Helicobacter Pylori and Gastric Cancer

Asma Ouakaa-Kchaou, Hella Elloumi, Dalila Gargouri, Jamel Kharrat, Abdeljabbar Ghorbel.

Department of gastroenterology, Habib Thameur Hospital, Tunis - Tunisia.

A. Ouakaa-Kchaou, H. Elloumi, D. Gargouri, J. Kharrat, A. Ghorbel.

Rôle de l'Hélicobacter Pylori dans le cancer gastrique

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RÉSUMÉ

Prérequis : L'infection chronique par l'Hélicobacter pylori, une bactérie à tropisme gastrique, entraîne une augmentation du risque de néoplasies gastriques et notamment l'adénocarcinome gastrique.

But : L'objectif de cette revue de la littérature était d'analyser la relation entre le carcinome gastrique et l'infection à Hélicobacter pylori et de proposer des attitudes préventives.

Méthodes : Nous avons consulté la base de données Pubmed en utilisant une requête documentaire combinant les mots clé cancer gastrique et Hélicobacter pylori.

Résultats : Les facteurs de risque du cancer gastrique incluent des facteurs environmentaux, génétiques et bactériens. L'Hélicobacter pylori possède deux principaux modes d'action : une action indirecte sur les cellules épithéliales gastriques par le biais de l'inflammation aboutissant à une atrophie gastrique et une métaplasie intestinale et une action directe entraînant une modulation des protéines cellulaires et des mutations génétiques.

SUMMARY

Background: Patients infected with Helicobacter pylori, a stomach colonizing bacteria, have an increased risk of developing gastric malignancies, in particular gastric carcinomas.

Aim : This review was aimed to analyze the relationship between gastric carcinoma and Helicobacter pylori infection and to rule out the possibility of preventive measures.

Methods: To identify articles for this review, a PubMed search was conducted using the following key words: gastric cancer, Helicobacter pylori.

Results: The risk for developing cancer includes environmental, host-genetic and bacterial factors, which induce physiologic and histologic changes in the stomach. There are two major pathways for the development of gastric cancer by helicobacter pylori: the indirect action on gastric epithelial cells through inflammation leading to gastric atrophy and intestinal metaplasia and the direct action through the induction of protein modulation and gene mutation.

Mots-clés

Hélicobater pylori ; cancer gastrique

Key-words

helicobacter pylori ; gastric cancer

علاقة الهيليكوبكتار بيلوري و سرطان المعدة

الباحثون : أ.واقعة-كشو، هـ.اللومي، د .قرقوري، ج .خراط، أ .غربال

الخمج المزمن بواسطة الهيليكوباكتر بيلوري يضاعف من خطر الإصابة بسرطان المعدة .الهدف من هذه الدراسة هو استعراض العلاقة بين سرطان المعدة و هذا الخمج و آقتراح الطرق الوقائية .عوامل خطر الإصابة بهذا السرطان متنوعة وهي إما بيئية أو جينية أو بكتيرية.

الكلمات الأساسية : هيليكوبكتار بيلوري - سرطان المعدة

Gastric carcinoma is one of the most common human malignant cancers in the world, with approximately 900.000 new cases diagnosed every year and a leading cause of cancer-related deaths in many parts of the world.

Although the etiopathological mechanism of human gastric cancer remains unclear, most researchers believe that the pathogenesis of this cancer is a multifactorial, multistage and multistep process. The epidemiological and histopathological studies have shown that infection with gastric bacterium Helicobacter pylori (HP) plays a role in the etiology of gastric cancer. The World Health Organization has categorized HP infection as a definite human carcinogen class I since 1994. Some years after this decision, it is well established that persistent infection with HP is associated with an increased risk for gastric malignancies.

This review was aimed to analyze the relationship between gastric carcinoma and HP infection and to rule out the possibility of preventive measures.

METHODS

To identify articles for this review, a PubMed search was conducted using the following key words individually and in various combinations: gastric malignancies, gastric carcinoma, Helicobacter pylori. Search of reference lists from pertinent articles identified additional publications.

RESULTS

Epidemiological features:

Around the world, the prevalence of HP infection ranges from 20% to over 90% in adult populations [1]. HP infection rates average at about 30% in Western populations, approximately 0.1 to 1% of the patients with HP induced gastritis will develop gastric cancer. Infection rates in Asian countries and in developing countries such as Tunisia are higher and range at 60-90%, gastric cancer is more frequent [1].

Concept of gastric carcinogenesis:

Most researchers believe that the pathogenesis of human gastric cancer is a multifactorial and multistage process [2, 3, 4].

There are two major pathways for the development of gastric cancer by HP infection: the indirect action of HP on gastric epithelial cells through inflammation, and the direct action of the bacteria on epithelial cells [5]. Studies have shown the importance of gastritis in the development of gastric cancer, however, it is also established that HP directly modulates epithelia cell function by bacterial agents [1, 5]. Both pathways appear to work together to promote gastric cancer development. Risk groups still show considerably higher risk of developing cancer, especially in patients infected with cytotoxin-associated gene A (cagA+) strains and the persons harboring genetic polymorphism of the IL-1B promoter and the corresponding IL-1 receptor antagonist [1,2].

Bacterial Virulence factors:

A major determinant of HP virulence is vacA (vacuolating cytotoxin), a cytotoxin that induces cytoplasmic vacuolation in gastric cells [6]. All HP strains possess the vacA gene, but not all of them induce vacuolation, pointing to the existence of genetic variability within vacA. Two major polymorphic regions have been identified: the signal region (type s1 or s2) and the midregion (type m1 or m2). Malignancy is associated with s1/m1 strains [6].

