NEW TRENDS IN GASTRIC CANCER

Background and Videosurgery

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edited by

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Preface

Despite the fact that the incidence of gastric cancer is declining in the Western world, it remains a significant problem with respect to accurate diagnosis and treatment since it has a high mortality rate.

In June 1989 an International Conference was held at the University of Rome "La Sapienza" entitled "New Trends in Gastric Cancer: Background and videosurgery". During this meeting background information on the aetiopathogenesis of gastric cancer was presented together with talks and video presentations on the latest advances in the treatment of gastric carcinoma, both from the European and Japanese experience.

Because of the poor prognosis of gastric carcinoma there is increasing pressure for early detection. Some of the problems in the early detection of gastric carcinoma are discussed together with methods of surveillance of high-risk subjects.

It is generally accepted that the surgical approach to gastric carcinoma should take into account the site and extent of the lesion and there are chapters on new methods for pre and intraoperative staging of the disease which allow a more logical approach to surgery. A comparison between Japanese and Western rule and results was attempted and reasons for the differences were investigated. Since the field is still evolving not all aspects could be covered, and those angles not approached in this book will be addressed in a second International Conference to be held in Rome in June 1990.

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Epidemiology and Mechanism of Gastric Carcinogenesis

M.J. HILL

Introduction

It is natural and sensible to consider epidemiology and aetiology together because they are so intellectually interdependent. It is rarely possible to construct sensible hypotheses on the mechanism of a disease with a long latency, such as gastric cancer, in the absence of some knowledge of the epidemiology of the disease. It is certainly difficult to devise sensible experiments with which to test hypotheses without such epidemiological information. Likewise, since epidemiological studies invariably yield many spurious "relationships" as well as, hopefully, indicating causal relationships it is important to assess the epidemiology in the light of various postulated mechanisms of the disease.

In this short review I will first consider the information that we have on the epidemiology of gastric cancer, then describe how this has been used to develop a hypothesis of the mechanism of carcinogenesis in the disease, then discuss the evidence that has been accumulated in the support of that hypothesis.

All research suggests more lines that should be investigated, and I will finish by listing some of the more obvious studies that arise from considerations of our current state of knowledge of the epidemiology and aetiology of gastric cancer.

Epidemiology

Until 1988 gastric cancer was the commonest cancer world-wide, although it has now been overtaken by lung cancer. Gastric cancer is very common in

Eastern Asia, South America and Eastern Europe and relatively uncommon in North America and in Australasia [1]. Within Europe the disease is more common in the Southern and the Eastern countries than in the Western part of the continent (Table 1). Migrants from populations with a high risk of the disease (e.g., Japan) to regions with a low incidence of the disease (e.g., Hawaii, California) retain their high risk of the disease unless they migrated in childhood or early adulthood; the children of migrants have a risk of the disease similar to that prevalent in their newly adopted homeland. These results suggest that the disease is caused by environmental factors which have their effect early in life.

Within populations, gastric cancer is more common in men than in women, it is inversely related to socioeconomic status and is associated with poor nutrition. There are a number of precancerous lesions and precursor states; the disease is weakly associated with blood group A status (indicating a role for genetic factors) and there is weak evidence of a familial predisposition to the disease. Precursor states include pernicious anaemia, gastric atrophy, chronic atrophic gastritis, intestinal metaplasia of the stomach, gastric epithelial dysplasia and hypogammaglobulinaemia. There is also an increased risk of the disease in patients who have been treated surgically for peptic ulcer [2].

There are two major histological types of gastric cancer in the classification of Lauren [3], namely the diffuse and intestinal types (together with an intermediate group). When subdivided in this way, the diffuse type was found to be equally common in men and women, and to have a familial association but no association with environmental factors. In contrast the intestinal type is much more common in men than in women, is not associated with genetic or familial factors but is strongly associated with environmental factors and gastric surgery. Whereas the incidence of the diffuse type is relatively even in all populations, the geographical variations in incidence (see Table 1) are mainly due to variations in the incidence of the intestinal type of gastric cancer. The precursor lesions of gastric atrophy, intestinal metaplasia and pernicious anaemia, all lead to gastric cancer of the intestinal type.

Since the stomach is the first resting place of food it seems reasonable to suggest that gastric cancer has a dietary aetiology. However, this has proved difficult to substantiate. Table 2 summarizes some of the studies that have been reported; these are described and discussed in more detail in reference 4. The general impression from such studies is that the disease is associated with a high intake of cereals and starchy foods, root vegetables, smoked or salted foods, and with low intakes of vitamins A and C and of fresh salad vegetables (principally lettuce). All of these associations are weak but

characterize the diet of low socioeconomic populations. There have been no studies of the relation between diet and gastric cancer of the intestinal type (the histological type known to be associated with environmental factors). However, the European Group for Cancer Prevention (ECP) is currently conducting a large international study of the relation between diet and intestinal metaplasia [5] – a precancerous stage in intestinal type gastric carcinogenesis – and early results should be reported in the autumn of 1989.

