMID:10587350

Honda S, Fujioka T, Tokieda M *et al.* (1998). Development of Helicobacter pylori-induced gastric carcinoma in Mongolian gerbils. *Cancer Res*, 58: 4255–4259. PMID:9766647

Hong SS, Jung HY, Choi KD *et al.* (2006). A prospective analysis of low-grade gastric malt lymphoma after Helicobacter pylori eradication. *Helicobacter*, 11: 569–573. doi:10.1111/j.1523-5378.2006.00460.x PMID:17083379

Houghton J, Stoicov C, Nomura S *et al.* (2004). Gastric cancer originating from bone marrow-derived cells. *Science*, 306: 1568–1571. doi:10.1126/science.1099513 PMID:15567866

Houghton JM, Bloch LM, Goldstein M *et al.* (2000). In vivo disruption of the fas pathway abrogates gastric growth alterations secondary to Helicobacter infection. *J Infect Dis*, 182: 856–864. doi:10.1086/315788 PMID:10950781

Hsu PI, Lai KH, Hsu PN *et al.* (2007). Helicobacter pylori infection and the risk of gastric malignancy. *Am J Gastroenterol*, 102: 725–730. doi:10.1111/j.1572-0241.2006.01109.x PMID:17324128

Huang JQ, Sridhar S, Chen Y, Hunt RH (1998). Meta-analysis of the relationship between Helicobacter pylori seropositivity and gastric cancer. *Gastroenterology*, 114: 1169–1179. doi:10.1016/S0016-5085(98)70422-6 PMID:9609753

Huang JQ, Zheng GF, Sumanac K *et al.* (2003). Meta-analysis of the relationship between cagA seropositivity and gastric cancer. *Gastroenterology*, 125: 1636–1644. doi:10.1053/j.gastro.2003.08.033 PMID:14724815

Huang Q, Ai L, Zhang ZY *et al.* (2004). Promoter hypermethylation and protein expression of the p16 gene: analysis of 43 cases of B-cell primary gastric lymphomas from China. *Mod Pathol*, 17: 416–422. doi:10.1038/modpathol.3800072 PMID:14976529

Hussell T, Isaacson PG, Crabtree JE, Spencer J (1993). The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to Helicobacter pylori. *Lancet*, 342: 571–574. doi:10.1016/0140-6736(93)91408-E PMID:8102718

Hyams KC, Taylor DN, Gray GC *et al.* (1995). The risk of Helicobacter pylori infection among U.S. military personnel deployed outside the United States. *Am J Trop Med Hyg*, 52: 109–112. PMID:7856819

IARC (1994). Schistosomes, liver flukes and Helicobacter pylori. *IARC Monogr Eval Carcinog Risks Hum*, 61: 1–241. PMID:7715068

Iijima K, Koike T, Abe Y *et al.* (2007). Extensive gastric atrophy: an increased risk factor for superficial esophageal squamous cell carcinoma in Japan. *Am J Gastroenterol*, 102: 1603–1609. doi:10.1111/j.1572-0241.2007.01257.x PMID:17488251

Ilver D, Arnqvist A, Ogren J *et al.* (1998). Helicobacter pylori adhesin binding fucosylated histo-blood group antigens revealed by retagging. *Science*, 279: 373–377. doi:10.1126/science.279.5349.373 PMID:9430586

Ilver D, Barone S, Mercati D *et al.* (2004). Helicobacter pylori toxin VacA is transferred to host cells via a novel contact-dependent mechanism. *Cell Microbiol*, 6: 167–174. doi:10.1046/j.1462-5822.2003.00349.x PMID:14706102

Isaacson PG (1999). Gastric MALT lymphoma: from concept to cure. *Ann Oncol*, 10: 637–645. doi:10.1023/A:1008396618983 PMID:10442184

Islami F & Kamangar F (2008). Helicobacter pylori and esophageal cancer risk: a meta-analysis. *Cancer Prev Res (Phila)*, 1: 329–338. doi:10.1158/1940-6207.CAPR-08-0109 PMID:19138977

Iwamoto H, Czajkowsky DM, Cover TL *et al.* (1999). VacA from Helicobacter pylori: a hexameric chloride channel. *FEBS Lett*, 450: 101–104. doi:10.1016/S0014-5793(99)00474-3 PMID:10350065

Jenab M, Riboli E, Ferrari P *et al.* (2006). Plasma and dietary vitamin C levels and risk of gastric cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Carcinogenesis*, 27: 2250–2257. doi:10.1093/carcin/bgl096 PMID:16774936

Jenks PJ, Jeremy AH, Robinson PA *et al.* (2003). Long-term infection with Helicobacter felis and inactivation of the tumour suppressor gene p53 cumulatively enhance the gastric mutation frequency in Big Blue transgenic mice. *J Pathol*, 201: 596–602. doi:10.1002/path.1488 PMID:14648663

Kamangar F, Cheng C, Abnet CC, Rabkin CS (2006b). Interleukin-1B polymorphisms and gastric cancer risk–a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 15: 1920–1928. doi:10.1158/1055-9965.EPI-06-0267 PMID:17035400

Kamangar F, Dawsey SM, Blaser MJ *et al.* (2006a). Opposing risks of gastric cardia and noncardia gastric adenocarcinomas associated with Helicobacter pylori seropositivity. *J Natl Cancer Inst*, 98: 1445–1452. doi:10.1093/jnci/djj393 PMID:17047193

Kamangar F, Qiao YL, Blaser MJ *et al.* (2007). Helicobacter pylori and oesophageal and gastric cancers in a prospective study in China. *Br J Cancer*, 96: 172–176. doi:10.1038/sj.bjc.6603517 PMID:17179990

Kato S, Tsukamoto T, Mizoshita T *et al.* (2006). High salt diets dose-dependently promote gastric chemical carcinogenesis in Helicobacter pylori-infected Mongolian gerbils associated with a shift in mucin production from glandular to surface mucous cells. *Int J Cancer*, 119: 1558–1566. doi:10.1002/ijc.21810 PMID:16646055

Kawahara Y, Mizuno M, Yoshino T *et al.* (2005). HLA-DQA1*0103-DQB1*0601 haplotype and Helicobacter pylori-positive gastric mucosa-associated lymphoid tissue lymphoma. *Clin Gastroenterol Hepatol*, 3: 865–868. doi:10.1016/S1542-3565(05)00185-0 PMID:16234023

Kelly SM, Pitcher MC, Farmery SM, Gibson GR (1994). Isolation of Helicobacter pylori from feces of patients with dyspepsia in the United Kingdom. *Gastroenterology*, 107: 1671–1674. PMID:7958677