Bacterial virulence factors, including genetic diversity in the cagA region, have been claimed to account for the diverging development. HP strains possessing the cagA gene are associated with an increased risk of gastric malignancy. CagA+ strains inject the cagA protein directly into host cells where it undergoes tyrosine phosphorylation [1, 5, 6]. Translocated cagA forms a physical complex with the SRC homology domain (SH2)-containing tyrosine phosphatase (SHP-2) and stimulates phosphatase activity. Deregulation of SHP-2 by cagA induces abnormal proliferation of gastric epithelial cells [1, 5, 6]. Another cellular phenotype associated with carcinogeneis is altered apoptosis, which is promoted more rapidly in cagA strains, inducing a reduced apoptosis [6]. Moreover, cagA+ HP strains express the babA product, which mediates adherence to Lewis antigens on gastric epithelial cells. So the relative risk for the development of distal gastric cancer is increased up to 20-fold. Determination of cagA+ status may thus help the physician to identify people who are at increased risk for gastric cancer either by a serological test or by a specific antibody staining for histological specimens.

Host factors:

In addition to bacterial factors, but less important in terms of relative risk increment, are host factors [1, 4]. Presence of genetic polymorphism of the host (genetic polymorphism of the IL-1B promoter and the corresponding IL-1 receptor antagonist), increase the relative risk for distal gastric cancer by 1.5 to 4-fold [1]. IL-1 promoter polymorphisms are associated with increased methylation and HP infection, and exec a synergistic effect with the bacteria to increase the frequency of methylated genes [6].

Gastric carcinogenesis: (figure 1)

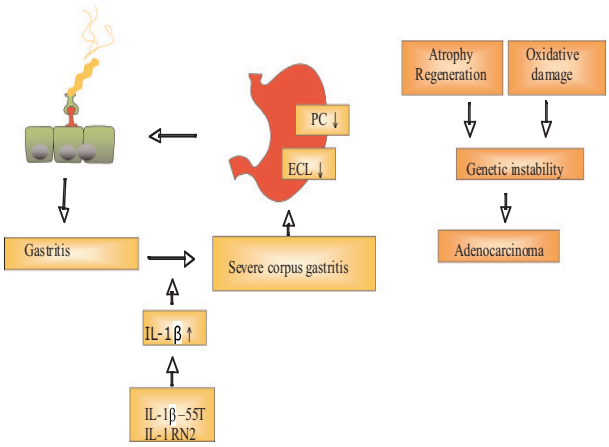
HP infection, especially with cagA+ strains, leads to a strong granulocytic and lymphocytic infiltration. A subgroup of infected patients will develop gastric cancer. CagA HP infection is associated with Th1-mediated cellular immunity in earlier stages of gastric cancer, while Th2-mediated humoral immunity dominates the advanced stages [5, 6]. Moreover, among immune responses associated with cagA HP infection, local immunity is predominant over systemic immunity and polarization of Th cells mediated immune response is associated with progression of gastric pathologies [6].

Reasons for the progression to cancer include also genetic polymorphism, which is associated with high levels of IL-1,. IL-1, is a strong antisecretory cytokine, leading to heightened cytokine release, which in turn decreases acid secretion [1, 4]. Subsequently, the association of hypochlorhydric conditions with the persistent inflammation in the gastric corpus is considered to be a true risk factor (relative risk: 34.5-fold) [1].

In addition to IL-1,, the production of other cytokines such as tumor necrosis factor-α (TNF-α), IL-6, IL-7, IL-11 is also

enhanced in the gastritis mucosa, and both IL-1, and TNF-α enhance NF-ÎB activation [5]. Several possible roles of NF-ÎB are being considered in the development of gastric cancer: anti-apoptotic action, acceleration of gastric inflammation by enhancing the production of cytokines, production of cyclooxygenase-2, mutagenesis (such as TP53) [5].

Figure 1 : Relationship between Helicobacter Pylori and gastric carcinogenesis [1]



Moreover, IL-6 appears to accelerate epithelial cell growth not only directly but also indirectly by stimulating RegIα through signal tranducers and activators of transcritption-3 (STAT3) activation in epithelial cells [5].

HP infection and IL-1 polymorphisms, via the increased production of IL-1,, predispose also to gastric carcinogenesis by enhancing CpG island methylation (aberrant DNA methylation), silencing tumor suppressor genes [5, 6].

Prophylaxis of gastric cancer:

Numerous studies have determined a clear correlation between HP infection and the risk of gastric cancer, however general eradication is not yet recommended as cancer prophylaxis and time points for treatment remain controversial in different areas of the world [1].

HP screening and general eradication is not recommended in populations at low risk for gastric cancer (such as Western countries) and is limited to risk groups in order to achieve a risk reduction [1, 4].

In contrast, infection rates are still high in other countries. A prevention strategy to treat infected persons may avoid the development of gastric cancer. However studies in China and Japan indicate that he prevention of gastric cancer is effective only in those patients that do not display severe histological changes such as atrophy, intestinal metaplasia and dysplasia. In fact, individuals with both HP or cagA seropositivity and a low pepsinogen (PG) I level or low PG I/II ratio, which is a marker of gastric atrophy, are highly susceptible to development of non-cardia gastric cancer [1, 4]. Thus, prophylactic strategies to prevent gastric cancer in high risk-populations such as China should therefore especially aim at individuals now at younger age when the histological alterations caused by bacterial infection were still reversible [1, 2, 4]. Current evidence suggests that HP eradication might represent a primary chemopreventive strategy in a subset of subjects without advanced precancerous gastric lesions; however, HP eradication in those patients who have already developed advanced precancerous gastric lesions does not prevent gastric cancer development [1, 3, 4, 5]. Prospective prophylactic long-term studies need to be evaluated.

However, HP eradication is recommended in post-gastric cancer resection and after endoscopic treatment of superficial gastric cancer to diminish the risk of recurrence [2, 7].

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