Helicobacter pylori and gastric cancer

Gastric cancer is a common form of cancer which generally has a poor prognosis.

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Gastric cancer is one of the most common forms of cancer worldwide, with an estimated 930 000 new cases diagnosed each year.[1] It is thought to be more prevalent in men than in women. In South Africa the latest cancer statistics show that 1 004 new cases were diagnosed and recorded in 2001. Gastric cancer is not only common but is second to lung cancer as a leading cause of cancer-related deaths,[2] with an estimated 700 000 deaths attributed to gastric cancer. Five-year survival statistics in gastric cancer are poor (less than 5%).[2,3] It is more prevalent in Asian countries, such as Japan, than in Europe and America. One of the most important features of gastric cancer is a steady decline in incidence and mortality in the developed world over the last 50 years.[3] It is, however, thought that the incidence of gastric cancer is increasing in the developing world,[4] although cancer records are not readily available for most developing countries. In South Africa the new cancer statistics made available by the National Cancer Registry in 2009 show that new cases of gastric cancer dropped from 1 217 in 1999 to 1 004 in 2001.

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Gastric cancer and Helicobacter pylori

Gastric cancers can be divided into two major types: the diffuse type, which is aetiologically linked to host genetic factors and the intestinal type, with an environmental aetiology.[5] Intestinal type gastric cancer develops through a series of precursor lesions, known as Correa's cascade.[6] In this model there is a gradual transformation of the normal gastric mucosa into one that is similar to intestinal epithelium, a state known as intestinal metaplasia. It usually begins with chronic gastritis, atrophic gastritis, intestinal metaplasia then dysplasia and finally adenocarcinoma of the stomach. On the other hand, diffuse type gastric cancer is thought to arise from single cell mutations, which subsequently proliferate and invade the rest of the stomach.[3] However, the biological background of gastric cancer of both the intestinal and diffuse types remains largely unknown. Specifically, the relative roles of host genetics factors and interaction with the environment remain unknown. Infection with *H. pylori* has been associated with both types of gastric cancer.

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H. pylori is an essential cause of gastric cancer, albeit not the only factor required to cause cancer. These bacteria were first observed in the human stomach in the 19th century but were only isolated and cultured in the early 1980s. The International Agency for Research on Cancer (IARC) classified *H. pylori* as a human carcinogen in 1994, making it the only known bacterial agent to cause cancer.[7] It is estimated that nearly 50% of the human population is infected with *H. pylori*. Intensive research in this area shows that *H. pylori* infection typically occurs in childhood[8,9] in all populations and persists indefinitely unless treated. The means by which *H. pylori* is transmitted is a major question in this field. However, seminal work conducted in our laboratory has given insight into its transmission in developing countries.[10] Countries with high *H. pylori* infection rates normally have higher gastric cancer incidence, as is seen in Asian countries. However, although *H. pylori* infection is quite common in Africa gastric cancer incidence is not as frequent as expected. This anomaly has been referred to as the 'African enigma'.

Despite its association with severe pathology worldwide, most *H. pylori* infections remain asymptomatic, with only 15% of those infected developing any significant pathology. Gastric cancer occurs in only 0.5 - 2% of all *H. pylori* infections.[11] Although the mechanisms by which *H. pylori* causes disease have been studied intensively, it remains to be shown why a majority (nearly 80%) of infected individuals do not develop clinical symptoms. Perhaps some of the answers can be found in the intimate association of *H. pylori* with humans. In a recent study it was shown that *H. pylori* has been infecting human stomachs for more than 60 000 years and was present when humans first migrated out of Africa.

Host genetic factors

The differences in clinical outcome of *H. pylori* infection have been studied intensively and variously attributed to host genetics, virulence of the infecting strain and/or environmental factors such as a high salt diet. Genetic association studies have found a link between gastric cancer and single nucleotide polymorphisms (SNPs) in certain cytokine genes. El-Omar *et al.*[12] showed that in the white population (Scotland) polymorphisms of the interleukin-1-beta (IL-1β) increase the risk for gastric cancer. It has also been shown that certain alleles of the interleukin receptor antagonist (IL-1RN) are more common in gastric cancer patients than in the general population. IL-1β is a potent inhibitor of gastric acid, which may explain its role in *H. pylori*-related pathology. Polymorphism

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studies in other populations have yielded conflicting results,[13] indicating that the frequency of these genetic polymorphisms differs both at the ethnic and geographic level. To date, no gastric cancer polymorphism study has been conducted in South Africa. A low frequency of these polymorphisms in the black population may explain the African enigma. Such an association study is being conducted in our laboratory in the University of Pretoria.

It is noteworthy that polymorphisms in other pro-inflammatory cytokine genes such as tumour necrosis-α (TNF-α), interferon-γ (IFN-γ) and IL-8 have been described and linked to gastric cancer.[14] They *et al.*[15] showed that a C→T transition at position –56 in the IFN-γ receptor gene associated with high antibody concentrations against *H. pylori* was more common in the black population compared with whites. This is indicative of a T-helper cell type 2 (Th-2) response, which has been shown to be less damaging to the gastric mucosa as opposed to a Th-1 response.[16] It has been suggested that the immune response to *H. pylori* in the black population is predominantly a Th-2 response but there is little direct evidence for that at the moment.