Kersulyte D, Chalkauskas H, Berg DE (1999). Emergence of recombinant strains of Helicobacter pylori during human infection. *Mol Microbiol*, 31: 31–43. doi:10.1046/j.1365-2958.1999.01140.x PMID:9987107

Kim DH, Kim SW, Song YJ *et al.* (2003). Long-term evaluation of mice model infected with Helicobacter pylori: focus on gastric pathology including gastric cancer. *Aliment Pharmacol Ther*, 18: Suppl 114–23. doi:10.1046/j.1365-2036.18.s1.4.x PMID:12925137

Knekt P, Teppo L, Aromaa A *et al.* (2006). Helicobacter pylori IgA and IgG antibodies, serum pepsinogen I and the risk of gastric cancer: changes in the risk with extended follow-up period. *Int J Cancer*, 119: 702–705. doi:10.1002/ijc.21884 PMID:16496404

Kokkola A, Kosunen TU, Puolakkainen P *et al.* (2003). Spontaneous disappearance of Helicobacter pylori antibodies in patients with advanced atrophic corpus gastritis. *APMIS*, 111: 619–624. doi:10.1034/j.1600-0463.2003.1110604.x PMID:12969017

Krause S, Barcena M, Pansegrau W *et al.* (2000). Sequence-related protein export NTPases encoded by the conjugative transfer region of RP4 and by the cag pathogenicity island of Helicobacter pylori share

similar hexameric ring structures. *Proc Natl Acad Sci U S A*, 97: 3067–3072. doi:10.1073/pnas.050578697 PMID:10716714

Kusters JG, Gerrits MM, Van Strijp JA, Vandenbroucke-Grauls CM (1997). Coccoid forms of Helicobacter pylori are the morphologic manifestation of cell death. *Infect Immun*, 65: 3672–3679. PMID:9284136

Kuzushita N, Rogers AB, Monti NA *et al.* (2005). p27kip1 deficiency confers susceptibility to gastric carcinogenesis in Helicobacter pylori-infected mice. *Gastroenterology*, 129: 1544–1556. doi:10.1053/j.gastro.2005.07.056 PMID:16285954

Ladeira MS, Rodrigues MA, Salvadori DM *et al.* (2004). DNA damage in patients infected by Helicobacter pylori. *Cancer Epidemiol Biomarkers Prev*, 13: 631–637. PMID:15066929

Langenberg W, Rauws EA, Oudbier JH, Tytgat GNJ (1990). Patient-to-patient transmission of Campylobacter pylori infection by fiberoptic gastroduodenoscopy and biopsy. *J Infect Dis*, 161: 507–511. doi:10.1093/infdis/161.3.507 PMID:2313129

Lee CW, Rickman B, Rogers AB *et al.* (2008). Helicobacter pylori eradication prevents progression of gastric cancer in hypergastrinemic INS-GAS mice. *Cancer Res*, 68: 3540–3548. doi:10.1158/0008-5472.CAN-07-6786 PMID:18441088

Lee SA, Kang D, Shim KN *et al.* (2003). Effect of diet and Helicobacter pylori infection to the risk of early gastric cancer. *J Epidemiol*, 13: 162–168. PMID:12749604

Lehtinen M, Ogmundsdottir HM, Bloigu A *et al.* (2005). Associations between three types of maternal bacterial infection and risk of leukemia in the offspring. *Am J Epidemiol*, 162: 662–667. doi:10.1093/aje/kwi261 PMID:16120707

Leone N, Pellicano R, Brunello F *et al.* (2003). Helicobacter pylori seroprevalence in patients with cirrhosis of the liver and hepatocellular carcinoma. *Cancer Detect Prev*, 27: 494–497. doi:10.1016/j.cdp.2003.07.004 PMID:14642558

Leung WK, Lin SR, Ching JY *et al.* (2004). Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on Helicobacter pylori eradication. *Gut*, 53: 1244–1249. doi:10.1136/gut.2003.034629 PMID:15306578

Leunk RD, Johnson PT, David BC *et al.* (1988). Cytotoxic activity in broth-culture filtrates of Campylobacter pylori. *J Med Microbiol*, 26: 93–99. doi:10.1099/00222615-26-2-93 PMID:3385767

Ley C, Mohar A, Guarner J *et al.* (2004). Helicobacter pylori eradication and gastric preneoplastic conditions: a randomized, double-blind, placebo-controlled trial. *Cancer Epidemiol Biomarkers Prev*, 13: 4–10. doi:10.1158/1055-9965.EPI-03-0124 PMID:14744726

Limburg PJ, Stolzenberg-Solomon RZ, Colbert LH *et al.* (2002). Helicobacter pylori seropositivity and colorectal cancer risk: a prospective study of male smokers. *Cancer Epidemiol Biomarkers Prev*, 11: 1095–1099. PMID:12376513

Lindkvist B, Johansen D, Borgström A, Manjer J (2008). A prospective study of Helicobacter pylori in relation to the risk for pancreatic cancer. *BMC Cancer*, 8: 321 doi:10.1186/1471-2407-8-321 PMID:18986545

Louw JA, Falck V, van Rensburg C *et al.* (1993). Distribution of Helicobacter pylori colonisation and associated gastric inflammatory changes: difference between patients with duodenal and gastric ulcers. *J Clin Pathol*, 46: 754–756. doi:10.1136/jcp.46.8.754 PMID:8408703

Lozniewski A, Haristoy X, Rasko DA *et al.* (2003). Influence of Lewis antigen expression by Helicobacter pylori on bacterial internalization by gastric epithelial cells. *Infect Immun*, 71: 2902–2906. doi:10.1128/IAI.71.5.2902-2906.2003 PMID:12704166

Macarthur M, Hold GL, El-Omar EM (2004). Inflammation and Cancer II. Role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy. *Am J Physiol Gastrointest Liver Physiol*, 286: G515–G520. doi:10.1152/ajpgi.00475.2003 PMID:15010360

Machida-Montani A, Sasazuki S, Inoue M *et al.* (2004). Association of Helicobacter pylori infection and environmental factors in non-cardia gastric cancer in Japan. *Gastric Cancer*, 7: 46–53. doi:10.1007/s10120-004-0268-5 PMID:15052440

Machida-Montani A, Sasazuki S, Inoue M *et al.* (2007). Atrophic gastritis, Helicobacter pylori, and colorectal cancer risk: a case-control study. *Helicobacter*, 12: 328–332. doi:10.1111/j.1523-5378.2007.00513.x PMID:17669106

Madinier IM, Fosse TM, Monteil RA (1997). Oral carriage of Helicobacter pylori: a review. *J Periodontol*, 68: 2–6. PMID:9029444

