CANCER RISK OF HELICOBACTER PYLORI INFECTION IN CHILDREN

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Summary:

Helicobacter pylori represents one of the most common and medically proeminent infections worldwide. Helicobacter pylori has been highlighted as an agent with an important role in gastric carcinogenesis. This action is due to morphopathological changes of the stomach as well as to bacterial virulence factors.

Key words: gastric cancer, Helicobacter pylori, children.

Helicobacter pylori can be considered as a health-care issue because of the mortality associated with the infection, owing to the risk of bleeding ulcers and gastric cancer. Infection with Helicobacter pylori can result in the development of gastritis in all infected humans, including children and adolescents (1).

Helicobacter pylori infection seems to be associated with an increased risk of developing gastric cancer. However, only a small number of infected individuals will develop gastric cancer (2), including mucosa-associated lymphoid tissue lymphoma and adenocarcinoma (3).

The infection is contracted primarly in childhood and infection from childhood appears to enhance the risk for carcinogenesis.
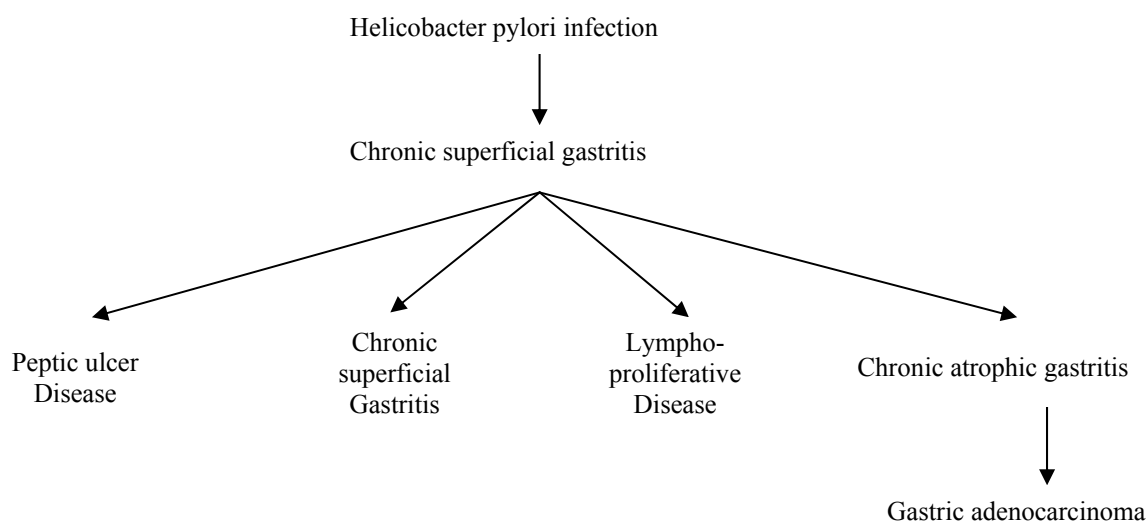
In 1994 Helicobacter pylori was classified as a group 1 carcinogen for gastric cancer by the International Agency for Research on Cancer.

Adenocarcinomas are the most common malignant tumors of the stomach comprising 97% of all gastric cancers with the remaining 3% being lymphomas or leiomyosarcomas. Infection with Helicobacter pylori has not been associated with proximal gastric carcinoma.

The strongest epidemiology evidence linking Helicobacter pylori infection with gastric cancer comes from 3 nested case-control studies published in 1991. These studies using stored serum demonstrated that Helicobacter pylori infected people are more likely to develop gastric cancer.

Case-control studies based on serologic evidence of infection may underestimate the association between Helicobacter pylori and gastric cancer because Helicobacter pylori colonization of the gastric mucosa decreased in association with the development of gastric atrophy.

The colonization with Helicobacter pylori determine the development of gastric atrophy, also called multifocal atrophic gastritis. This involves loss of gastric mucosal glands and hence altered gastric secretion. The evolution of gastric atrophy may be the first step towards the development of gastric cancer. This lesion might then lead to further changes, among them intestinal metaplasia and dysplasia, conditions that typically precede cancer (4).

Helicobacter pylori infection

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Chronic superficial gastritis

Peptic ulcer Disease | Chronic superficial Gastritis | Lympho-proliferative Disease | Chronic atrophic gastritis

↓

Gastric adenocarcinoma

It has been proposed that specific bacterial virulence factors may play a role in the development of gastric cancer. Strains of Helicobacter pylori can be differentiated based on whether they contain the cytotoxin associated gene (cag).

The cagA gene codes for the Cag-A protein, which seems to stimulate the production of chemotactic factors for the neutrophils by the gastric epithelium of the host. A certain portion of Helicobacter strains (40%), by unexplained causes, does not produce this protein.

