Best Practice & Research Clinical Gastroenterology 25 (2011) 581–592

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Gastroenterology

12

Chemoprevention for gastric cancer

Alexander C. Ford, MBChB, MD, MRCP, Senior Lecturer, Honorary Consultant Gastroenterologist [a,b,*]

[a] *Leeds Gastroenterology Institute, Leeds General Infirmary, Leeds, UK*
[b] *Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK*

Keywords:
Gastric cancer
Helicobacter pylori
Aspirin
Non-steroidal anti-inflammatory drugs
Anti-oxidants
Selenium
Chemoprevention

Gastric cancer remains the fourth commonest cancer, and the second commonest cause of cancer death, globally. Chemopreventive strategies to reduce the incidence of gastric cancer are required, particularly as the number of deaths per year is likely to rise for the foreseeable future. There is some evidence that population screening and treatment for *Helicobacter pylori* in high-risk populations may reduce incidence of gastric cancer. Trials studying the effect of anti-oxidants and selenium are conflicting. A recent meta-analysis demonstrated that aspirin use led to a reduced risk of gastric cancer after 10–20 years of follow-up. There is little convincing evidence that statins have any effect on risk of gastric cancer. More trials on chemoprevention for gastric cancer are therefore urgently required.

Introduction

Gastric cancer is common. According to the latest estimates of the worldwide burden of cancer produced by GLOBOCAN for 2008 [1], the disease is the fourth commonest cancer in terms of incidence, and it remains the second commonest cause of cancer death worldwide, responsible for almost three quarters of a million deaths annually. This is an increase in global mortality from the disease, compared with an estimated two thirds of a million deaths per year in 2002 [2]. Despite a declining incidence in many countries in the developed world, the total number of deaths from gastric cancer may well continue to rise for the foreseeable future [3], due to an increase in the average age of the world's population.

* Corresponding author. Leeds Gastroenterology Institute, D Floor, Clarendon Wing, Leeds General Infirmary, Great George Street, Leeds, LS1 3EX, United Kingdom. Tel.: +44 1132684963; fax: +44 1132429722.
E-mail address: alexf12399@yahoo.com.

1521-6918/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bpg.2011.09.002

Unfortunately, many patients are diagnosed at a late stage, meaning that the efficacy of treatment for gastric cancer is unsatisfactory. Almost half of patients' disease is inoperable at the time of presentation [4], and 5-year survival in this group of individuals is close to zero. Even among those who are suitable for surgical treatment, extensive surgery is often required, and 5-year survival rates are in the order of 20%–30%. [5].

Survival may be improved if the disease were able to be diagnosed at an earlier stage [6]. Population screening for gastric cancer, via upper gastrointestinal (GI) endoscopy, is feasible, but the costs of adopting such a strategy are likely to be prohibitive in many countries, as thousands of asymptomatic people would need to undergo endoscopy in order to detect one case of cancer. Even if only those with upper GI symptoms that may be indicative of an occult gastric cancer, such as dyspepsia, were screened by endoscopy the cost of detecting one malignant lesion has been estimated to be as high as $83,000 [7].

As a result, chemoprevention strategies to reduce the incidence of, and therefore mortality from, gastric cancer may be an attractive alternative to mass screening of the general population, or subgroups of the population who may be at increased risk of gastric cancer. The remainder of this article will focus on the available evidence for any efficacy of a variety of proposed chemopreventive agents for gastric cancer.

Eradication therapy for *Helicobacter pylori* in the prevention of gastric cancer

Rationale for use of eradication therapy for Helicobacter pylori *in the prevention of gastric cancer*

In early models of the natural history and evolution of gastric cancer an unknown environmental factor was thought to induce a chronic inflammatory response in the gastric mucosa, causing a superficial gastritis, which eventually progressed to gastric atrophy, and ultimately intestinal metaplasia [8,9]. Both atrophy and intestinal metaplasia have been proposed as potential precursor lesions of gastric cancer, with atypical changes then taking place within the gastric mucosa, resulting in dysplasia. In support of this model is a study of individuals from communities in Colombia, with differing risks of gastric cancer, in which less than a quarter of individuals from the highest risk region had an entirely normal gastric mucosa by the age of 25 years [10].

Until the discovery of *Helicobacter pylori* (*H. pylori*), the environmental agent that triggered this sequence of events was unknown, but factors such as a high dietary salt intake, bile reflux, and bacterial production of nitrites, from nitrogenous constituents in food, breaching the mucus barrier of the stomach were implicated. Following Warren and Marshall's identification of the bacterium [11], and their description of its association with chronic active gastritis and peptic ulcer [12], it was postulated that infection with *H. pylori* acted as the chronic inflammatory stimulus that induced progression of gastritis to gastric atrophy, and that it was therefore causally related to the development of gastric cancer. Subsequent studies have lent credence to this theory, with atrophy, intestinal metaplasia, and dysplasia all occurring more commonly in *H. pylori*-positive compared with negative individuals [13], and eradication therapy, consisting of an acid suppressant drug (usually a proton pump inhibitor) or bismuth in combination with one or more antibiotics, leading to significant improvements in the degree of gastritis and severity of gastric atrophy, as well as regression of intestinal metaplasia [14,15].

In 1991, three prospective nested case–control studies comparing rates of *H. pylori* infection in patients with gastric cancer with healthy individuals were published, with odds ratios for infection with the bacterium in gastric cancer of between three and six [16–18]. The estimated proportion of gastric cancers directly attributable to infection with *H. pylori* in these three studies ranged from 35% to almost 90%. As a result of the findings of these, and other studies, the World Health Organisation concluded in 1994 that sufficient evidence existed to support a causal role for *H. pylori* in the development of gastric cancer, and the bacterium was therefore classed as carcinogenic to humans [19].

Subsequent studies have yielded conflicting results [20–23], and several meta-analyses examining this issue have been conducted. The two most rigorous of these included only prospective case–control studies [24,25], and both demonstrated a pooled odds ratios for gastric cancer in *H. pylori*-positive individuals of between two and three [24]. A policy of screening populations at high-risk of