Virulence factors

H. pylori isolates show considerable genetic diversity, even within isolates from the same patient. Whole genome sequences of certain isolates reveal differences in sequence as well as gene content. In some cases up to 25% of genes are missing in some strains. This is a result of frequent recombination, which makes *H. pylori* one of the most genetically diverse bacteria.[17] This genetic diversity has been used to demonstrate globally distinct strains that show clear phylogeographic differentiation. Multi-locus sequence typing (MLST) analysis of a few isolates showed that one of these strains (HpAfrica2) found only in South Africa[18] does not have *cagA*, a virulence gene discussed below. However, the prevalence of this strain in South Africa and the role it plays in gastric pathology remains to be elucidated.

The differences in clinical outcomes among *H. pylori*-infected individuals have also been linked to different virulence factors in infecting strains. The best-studied virulence factor is the *cagA* gene which serves as a marker for a 40 kb chromosomal fragment known as cag Pathogenecity Island (cagPAI).[19] *H. pylori* strains with the *cagA* gene are associated with an increased IL-8 expression and more severe atrophy. The *cagA* protein is injected into epithelial cells via a type IV secretion. Cytoplasmic *cagA* is phosphorylated by *Src* family kinases on tyrosine motifs. Phosphorylated *cagA* is known to disrupt tight cell junctions, resulting in cell elongation and the formation of the so-called 'hummingbird phenotype'. This process may result in sloughing off of epithelial cells and compensatory cell proliferation. This may explain why *cagA*-positive strains are more common in patients with peptice ulcer disease (PUD), intestinal metaplasia and gastric cancer compared with asymptomatic patients. Sequence variation in the 3` region of *cagA* also influences phosphorylation of the protein, immunogeneticity and pathogenecity of the specific strain.[20,21]

Another well-characterised virulence gene is the vacuolating cytotoxin gene (*vacA*), which causes vacuoles in epithelial cells. Although the gene is thought to occur in all *H. pylori* strains, only about 50% of isolates cause vacuolation in epithelial cells.[22] This difference is due to polymorphisms in the signal (s), middle (m) and intermediate (i) regions of the gene. This gives rise to s1 or s2, m1 or m2 and i1 or i2 strains. *vacA* s1m1 and s1/m2 that cause more vacuolation are associated with PUD while s1m1 strains have been associated with gastric cancer. *vacA* s2m2 strains are generally non-pathogenic; naturally occurring *vacA* s2m1 strains are very rare. A recent study of the i-region showed that i1 strains are exclusively s1m1 while i2 types are exclusive s2m2.[23] It has been shown that *vacA* may cause T-cell suppression, allowing for persistence of *H. pylori*. Recent *in vitro* studies found that pathogenic *vacA* alleles induced increased expression of IL-8 and growth-related oncogene alpha (GRO-α).[24]

Treatment of H. pylori infection: Are all Helicobacters bad?

It is true that *H. pylori*-related disease constitutes a global health problem. Most gastric cancers are identified at a late stage due to lack of screening in most countries, which makes them difficult to treat. However, in South Africa *H. pylori* infects more than 80% of the population, yet gastric cancer is extremely uncommon. Further studies in this field will enable the identification of patients at risk of developing gastric cancer years before the onset of disease. Treatment can be targeted where it is needed most rather than focusing on a majority of infected individuals who will never develop clinical symptoms. Targeting treatment to only those infected with virulent strains and with a genetic susceptibility will help reduce the burden on resource-limited health systems in countries such as South Africa. Knowledge of the specific mechanisms leading to gastric cancer may be useful in the treatment of other cancers. Currently no guidelines exist specifically tailored in addressing *H. pylori* infection in high-prevalence societies that have low risk of developing gastric cancer. We therefore propose that *H. pylori* infection be eradicated in the following settings in South Africa:

- as part of specific therapy in healing of gastric or duodenal ulcers (triple or quadruple therapy)
- in the therapy of low-grade MALT lymphoma of the stomach.

The eradication of *H. pylori* in subpopulations with higher risk of gastric cancer, such as people of mixed ancestry in Cape Town or in populations that carry virulent HpAsia strains, remains to be studied.

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In a nutshell

- Gastric cancer is one of the most common forms of cancer worldwide, with an estimated 930 000 new cases diagnosed each year.
- Five-year survival statistics in gastric cancer are poor (less than 5%).
- One of the most important features of gastric cancer is a steady decline in incidence and mortality in the developed world over the last 50 years.
- However, the incidence is thought to be increasing in the developing world.
- Gastric cancers can be divided into two major types: the diffuse type, which is aetiologically linked to host genetic factors and the intestinal type, with an environmental aetiology.
- Intestinal type gastric cancer develops through a series of precursor lesions, known as Correa's cascade.
- Diffuse type gastric cancer is thought to arise from single cell mutations which subsequently proliferate and invade the rest of the stomach.
- Infection with *H. pylori* has been associated with both types of gastric cancer.
- Countries with high *H. pylori* infection rates normally have higher gastric cancer incidence, as is seen in Asian countries.
- Although *H. pylori* infection is quite common in Africa, gastric cancer incidence is not as frequent as expected. This anomaly has been referred to as the 'African enigma'.
- Gastric cancer occurs in only 0.5 - 2% of all *H. pylori* infections.
- The differences in clinical outcome of *H. pylori* infection have been studied intensively and variously attributed to host genetics, virulence of the infecting strain and/or environmental factors such as a high salt diet.
- Treatment can be targeted where it is needed most rather than focusing on a majority of infected individuals who will never develop clinical symptoms.