Cag is a marker for the presence of a pathogenicity island in the Helicobacter pylori genome and may be a marker for a more virulent type of Helicobacter pylori.

Later research indicated that people infected with Helicobacter pylori strins bearing the cagA gene have a higher risk of acquiring peptic ulcer disease or stomach cancer than people with strains lacking the gene.

We know now that cagA is a part of a region in the Helicobacter pylori chromosome that also contains genes encoding proteins that form a type IV secretion system (TFSS). Bacterial cells assemble these systems to export large, complex molecules into host cells. Several of the Helicobacter pylori genes near cagA encode TFSS proteins that assemble into a structure analogous to a miniature hypodermic needle. This structure injects the CagA protein into the epithelial cells that line the human stomach.

After cagA enters an epithelial cell, enzymes in the host chemically transform the protein, allowing it to interact to several humans protein. These interactions ultimately affect the cell's shape, secretion and signals to other cells. Strains of Helicobacter pylori bearing the cagA gene cause more severe inflammation and tissue injury in the stomach lining than do the strains without the gene. These differences may explain the increased disease risk in people carrying the cagA strains.

After the exposure to cagA positive Helicobacter pylori strains, an increase has been reported in catalase, glutathione peroxidase, and superoxide dismutase activity. This increase is associated with fewer DNA adducts and reduced susceptibility of the gastric cells to the irreversible injuries from reactive oxygen species (ROS) compared with exposure to cagA negative strains. Such alterations of the ROS scavenging enzymes may partly account for the increased risk of gastric cancer in individuals with Helicobacter pylori infection.

There are some Helicobacter pylori strains that caused large holes, called vacuoles, to form in epithelial cells in culture. The active agent was a toxin, dubbed VacA, encoded by a gene that is named vacA. In addition to forming the vacuoles, VacA turns off the infection-fighting white blood cells in the stomach, diminishing the immune response to Helicobacter pylori. Unlike cagA, vacA is present in every Helicobacter pylori strain, but because the gene's sequence varies substantilly, only some of the strains produce a fully functional toxin. John C. Artherton found four major variations in vacA: two (m1 and m2) in the middle region of the gene and two (s1 and s2) in the region that encodes the protein's signal sequence, which enables the protein to move through cell membranes. Helicobacter pylori strains with both m1 and s1 variations produce the most damaging form of the VacA toxin (5).

It has been observed that a higher number of antigenic proteins can be detected by immunoblotting among controls than among gastric cancer cases. Immunoblotting has also been shown to be both a more sensitive and a more specific detection method for Helicobacter pylori infection than enzyme immunoassay, EIA. The combination of antibodies towards the VacA and CagA protein is associated with an increased risk of gastric adenocarcinoma, and subjects infected with strains expressing the CagA protein have a higher risk of gastirc cancer. In a study reported by swedish researchers in 2002, antibodies towards the CagA protein and towards p30 (UreA) were associated with an increased cancer risk. This observation is consistent with a particulary strong link between infection with CagA positive Helicobacter pylori strains and risk of gastric cancer (6).

The severity of gastritis associated with Helicobacter pylori infection was correlated with mucosal expression of tumor necrosis factor alpha subunit and IFN-gamma. The robustness of the mucosal Th1 response has been associated with progression to atrophic gastritis and gastric cancer, as supported by animal models (7).

There is a evidence suggesting an association between Helicobacter pylori infection, which is almost always acquired in childhood, and gastric cancer occuring in adulthood. This association is specific to gastric cancer occuring distal to the cardia. However, we have to remember that only aproximative 15 of Helicobacter pylori – infected children will develop gastric cancer. Furthermore, infection alone may not be sufficient to cause cancer, and a number of others factors have been associated with an increased risk of gastric cancer. These include blood group A, poor dietary intake of vitamin C or carotenoids, as well as increased intake of salted and smoked foods. Whether the eradication of Helicobacter pylori can prevent the development of a significant number of cases of gastric cancer despite the persistence of other risk factors remains unknown.

Although definitive studies on the role of Helicobacter pylori in gastric cancer may therefore never be achived, or will at least take many years to carry out, a consensus as to the significance of Helicobacter pylori infection in childhood in relation to the risk of gastric cancer is urgently required. The major question that arises for clinicians is how to respond to H pylori infection when it is identified at endoscopy or by noninvasive methods such as 13C-urea breath testing. A decision to treat all infected children to reduce their risk of developing gastirc cancer implies that community screening for this infection in childhood should be undertaken to identify and treat all infected children. Nevertheless, parents of children undergoing investigation will have to be informed when this infection is identified. The recent findings of Brenner et al and El-Omar et al (2) suggest that we should treat infected children who have a family history of gastric cancer.

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