Table 1 Standardised incidence rates for gastric cancer (data from [4]) (rates are per 100,000 per annum, age standardised to world populations)

Country	*Death Rate*	
	M	*F*
Asia		
Japan – Miyagi	79.6	36.0
China – Shanghai	58.3	24.6
Hong Kong	19.2	9.6
India – Bangalore	12.6	7.1
Israel – all Jews	16.2	9.3
Singapore – Chinese	37.3	15.4
South America		
Brazil – Sao Paulo	53.6	25.1
Colombia – Cali	49.6	24.6
Costa Rica	58.8	25.2
Martinique	25.3	10.9
North America		
Canada – all	13.2	5.9
– British Columbia	11.9	5.0
– Ontario	11.5	5.5
USA – Alameda County		
– White	10.7	4.2
– Black	16.7	7.1
– Japanese	24.3	10.8
– Connecticut – White	10.8	4.3
– Atlanta – White	6.1	3.1
Oceania		
Australia – New South Wales	13.6	6.2
New Zealand – Maori	29.8	19.7
– non-Maori	13.7	6.0
Hawaii – White	11.8	6.0
– Japanese	28.4	14.1

Table 1 *(continued)*

Country		*Death Rate*	
		M	*F*
Europe			
East	Czechoslovakia	31.7	14.5
	GDR	25.2	12.3
	Hungary	32.4	12.8
	Poland – Cracow	32.9	13.4
	– Nowy Sacz	43.7	17.0
North	Denmark	14.3	6.7
	Finland	24.6	12.9
	Norway	18.1	9.2
	Sweden	15.0	7.5
West	FRG – Hamburg	23.7	11.7
	France – Bas-Rhin	15.5	7.4
	Ireland	12.4	4.2
	Netherlands	20.7	9.5
	Switzerland – Basel	19.6	8.1
South	Italy – Lombardy	39.0	17.1
	– Parma	44.0	19.9
	Romania	34.2	13.6
	Spain – Navarra	31.6	13.5
	Yugoslavia	34.9	15.1
UK			
England and Wales		18.5	7.8
	– South Thames	15.7	6.6
	– Liverpool	21.8	9.9
Scotland	– East	22.0	10.4
	– West	14.7	6.2

Table 2 The relation between diet and gastric cancer in various studies [4]

Populations Studied	*Dietary Item*
Finland	Grain products
Norway	Cereals; Smoked or salted foods
Iceland	Smoked fish and birds
United States	Starchy foods, root vegetables
Japan	Rice
China	Root vegetables
Colombia	Corn products, root vegetables
Slovenia	Potatoes

Aetiopathogenesis

The diffuse type of gastric cancer is associated with genetic and familial factors and is not associated with environmental factors; there are no postulates of the mechanism of carcinogenesis of this histological type. The intestinal type, in contrast, is associated with environmental factors, and with chronic atrophic gastritis (CAG), intestinal metaplasia (IM) and increasingly severe epithelial dysplasia (ED). Correa *et al* [6] postulated a histopathological sequence in intestinal type gastric carcinogenesis, the initial lesion in which is CAG. In a proportion of CAG patients the lesion progresses to IM, in which ED develops in some cases and progresses to gastric carcinoma. They proposed a mechanism for this (Figure 1), the first stage of which is loss of gastric acidity which permits the development of a resident bacterial flora. This flora reduces dietary nitrate to nitrite and may also catalyse the formation of N-nitroso compounds; the latter are responsible for the progression through IM and ED to gastric cancer.

The value of this hypothesis is that it can be tested, and it has consequences that can also be tested. If the hypothesis is correct then:

(a) Any disease state, surgical procedure, medical treatment, etc. which results in loss of gastric acidity should be associated with an increased risk of gastric cancer;
(b) these associated disease states should be associated with the development of a resident bacterial flora and with high gastric juice concentrations of nitrite and N-nitroso compounds;
(c) the gastric juice analyses should be correlated with the rate of progression through IM and ED to gastric cancer;
(d) it is unlikely that only locally acting N-nitroso compounds would be formed. Consequentially, if the amount of locally acting N-nitroso compounds is sufficient to be responsible for the gastric carcinogenesis, tumours at distant sites should also be associated with gastric juice N-nitroso compounds;
(e) if the postulated mechanism is correct, then chronic infection at other sites, if it can result in local formation of N-nitroso compounds, should also be associated with local carcinogenesis.