Maekita T, Nakazawa K, Mihara M *et al.* (2006). High levels of aberrant DNA methylation in Helicobacter pylori-infected gastric mucosae and its possible association with gastric cancer risk. *Clin Cancer Res*, 12: 989–995. doi:10.1158/1078-0432.CCR-05-2096 PMID:16467114

Magari H, Shimizu Y, Inada K *et al.* (2005). Inhibitory effect of etodolac, a selective cyclooxygenase-2 inhibitor, on stomach carcinogenesis in Helicobacter pylori-infected Mongolian gerbils. *Biochem Biophys Res Commun*, 334: 606–612. doi:10.1016/j.bbrc.2005.06.132 PMID:16009342

Mahdavi J, Sondén B, Hurtig M *et al.* (2002). Helicobacter pylori SabA adhesin in persistent infection and chronic inflammation. *Science*, 297: 573–578. doi:10.1126/science.1069076 PMID:12142529

Malaty HM & Graham DY (1994). Importance of childhood socioeconomic status on the current prevalence of Helicobacter pylori infection. *Gut*, 35: 742–745. doi:10.1136/gut.35.6.742 PMID:8020796

Malaty HM, Paykov V, Bykova O *et al.* (1996). Helicobacter pylori and socioeconomic factors in Russia.

Helicobacter, 1: 82–87. doi:10.1111/j.1523-5378.1996.tb00015.x PMID:9398883

Marchetti M & Rappuoli R (2002). Isogenic mutants of the cag pathogenicity island of Helicobacter pylori in the mouse model of infection: effects on colonization efficiency. *Microbiology*, 148: 1447–1456. PMID:11988519

Marcos NT, Magalhães A, Ferreira B *et al.* (2008). Helicobacter pylori induces beta3GnT5 in human gastric cell lines, modulating expression of the SabA ligand sialyl-Lewis x. *J Clin Invest*, 118: 2325–2336. PMID:18483624

Matsumoto A, Isomoto H, Nakayama M *et al.* (2011). Helicobacter pylori VacA reduces the cellular expression of STAT3 and pro-survival Bcl-2 family proteins, Bcl-2 and Bcl-XL, leading to apoptosis in gastric epithelial cells. *Dig Dis Sci*, 56: 999–1006. doi:10.1007/s10620-010-1420-1 PMID:20927590

Miehlke S, Kirsch C, Agha-Amiri K *et al.* (2000). The Helicobacter pylori vacA s1, m1 genotype and cagA is associated with gastric carcinoma in Germany. *Int J Cancer*, 87: 322–327. doi:10.1002/1097-0215(20000801)87:3<322::AID-IJC3>3.0.CO;2-M PMID:10897035

Matsumoto Y, Marusawa H, Kinoshita K *et al.* (2007). Helicobacter pylori infection triggers aberrant expression of activation-induced cytidine deaminase in gastric epithelium. *Nat Med*, 13: 470–476. doi:10.1038/nm1566 PMID:17401375

Mégraud F & Lehours P (2007). Helicobacter pylori detection and antimicrobial susceptibility testing. *Clin Microbiol Rev*, 20: 280–322. doi:10.1128/CMR.00033-06 PMID:17428887

Mera R, Fontham ET, Bravo LE *et al.* (2005). Long term follow up of patients treated for Helicobacter pylori infection. *Gut*, 54: 1536–1540. doi:10.1136/gut.2005.072009 PMID:15985559

Meucci G, Tatarella M, Vecchi M *et al.* (1997). High prevalence of Helicobacter pylori infection in patients with colonic adenomas and carcinomas. *J Clin Gastroenterol*, 25: 605–607. doi:10.1097/00004836-199712000-00011 PMID:9451672

Mimuro H, Suzuki T, Nagai S *et al.* (2007). Helicobacter pylori dampens gut epithelial self-renewal by inhibiting apoptosis, a bacterial strategy to enhance colonization of the stomach. *Cell Host Microbe*, 2: 250–263. doi:10.1016/j.chom.2007.09.005 PMID:18005743

Mitchell H, English DR, Elliott F *et al.* (2008). Immunoblotting using multiple antigens is essential to demonstrate the true risk of Helicobacter pylori infection for gastric cancer. *Aliment Pharmacol Ther*, 28: 903–910. PMID:18624791

Moran AP, Prendergast MM, Appelmelk BJ (1996). Molecular mimicry of host structures by bacterial lipopolysaccharides and its contribution to disease. *FEMS Immunol Med Microbiol*, 16: 105–115. doi:10.1111/j.1574-695X.1996.tb00127.x PMID:8988391

Moss SF & Blaser MJ (2005). Mechanisms of disease: Inflammation and the origins of cancer. *Nat Clin Pract Oncol*, 2: 90–97, quiz 1, 113. doi:10.1038/ncponc0081 PMID:16264881

Moss SF, Neugut AI, Garbowski GC *et al.* (1995). Helicobacter pylori seroprevalence and colorectal neoplasia: evidence against an association. *J Natl Cancer Inst*, 87: 762–763. doi:10.1093/jnci/87.10.762 PMID:7563155

Moss SF, Valle J, Abdalla AM *et al.* (1999). Gastric cellular turnover and the development of atrophy after 31 years of follow-up: a case-control study. *Am J Gastroenterol*, 94: 2109–2114. doi:10.1111/j.1572-0241.1999.01286.x PMID:10445536

Mueller NE, Birmann BM, Parsonnet J *et al.* (2006) Infectious Agents. In: Schottenfeld D, Fraumeni JF, Jr. (eds) 3th *Cancer Epidemiology and Prevention.* 507–548.

Najafizadeh K, Falah Tafti S, Shiehmorteza M *et al.* (2007). H pylori seroprevalence in patients with lung cancer. *World J Gastroenterol*, 13: 2349–2351. PMID:17511036

Nakamura S, Matsumoto T, Suekane H *et al.* (2005). Long-term clinical outcome of Helicobacter pylori eradication for gastric mucosa-associated lymphoid tissue lymphoma with a reference to second-line treatment. *Cancer*, 104: 532–540. doi:10.1002/cncr.21152 PMID:15937928

Nakamura T, Seto M, Tajika M *et al.* (2008). Clinical features and prognosis of gastric MALT lymphoma with special reference to responsiveness to H. pylori eradication and API2-MALT1 status. *Am J Gastroenterol*, 103: 62–70. PMID:17894851

Namavar F, Roosendaal R, Kuipers EJ *et al.* (1995). Presence of Helicobacter pylori in the oral cavity, oesophagus, stomach and faeces of patients with gastritis. *Eur J Clin Microbiol Infect Dis*, 14: 234–237. doi:10.1007/BF02310363 PMID:7614967

Nardone G, Compare D, De Colibus P *et al.* (2007). Helicobacter pylori and epigenetic mechanisms underlying gastric carcinogenesis. *Dig Dis*, 25: 225–229. doi:10.1159/000103890 PMID:17827945

Neubauer A, Thiede C, Morgner A *et al.* (1997). Cure of Helicobacter pylori infection and duration of remission of low-grade gastric mucosa-associated lymphoid tissue lymphoma. *J Natl Cancer Inst*, 89: 1350–1355. doi:10.1093/jnci/89.18.1350 PMID:9308704

Nguyen AM, Engstrand L, Genta RM *et al.* (1993). Detection of Helicobacter pylori in dental plaque by reverse transcription-polymerase chain reaction. *J Clin Microbiol*, 31: 783–787. PMID:8463387

Nguyen VQ, Caprioli RM, Cover TL (2001). Carboxy-terminal proteolytic processing of Helicobacter pylori vacuolating toxin. *Infect Immun*, 69: 543–546. doi:10.1128/IAI.69.1.543-546.2001 PMID:11119549

Nilsson HO, Stenram U, Ihse I, Wadström T (2002). Re: Helicobacter pylori seropositivity as a risk factor for

pancreatic cancer. *J Natl Cancer Inst*, 94: 632–633. PMID:11959898

Nomura AM, Kolonel LN, Miki K *et al.* (2005). Helicobacter pylori, pepsinogen, and gastric adenocarcinoma in Hawaii. *J Infect Dis*, 191: 2075–2081. doi:10.1086/430353 PMID:15897993

Nomura AM, Lee J, Stemmermann GN *et al.* (2002a). Helicobacter pylori CagA seropositivity and gastric carcinoma risk in a Japanese American population. *J Infect Dis*, 186: 1138–1144. doi:10.1086/343808 PMID:12355365

Nomura AM, Pérez-Pérez GI, Lee J *et al.* (2002b). Relation between Helicobacter pylori cagA status and risk of peptic ulcer disease. *Am J Epidemiol*, 155: 1054–1059. doi:10.1093/aje/155.11.1054 PMID:12034584

Nozaki K, Shimizu N, Ikehara Y *et al.* (2003). Effect of early eradication on Helicobacter pylori-related gastric carcinogenesis in Mongolian gerbils. *Cancer Sci*, 94: 235–239. doi:10.1111/j.1349-7006.2003.tb01426.x PMID:12824915

Nozaki K, Shimizu N, Inada K *et al.* (2002). Synergistic promoting effects of Helicobacter pylori infection and high-salt diet on gastric carcinogenesis in Mongolian gerbils. *Jpn J Cancer Res*, 93: 1083–1089. PMID:12417037

Nurgalieva ZZ, Graham DY, Dahlstrom KR *et al.* (2005). A pilot study of Helicobacter pylori infection and risk of laryngopharyngeal cancer. *Head Neck*, 27: 22–27. doi:10.1002/hed.20108 PMID:15459921

Odenbreit S (2005). Adherence properties of Helicobacter pylori: impact on pathogenesis and adaptation to the host. *Int J Med Microbiol*, 295: 317–324. doi:10.1016/j.ijmm.2005.06.003 PMID:16173498

Oderda G (1999). Transmission of Helicobacter pylori infection. *Can J Gastroenterol*, 13: 595–597. PMID:10519958

Ogiwara H, Graham DY, Yamaoka Y (2008). vacA i-region subtyping. *Gastroenterology*, 134: 1267–, author reply 1268. doi:10.1053/j.gastro.2007.11.062 PMID:18395110

Oh JD, Kling-Bäckhed H, Giannakis M *et al.* (2006). The complete genome sequence of a chronic atrophic gastritis Helicobacter pylori strain: evolution during disease progression. *Proc Natl Acad Sci U S A*, 103: 9999–10004. doi:10.1073/pnas.0603784103 PMID:16788065

Ohnishi N, Yuasa H, Tanaka S *et al.* (2008). Transgenic expression of Helicobacter pylori CagA induces gastrointestinal and hematopoietic neoplasms in mouse. *Proc Natl Acad Sci U S A*, 105: 1003–1008. doi:10.1073/pnas.0711183105 PMID:18192401

Ohtani M, García A, Rogers AB *et al.* (2007). Protective role of 17 beta -estradiol against the development of Helicobacter pylori-induced gastric cancer in INS-GAS mice. *Carcinogenesis*, 28: 2597–2604. doi:10.1093/carcin/bgm150 PMID:17724378

Palli D, Masala G, Del Giudice G *et al.* (2007). CagA+ Helicobacter pylori infection and gastric cancer risk in

the EPIC-EURGAST study. *Int J Cancer*, 120: 859–867. doi:10.1002/ijc.22435 PMID:17131317

Parsonnet J (1998). Helicobacter pylori: the size of the problem. *Gut*, 43: Suppl 1S6–S9. doi:10.1136/gut.43.2008.S6 PMID:9764031

Parsonnet J, Friedman GD, Orentreich N, Vogelman H (1997). Risk for gastric cancer in people with CagA positive or CagA negative Helicobacter pylori infection. *Gut*, 40: 297–301. PMID:9135515

Parsonnet J, Hansen S, Rodriguez L *et al.* (1994). Helicobacter pylori infection and gastric lymphoma. *N Engl J Med*, 330: 1267–1271. doi:10.1056/NEJM199405053301803 PMID:8145781

Parsonnet J, Shmuely H, Haggerty T (1999). Fecal and oral shedding of Helicobacter pylori from healthy infected adults. *JAMA*, 282: 2240–2245. doi:10.1001/jama.282.23.2240 PMID:10605976

Peach HG, Pearce DC, Farish SJ (1997). Helicobacter pylori infection in an Australian regional city: prevalence and risk factors. *Med J Aust*, 167: 310–313. PMID:9322776

Peck B, Ortkamp M, Diehl KD *et al.* (1999). Conservation, localization and expression of HopZ, a protein involved in adhesion of Helicobacter pylori. *Nucleic Acids Res*, 27: 3325–3333. doi:10.1093/nar/27.16.3325 PMID:10454640

Peek RM Jr & Blaser MJ (2002). Helicobacter pylori and gastrointestinal tract adenocarcinomas. *Nat Rev Cancer*, 2: 28–37. doi:10.1038/nrc703 PMID:11902583

Peek RM Jr, Moss SF, Tham KT *et al.* (1997). Helicobacter pylori cagA+ strains and dissociation of gastric epithelial cell proliferation from apoptosis. *J Natl Cancer Inst*, 89: 863–868. doi:10.1093/jnci/89.12.863 PMID:9196252

Pel PK (1913) *De ziekten van de maag met het oog op de behoeften der geneeskundige praktijk geschetst.* 3rd, Bohn F (ed) Haarlem, the Netherlands: De Erven.