All of these consequences have been examined and discussed in detail elsewhere [4,7], and all have been found to be valid. All diseases associated with gastric atrophy, gastric surgery involving vagotomy and genetically determined disease in which pernicious anaemia is part of the spectrum, are associated with an increased risk of gastric cancer. In 24 studies reviewed by Hill [7] there was an increased bacterial flora (particularly the nitrate-reducing bacteria) and nitrite concentration in the gastric juice of

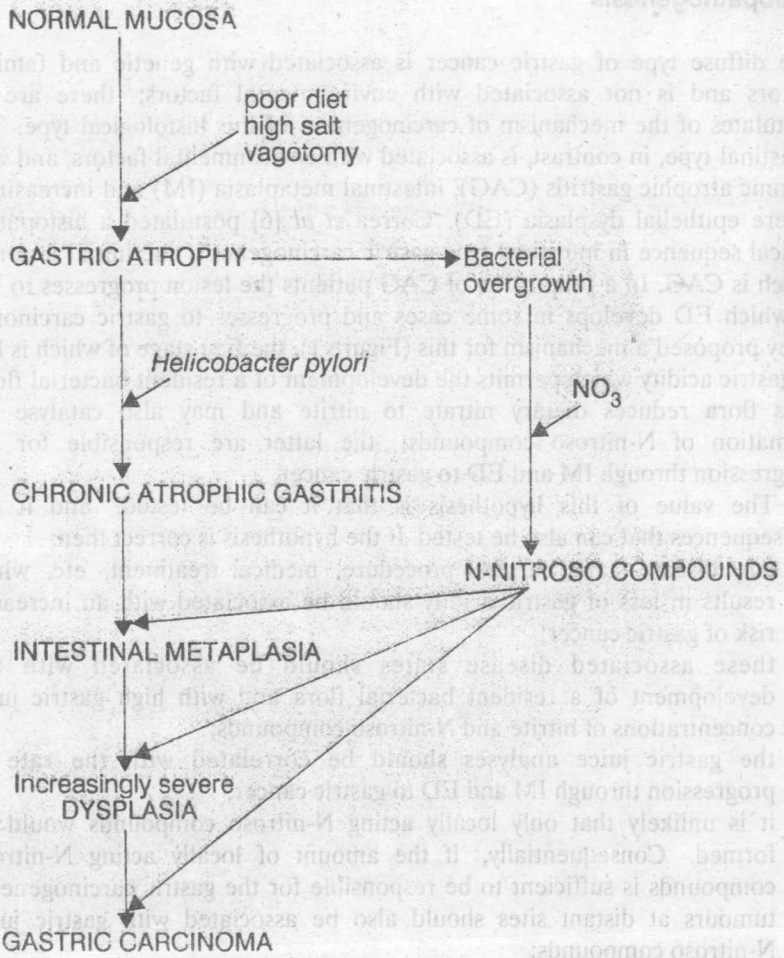

Figure 1 The postulated mechanism of gastric carcinogenesis of the intestinal type (based on Correa *et al* [6])

patients with raised gastric pH. In a number of these studies the relation between gastric juice analyses and the histopathology has been studied; both the gastric flora and the nitrite concentration have been shown to be correlated with the severity of ED. These results only correlate the conditions needed for N-nitroso compound formation and do not assess the

actual production of such carcinogens. There are major difficulties in the assay of N-nitroso compounds and this has led to considerable confusion in the literature with some studies [8,9] showing a strong correlation between N-nitroso compound concentration in gastric juices and both gastric pH and risk of gastric cancer, and other studies showing no relationship. Assay methods have recently been reassessed by Pignatelli *et al* [10] who confirmed the relationship observed by Reed *et al* [8] and in agreement with the Correa hypothesis. Caygill *et al* have studied the risk in gastric surgery patients not only of gastric cancer [2], but also of cancer at distant sites [11] and noted an excess risk (after a latency of 20 years, as with gastric cancer) of cancer at a number of sites including the biliary tract, colorectum, oesophagus, breast and pancreas. Some of these have since (or in retrospect) been confirmed by others [12–14]. Finally, chronic bacterial infection and the local production of N-nitroso compounds has been associated with local cancers in the infected bladder [15,16], the infected cervix [17] and in the special situation of ureterocolic anastomosis [17]. Thus, there is now a large body of evidence in favour of the Correa hypothesis of gastric carcinogenesis and it is clear that this multi-stage hypothesis has a number of important implications for our understanding of gastric carcinogenesis and its prevention.

Future Work in Gastric Cancer Epidemiology

The value of the Lauren classification was demonstrated by, for example, the work of Lehtola [18] who confirmed that there was a strong genetic component in the causation of diffuse type gastric cancer with, for example, a 7-fold excess risk of gastric cancer in relatives of diffuse type cases but no excess risk in relatives of intestinal type cases. In contrast the intestinal type was associated with environmental factors [19,20]. There is, therefore, a clear need to reassess the relation between diet and the two types of gastric cancer in case-control or population studies; it would be expected that when intestinal type cases were considered alone the correlations with dietary factors would be very much stronger.

It is clear from the Correa model that different dietary factors could be important at the different stages of carcinogenesis and that, therefore, attempts to study the stages in isolation were more likely than studies of the overall process to yield clear results. With this aim, the ECP is studying the role of dietary factors in the causation of intestinal metaplasia [5] and the UK part of that study is also studying the relation between diet and the progression of the disease. It is confidently expected that these studies will yield data which will provide a sound scientific basis for dietary intervention