Penman ID, el-Omar E, Ardill JE *et al.* (1994). Plasma gastrin concentrations are normal in patients with colorectal neoplasia and unaltered following tumor resection. *Gastroenterology*, 106: 1263–1270. PMID:8174887

Perri F, Piepoli A, Bonvicini C *et al.* (2005). Cytokine gene polymorphisms in gastric cancer patients from two Italian areas at high and low cancer prevalence. *Cytokine*, 30: 293–302. doi:10.1016/j.cyto.2005.01.011 PMID:15927855

Perry S, de la Luz Sanchez M, Yang S *et al.* (2006). Gastroenteritis and transmission of Helicobacter pylori infection in households. *Emerg Infect Dis*, 12: 1701–1708. PMID:17283620

Philippou N, Koursarakos P, Anastasakou E *et al.* (2004). Helicobacter pylori seroprevalence in patients with lung cancer. *World J Gastroenterol*, 10: 3342–3344. PMID:15484314

Phukan RK, Narain K, Zomawia E *et al.* (2006). Dietary habits and stomach cancer in Mizoram, India. *J Gastroenterol*, 41: 418–424. doi:10.1007/s00535-006-1761-x PMID:16799882

Pinotti G, Zucca E, Roggero E et al. (1997). Clinical features, treatment and outcome in a series of 93 patients with low-grade gastric MALT lymphoma. *Leuk Lymphoma*, 26: 527–537. PMID:9389360

Preston-Martin S, Pike MC, Ross RK et al. (1990). Increased cell division as a cause of human cancer. *Cancer Res*, 50: 7415–7421. PMID:2174724

Pride DT & Blaser MJ (2002). Concerted evolution between duplicated genetic elements in Helicobacter pylori. *J Mol Biol*, 316: 629–642. doi:10.1006/jmbi.2001.5311 PMID:11866522

Raderer M, Wrba F, Kornek G et al. (1998). Association between Helicobacter pylori infection and pancreatic cancer. *Oncology*, 55: 16–19. doi:10.1159/000011830 PMID:9428370

Raymond J, Thiberg JM, Chevalier C et al. (2004). Genetic and transmission analysis of Helicobacter pylori strains within a family. *Emerg Infect Dis*, 10: 1816–1821. PMID:15504269

Replogle ML, Glaser SL, Hiatt RA, Parsonnet J (1995). Biologic sex as a risk factor for Helicobacter pylori infection in healthy young adults. *Am J Epidemiol*, 142: 856–863. PMID:7572962

Rhead JL, Letley DP, Mohammadi M et al. (2007). A new Helicobacter pylori vacuolating cytotoxin determinant, the intermediate region, is associated with gastric cancer. *Gastroenterology*, 133: 926–936. doi:10.1053/j.gastro.2007.06.056 PMID:17854597

Rogers AB, Taylor NS, Whary MT et al. (2005). Helicobacter pylori but not high salt induces gastric intraepithelial neoplasia in B6129 mice. *Cancer Res*, 65: 10709–10715. doi:10.1158/0008-5472.CAN-05-1846 PMID:16322215

Rokkas T, Pistiolas D, Sechopoulos P et al. (2007). Relationship between Helicobacter pylori infection and esophageal neoplasia: a meta-analysis. *Clin Gastroenterol Hepatol*, 5: 1413–1417, 1417, e1–e2. doi:10.1016/j.cgh.2007.08.010 PMID:17997357

Romero-Gallo J, Harris EJ, Krishna U et al. (2008). Effect of Helicobacter pylori eradication on gastric carcinogenesis. *Lab Invest*, 88: 328–336. doi:10.1038/labinvest.3700719 PMID:18180700

Roosendaal R, Kuipers EJ, Buitenwerf J et al. (1997). Helicobacter pylori and the birth cohort effect: evidence of a continuous decrease of infection rates in childhood. *Am J Gastroenterol*, 92: 1480–1482. PMID:9317067

Rosenstiel P, Hellmig S, Hampe J et al. (2006). Influence of polymorphisms in the NOD1/CARD4 and NOD2/CARD15 genes on the clinical outcome of Helicobacter pylori infection. *Cell Microbiol*, 8: 1188–1198. doi:10.1111/j.1462-5822.2006.00701.x PMID:16819970

Rothenbacher D, Bode G, Berg G et al. (1998). Prevalence and determinants of Helicobacter pylori infection in preschool children: a population-based study from Germany. *Int J Epidemiol*, 27: 135–141. doi:10.1093/ije/27.1.135 PMID:9563707

Rubin JS, Benjamin E, Prior A, Lavy J (2003). The prevalence of Helicobacter pylori infection in malignant and premalignant conditions of the head and neck. *J Laryngol Otol*, 117: 118–121. doi:10.1258/002221503762624558 PMID:12625884

Sagaert X, De Wolf-Peeters C, Noels H, Baens M (2007). The pathogenesis of MALT lymphomas: where do we stand? *Leukemia*, 21: 389–396. doi:10.1038/sj.leu.2404517 PMID:17230229

Salama N, Guillemin K, McDaniel TK et al. (2000). A whole-genome microarray reveals genetic diversity among Helicobacter pylori strains. *Proc Natl Acad Sci U S A*, 97: 14668–14673. doi:10.1073/pnas.97.26.14668 PMID:11121067

Salaün L, Linz B, Suerbaum S, Saunders NJ (2004). The diversity within an expanded and redefined repertoire of phase-variable genes in Helicobacter pylori. *Microbiology*, 150: 817–830. doi:10.1099/mic.0.26993-0 PMID:15073292

Sanduleanu S, Jonkers D, de Bruïne A et al. (2001). Changes in gastric mucosa and luminal environment during acid-suppressive therapy: a review in depth. *Dig Liver Dis*, 33: 707–719. doi:10.1016/S1590-8658(01)80050-5 PMID:11785719

Sasaki K, Tajiri Y, Sata M et al. Kanae Sasaki, Yoshito Tajiri, Michi (1999). Helicobacter pylori in the natural environment. *Scand J Infect Dis*, 31: 275–279. doi:10.1080/00365549950163572 PMID:10482057

Sasazuki S, Inoue M, Iwasaki M et al. Japan Public Health Center Study Group (2006). Effect of Helicobacter pylori infection combined with CagA and pepsinogen status on gastric cancer development among Japanese men and women: a nested case-control study. *Cancer Epidemiol Biomarkers Prev*, 15: 1341–1347. doi:10.1158/1055-9965.EPI-05-0901 PMID:16835334

Savio A, Zamboni G, Capelli P et al. (2000). Relapse of low-grade gastric MALT lymphoma after Helicobacter pylori eradication: true relapse or persistence? Long-term post-treatment follow-up of a multicenter trial in the north-east of Italy and evaluation of the diagnostic protocol's adequacy. *Recent Results Cancer Res*, 156: 116–124. PMID:10802871

Schmitt W & Haas R (1994). Genetic analysis of the Helicobacter pylori vacuolating cytotoxin: structural similarities with the IgA protease type of exported protein. *Mol Microbiol*, 12: 307–319. doi:10.1111/j.1365-2958.1994.tb01019.x PMID:8057855

Shikata K, Kiyohara Y, Kubo M et al. (2006). A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. *Int J Cancer*, 119: 196–201. doi:10.1002/ijc.21822 PMID:16450397

Shimizu N, Inada K, Nakanishi H et al. (1999). Helicobacter pylori infection enhances glandular stomach carcinogenesis in Mongolian gerbils treated with chemical

carcinogens. *Carcinogenesis*, 20: 669–676. doi:10.1093/carcin/20.4.669 PMID:10223198

Shin A, Shin HR, Kang D *et al.* (2005). A nested case-control study of the association of Helicobacter pylori infection with gastric adenocarcinoma in Korea. *Br J Cancer*, 92: 1273–1275. doi:10.1038/sj.bjc.6602467 PMID:15756269

Shirin H, Sordillo EM, Kolevska TK *et al.* (2000). Chronic Helicobacter pylori infection induces an apoptosis-resistant phenotype associated with decreased expression of p27(kip1). *Infect Immun*, 68: 5321–5328. doi:10.1128/IAI.68.9.5321-5328.2000 PMID:10948161

Shirin H, Weinstein IB, Moss SF (2001). Effects of H. pylori infection of gastric epithelial cells on cell cycle control. *Front Biosci*, 6: E104–E118. doi:10.2741/Shirin PMID:11578975

Shmuely H, Passaro D, Figer A *et al.* (2001). Relationship between Helicobacter pylori CagA status and colorectal cancer. *Am J Gastroenterol*, 96: 3406–3410. doi:10.1111/j.1572-0241.2001.05342.x PMID:11774957

Siddheshwar RK, Muhammad KB, Gray JC, Kelly SB (2001). Seroprevalence of Helicobacter pylori in patients with colorectal polyps and colorectal carcinoma. *Am J Gastroenterol*, 96: 84–88. doi:10.1111/j.1572-0241.2001.03355.x PMID:11197293

Simán JH, Forsgren A, Berglund G, Florén CH (1997). Association between Helicobacter pylori and gastric carcinoma in the city of Malmö, Sweden. A prospective study. *Scand J Gastroenterol*, 32: 1215–1221. PMID:9438319

Simán JH, Engstrand L, Berglund G *et al.* (2007). Helicobacter pylori and CagA seropositivity and its association with gastric and oesophageal carcinoma. *Scand J Gastroenterol*, 42: 933–940. doi:10.1080/00365520601173863 PMID:17613922

Sisto F, Brenciaglia MI, Scaltrito MM, Dubini F (2000). Helicobacter pylori: ureA, cagA and vacA expression during conversion to the coccoid form. *Int J Antimicrob Agents*, 15: 277–282. doi:10.1016/S0924-8579(00)00188-6 PMID:10929877

Solnick JV, Hansen LM, Salama NR *et al.* (2004). Modification of Helicobacter pylori outer membrane protein expression during experimental infection of rhesus macaques. *Proc Natl Acad Sci U S A*, 101: 2106–2111. doi:10.1073/pnas.0308573100 PMID:14762173

Starzyńska T, Ferenc K, Wex T *et al.* (2006). The association between the interleukin-1 polymorphisms and gastric cancer risk depends on the family history of gastric carcinoma in the study population. *Am J Gastroenterol*, 101: 248–254. doi:10.1111/j.1572-0241.2006.00422.x PMID:16454826

Stathis A, Chini C, Bertoni F *et al.* (2009). Long-term outcome following Helicobacter pylori eradication in a retrospective study of 105 patients with localized gastric marginal zone B-cell lymphoma of MALT

type. *Ann Oncol*, 20: 1086–1093. doi:10.1093/annonc/mdn760 PMID:19193705

Stolte M, Eidt S, Bayerdörffer E *et al.* (1994) *H. Pylori*-associated gastric lymphoma. In: Hunt RH, Tytgat GNJ (eds) *Helicobacter Pylori. Basic Mechanisms to Clinical Cure.* Dordrecht: Kluwer, 498–503.

Stolzenberg-Solomon RZ, Blaser MJ, Limburg PJ *et al.* ATBC Study (2001). Helicobacter pylori seropositivity as a risk factor for pancreatic cancer. *J Natl Cancer Inst*, 93: 937–941. doi:10.1093/jnci/93.12.937 PMID:11416115

Suárez S, Sueiro RA, Araujo M *et al.* (2007). Increased frequency of micronuclei in peripheral blood lymphocytes of subjects infected with Helicobacter pylori. *Mutat Res*, 626: 162–170. PMID:17112778

Suerbaum S & Josenhans C (2007). Helicobacter pylori evolution and phenotypic diversification in a changing host. *Nat Rev Microbiol*, 5: 441–452. doi:10.1038/nrmicro1658 PMID:17505524

Suerbaum S, Josenhans C, Labigne A (1993). Cloning and genetic characterization of the Helicobacter pylori and Helicobacter mustelae flaB flagellin genes and construction of H. pylori flaA- and flaB-negative mutants by electroporation-mediated allelic exchange. *J Bacteriol*, 175: 3278–3288. PMID:8501031

Suerbaum S & Michetti P (2002). Helicobacter pylori infection. *N Engl J Med*, 347: 1175–1186. doi:10.1056/NEJMra020542 PMID:12374879

Sugiyama A, Maruta F, Ikeno T *et al.* (1998). Helicobacter pylori infection enhances N-methyl-N-nitrosourea-induced stomach carcinogenesis in the Mongolian gerbil. *Cancer Res*, 58: 2067–2069. PMID:9605743

Sutton P, O'Rourke J, Wilson J *et al.* (2004). Immunisation against Helicobacter felis infection protects against the development of gastric MALT Lymphoma. *Vaccine*, 22: 2541–2546. doi:10.1016/j.vaccine.2003.12.014 PMID:15193379

Tahara T, Arisawa T, Shibata T *et al.* (2007). Risk prediction of gastric cancer by analysis of aberrant DNA methylation in non-neoplastic gastric epithelium. *Digestion*, 75: 54–61. doi:10.1159/000101775 PMID:17438355

Takaishi S, Cui G, Frederick DM *et al.* (2005). Synergistic inhibitory effects of gastrin and histamine receptor antagonists on Helicobacter-induced gastric cancer. *Gastroenterology*, 128: 1965–1983. doi:10.1053/j.gastro.2005.03.027 PMID:15940630

Takeshima E, Tomimori K, Takamatsu R *et al.* (2009). Helicobacter pylori VacA activates NF-kappaB in T cells via the classical but not alternative pathway. *Helicobacter*, 14: 271–279. doi:10.1111/j.1523-5378.2009.00683.x PMID:19674131

Tamura G (2004). Promoter methylation status of tumor suppressor and tumor-related genes in neoplastic and non-neoplastic gastric epithelia. *Histol Histopathol*, 19: 221–228. PMID:14702190

Telford JL, Ghiara P, Dell'Orco M *et al.* (1994). Gene structure of the Helicobacter pylori cytotoxin and evidence

of its key role in gastric disease. *J Exp Med*, 179: 1653–1658. doi:10.1084/jem.179.5.1653 PMID:8163943

Terai S, Iijima K, Kato K *et al.* (2008). Long-term outcomes of gastric mucosa-associated lymphoid tissue lymphomas after Helicobacter pylori eradication therapy. *Tohoku J Exp Med*, 214: 79–87. doi:10.1620/tjem.214.79 PMID:18212490

The EUROGAST Study Group (1993). Epidemiology of, and risk factors for, Helicobacter pylori infection among 3194 asymptomatic subjects in 17 populations. *Gut*, 34: 1672–1676. doi:10.1136/gut.34.12.1672 PMID:8282253

Thorburn CM, Friedman GD, Dickinson CJ *et al.* (1998). Gastrin and colorectal cancer: a prospective study. *Gastroenterology*, 115: 275–280. doi:10.1016/S0016-5085(98)70193-3 PMID:9679032

Tokieda M, Honda S, Fujioka T, Nasu M (1999). Effect of Helicobacter pylori infection on the N-methyl-N'-nitro-N-nitrosoguanidine-induced gastric carcinogenesis in mongolian gerbils. *Carcinogenesis*, 20: 1261–1266. doi:10.1093/carcin/20.7.1261 PMID:10383899

Tomb JF, White O, Kerlavage AR *et al.* (1997). The complete genome sequence of the gastric pathogen Helicobacter pylori. *Nature*, 388: 539–547. doi:10.1038/41483 PMID:9252185

Tombola F, Carlesso C, Szabò I *et al.* (1999). Helicobacter pylori vacuolating toxin forms anion-selective channels in planar lipid bilayers: possible implications for the mechanism of cellular vacuolation. *Biophys J*, 76: 1401–1409. doi:10.1016/S0006-3495(99)77301-7 PMID:10049322

Touati E, Michel V, Thiberge JM *et al.* (2003). Chronic Helicobacter pylori infections induce gastric mutations in mice. *Gastroenterology*, 124: 1408–1419. doi:10.1016/S0016-5085(03)00266-X PMID:12730880

Tu S, Bhagat G, Cui G *et al.* (2008). Overexpression of interleukin-1beta induces gastric inflammation and cancer and mobilizes myeloid-derived suppressor cells in mice. *Cancer Cell*, 14: 408–419. doi:10.1016/j.ccr.2008.10.011 PMID:18977329

Tulinius H, Ogmundsdottir HM, Kristinsson KG *et al.* (2001). Helicobacter pylori antibodies and gastric cancer in Iceland - The decline in IgG antibody level is a risk factor. *APMIS*, 109: 835–841. doi:10.1034/j.1600-0463.2001.091205.x PMID:11846724

Tytgat GN (1995). Endoscopic transmission of Helicobacter pylori. *Aliment Pharmacol Ther*, 9: Suppl 2105–110. PMID:8547522

Uemura N, Mukai T, Okamoto S *et al.* (1997). Effect of Helicobacter pylori eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. *Cancer Epidemiol Biomarkers Prev*, 6: 639–642. PMID:9264278

Uemura N, Okamoto S, Yamamoto S *et al.* (2001). Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med*, 345: 784–789. doi:10.1056/NEJMoa001999 PMID:11556297

Unemo M, Aspholm-Hurtig M, Ilver D *et al.* (2005). The sialic acid binding SabA adhesin of Helicobacter pylori is essential for nonopsonic activation of human neutrophils. *J Biol Chem*, 280: 15390–15397. doi:10.1074/jbc.M412725200 PMID:15689619

Vaira D, Gatta L, Ricci C, Miglioli M (2002). Review article: diagnosis of Helicobacter pylori infection. *Aliment Pharmacol Ther*, 16: Suppl 116–23. doi:10.1046/j.1365-2036.2002.0160s1016.x PMID:11849123

Van Doorn LJ, Figueiredo C, Mégraud F *et al.* (1999). Geographic distribution of vacA allelic types of Helicobacter pylori. *Gastroenterology*, 116: 823–830. doi:10.1016/S0016-5085(99)70065-X PMID:10092304

van Zwet AA, Thijs JC, Kooistra-Smid AM *et al.* (1994). Use of PCR with feces for detection of Helicobacter pylori infections in patients. *J Clin Microbiol*, 32: 1346–1348. PMID:7519630

Wang KX, Wang XF, Peng JL *et al.* (2003a). Detection of serum anti-Helicobacter pylori immunoglobulin G in patients with different digestive malignant tumors. *World J Gastroenterol*, 9: 2501–2504. PMID:14606084

Wang X, Willén R, Svensson M *et al.* (2003b). Two-year follow-up of Helicobacter pylori infection in C57BL/6 and Balb/cA mice. *APMIS*, 111: 514–522. doi:10.1034/j.1600-0463.2003.1110410.x PMID:12780527

Warren JR (1983). Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet*, 1: 1273–1275. PMID:6134060

Watabe H, Mitsushima T, Yamaji Y *et al.* (2005). Predicting the development of gastric cancer from combining Helicobacter pylori antibodies and serum pepsinogen status: a prospective endoscopic cohort study. *Gut*, 54: 764–768. doi:10.1136/gut.2004.055400 PMID:15888780

Watanabe T, Tada M, Nagai H *et al.* (1998). Helicobacter pylori infection induces gastric cancer in mongolian gerbils. *Gastroenterology*, 115: 642–648. doi:10.1016/S0016-5085(98)70143-X PMID:9721161

Wei J, O'Brien D, Vilgelm A *et al.* (2008). Interaction of Helicobacter pylori with gastric epithelial cells is mediated by the p53 protein family. *Gastroenterology*, 134: 1412–1423. doi:10.1053/j.gastro.2008.01.072 PMID:18343378

Wen S & Moss SF (2009). Helicobacter pylori virulence factors in gastric carcinogenesis. *Cancer Lett*, 282: 1–8. doi:10.1016/j.canlet.2008.11.016 PMID:19111390

Whary MT, Sundina N, Bravo LE *et al.* (2005). Intestinal helminthiasis in Colombian children promotes a Th2 response to Helicobacter pylori: possible implications for gastric carcinogenesis. *Cancer Epidemiol Biomarkers Prev*, 14: 1464–1469. doi:10.1158/1055-9965.EPI-05-0095 PMID:15941957

Willén R, Carlén B, Wang X *et al.* (2000). Morphologic conversion of Helicobacter pylori from spiral to coccoid form. Scanning (SEM) and transmission electron microscopy (TEM) suggest viability. *Ups J Med Sci*, 105: 31–40. PMID:10893051

Wong BC, Lam SK, Wong WM *et al.*China Gastric Cancer Study Group (2004). Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA*, 291: 187–194. doi:10.1001/jama.291.2.187 PMID:14722144

Wotherspoon AC, Doglioni C, Diss TC *et al.* (1993). Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. *Lancet*, 342: 575–577. doi:10.1016/0140-6736(93)91409-F PMID:8102719

Wu AH, Crabtree JE, Bernstein L *et al.* (2003). Role of Helicobacter pylori CagA+ strains and risk of adenocarcinoma of the stomach and esophagus. *Int J Cancer*, 103: 815–821. doi:10.1002/ijc.10887 PMID:12516104

Wu DC, Wu IC, Lee JM *et al.* (2005). Helicobacter pylori infection: a protective factor for esophageal squamous cell carcinoma in a Taiwanese population. *Am J Gastroenterol*, 100: 588–593. doi:10.1111/j.1572-0241.2005.40623.x PMID:15743356

Wündisch T, Thiede C, Morgner A *et al.* (2005). Long-term follow-up of gastric MALT lymphoma after Helicobacter pylori eradication. *J Clin Oncol*, 23: 8018–8024. doi:10.1200/JCO.2005.02.3903 PMID:16204012

Xuan SY, Xin YN, Chen AJ *et al.* (2008). Association between the presence of H pylori in the liver and hepatocellular carcinoma: a meta-analysis. *World J Gastroenterol*, 14: 307–312. doi:10.3748/wjg.14.307 PMID:18186573

Yamagata H, Kiyohara Y, Aoyagi K *et al.* (2000). Impact of Helicobacter pylori infection on gastric cancer incidence in a general Japanese population: the Hisayama study. *Arch Intern Med*, 160: 1962–1968. doi:10.1001/archinte.160.13.1962 PMID:10888970

Yamaoka Y (2008). Roles of Helicobacter pylori BabA in gastroduodenal pathogenesis. *World J Gastroenterol*, 14: 4265–4272. doi:10.3748/wjg.14.4265 PMID:18666312

Yamaoka Y, Kodama T, Kashima K *et al.* (1998). Variants of the 3′ region of the cagA gene in Helicobacter pylori isolates from patients with different H. pylori-associated diseases. *J Clin Microbiol*, 36: 2258–2263. PMID:9666002

Yamazaki S, Yamakawa A, Ito Y *et al.* (2003). The CagA protein of Helicobacter pylori is translocated into epithelial cells and binds to SHP-2 in human gastric mucosa. *J Infect Dis*, 187: 334–337. doi:10.1086/367807 PMID:12552462

Yanaoka K, Oka M, Yoshimura N *et al.* (2008). Risk of gastric cancer in asymptomatic, middle-aged Japanese subjects based on serum pepsinogen and Helicobacter pylori antibody levels. *Int J Cancer*, 123: 917–926. doi:10.1002/ijc.23571 PMID:18508314

Ye W, Held M, Lagergren J *et al.* (2004). Helicobacter pylori infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. *J Natl Cancer Inst*, 96: 388–396. doi:10.1093/jnci/djh057 PMID:14996860

Yoo JY, Kim N, Park YS *et al.* (2007). Detection rate of Helicobacter pylori against a background of atrophic gastritis and/or intestinal metaplasia. *J Clin Gastroenterol*, 41: 751–755. doi:10.1097/MCG.0b013e31802c347d PMID:17700423

You WC, Brown LM, Zhang L *et al.* (2006). Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. *J Natl Cancer Inst*, 98: 974–983. doi:10.1093/jnci/djj264 PMID:16849680

You WC, Zhang L, Gail MH *et al.* (2000). Gastric dysplasia and gastric cancer: Helicobacter pylori, serum vitamin C, and other risk factors. *J Natl Cancer Inst*, 92: 1607–1612. doi:10.1093/jnci/92.19.1607 PMID:11018097

Yu J, Leung WK, Go MY *et al.* (2002). Relationship between Helicobacter pylori babA2 status with gastric epithelial cell turnover and premalignant gastric lesions. *Gut*, 51: 480–484. doi:10.1136/gut.51.4.480 PMID:12235067

Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V (2000). Alcohol consumption, smoking and risk of gastric cancer: case-control study from Moscow, Russia. *Cancer Causes Control*, 11: 363–371. doi:10.1023/A:1008907924938 PMID:10843447

Zhang J, Dou C, Song Y *et al.* (2008). Polymorphisms of tumor necrosis factor-alpha are associated with increased susceptibility to gastric cancer: a meta-analysis. *J Hum Genet*, 53: 479–489. doi:10.1007/s10038-008-0273-3 PMID:18350251

Zhang L, Blot WJ, You WC *et al.* (1996). Helicobacter pylori antibodies in relation to precancerous gastric lesions in a high-risk Chinese population. *Cancer Epidemiol Biomarkers Prev*, 5: 627–630. PMID:8824365

Zheng Q, Chen XY, Shi Y, Xiao SD (2004). Development of gastric adenocarcinoma in Mongolian gerbils after long-term infection with Helicobacter pylori. *J Gastroenterol Hepatol*, 19: 1192–1198. doi:10.1111/j.1440-1746.2004.03469.x PMID:15377299

Zhuo X, Zhang Y, Wang Y *et al.* (2008). Helicobacter pylori infection and oesophageal cancer risk: association studies via evidence-based meta-analyses. *Clin Oncol (R Coll Radiol)*, 20: 757–762. PMID:18793831

Zumkeller N, Brenner H, Chang-Claude J *et al.* (2007). Helicobacter pylori infection, interleukin-1 gene polymorphisms and the risk of colorectal cancer: evidence from a case-control study in Germany. *Eur J Cancer*, 43: 1283–1289. doi:10.1016/j.ejca.2007.03.005 PMID:17446060

Zumkeller N, Brenner H, Zwahlen M, Rothenbacher D (2006). Helicobacter pylori infection and colorectal cancer risk: a meta-analysis. *Helicobacter*, 11: 75–80. doi:10.1111/j.1523-5378.2006.00381.x PMID:16579836