Gastric Cancer

Edited by
Ch. Herfarth and P. Schlag

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With 161 Figures and 144 Tables

Springer-Verlag
Berlin Heidelberg New York 1979

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ISBN 3-540-09467-9 Springer-Verlag Berlin Heidelberg New York
ISBN 0-387-09467-9 Springer-Verlag New York Heidelberg Berlin

Library of Congress Cataloging in Publication Data. Main entry under title: Gastric cancer.
1. Stomach–Cancer. 2. Stomach–Surgery. I. Herfarth, Christian, 1933- II. Schlag, P., 1948-
RC280.S8G37 616.9'94'33 79-19624 ISBN 0-387-09467-9

Typesetting: Fotosatz GmbH, Beerfelden; Printing: Beltz Offsetdruck, Hemsbach/Bergstr.
Bookbinding: J. Schäffer OHG, Grünstadt
2127/3140-543210

Preface

The problem of gastric cancer, with its multifaceted aspects, offers an example of diversified oncological research, which includes epidemiology, pathogenesis, histomorphology, surgical and conservative therapy in its spectrum. This disease not only constitutes an interesting and important subject for research, but it is also a challenge for the practitioner due to its inordinately poor prognosis.

It therefore appeared a rewarding task to the editors to collect information from individual experts, in order to gain a topical summary of the problems pertaining to gastric cancer, as well as to provide a survey of the progress and the therapeutic possibilities in this field.

This task was particularly enticing, as gastric cancer has lately come to belong to those tumors somewhat relegated to the shadows, although it is, despite its decreased frequency in some western countries, still one of the most prevalent malignant diseases.

This collection should emphasize the need for broadly based knowledge of individual problems as a prerequisite for any satisfactory therapy of an organ tumor. It is therefore the primary concern of this book to furnish anyone with an interest in oncology with this necessary survey.

The editors thank Mrs. Karin Dohmeier and Mrs. Karin Kluge from Springer-Verlag for their cooperation in preparing this monograph. We extend our thanks to Mrs. Susanne Schenk and Mrs. Marga Wild, who contributed so much by her secretarial experience for the success of this volume.

Ulm, September 1979

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1 Epidemiology and Pathogenesis

Exogenous Factors in the Epidemiology of Gastric Carcinoma

Carl J. Pfeiffer

Introduction

During the past decade, the great importance of exogenous factors, i.e., environmentally-related factors, has become recognized for cancers of all sites. Although this type of association for cancers of a few sites was considered for many years, there is now a very general recognition that exogenous carcinogenic agents, particularly chemical, but also viral factors, are involved in human cancer etiology, and that other exogenous factors either promote malignant transformations or enhance host susceptibility. The role of exogenous factors in the causation of gastric cancer appear paramount, although this conclusion has been derived by implication, rather than by direct proof of the causative agents. Thus, the demonstration of (a) the lack of importance of hereditary-racial factors generally, (b) the reliable production of gastric cancer in animals by chemical carcinogens, (c) the slowly mounting evidence of specific risk factors in the human environment for gastric cancer, and (d) the massive evidence of carcinogenic-associated exogenous factors for cancers of other sites without any rationale that carcinogenesis in the stomach should be unique, all suggest exogenous carcinogenic factors for gastric carcinoma.

The epidemiologic approach to this problem has already and will continue to contribute much to understanding the early pathogenesis of gastric carcinoma and to identifying risk factors. Although epidemiologic investigation may or may not provide ultimate proof of gastric cancer causation, it will likely clarify the pathogenesis, will lead the way to appropriate laboratory investigations, and should identify control measures which may prevent or decrease the risk of acquiring gastric carcinoma. The criteria for ascertaining the validity of epidemiologic associations relating gastric cancer to exogenous factors are standard criteria, consisting of the strength of statistical association, the presence of a graded or "dose response" relationship, the effectiveness of predictability in prospective studies with human subjects, confirmation in several populations, reconcilation with other types of clinical or laboratory investigations, etc.

The causes of gastric cancer remain unknown and many hypotheses to explain the pathogenesis of this disease, and exogenous agents have been considered. These factors have been reviewed many times previously [5, 11, 21] and will not be discussed exhaustively here. Table 1 outlines a broad array of exogenous factors that have been suggested as being involved in gastric carcinogenesis. The purpose of the present account is (a) to emphasize some of the most important exogenous factors that consistently have been shown to be

Table 1. Sources of exogenous factors associated[a] with increased risk for gastric carcinoma

Environmental	
Acidic or peaty soil	High nitrate content in water
Urban residency	Exposure to environmental talc
Extensive use of nitrate fertilizers	Volcanic rock background
Soft water	Elevated lead or zinc in water
Littoral environment	
Dietary	
Highly salted food	
Smoked foods	
High fat or contaminated oil intake	
Smoking and Drinking	
Cigarette smoking	
Consumption of sake or contaminated whiskey	
Occupational	
Lower socio-economic classes	Agricultural workers
Workers in mines and quarries	Painters
Metal industry workers	Transportation equipment repair and assembly workers
Fishermen	Textile workers
Printers and bookbinders	Ceramic, clay, and stone workers
Construction workers	Clerical workers

[a] In most instances, these factors have been risk-associated in more than one country, but these correlations have not always been confirmed.

associated with gastric carcinoma, (b) to review some of the most recent findings incriminating exogenous factors in gastric carcinogenesis, and (c) to comment briefly on recent data from our own investigations which have suggested the role of exogenous factors in gastric cancer causation.

General Epidemiologic Findings

Epidemiologic data now allow several assumptions to be made about gastric cancer. These include, among other conclusions, the following: (a) more than one carcinogen can likely initiate gastric carcinogenesis, (b) chemical agents, perhaps ingested or formed in vivo, rather than viral agents, are likely inducing agents in most instances, (c) the pathogenesis is very slowly developing, after initial mutagenic changes in gastric stem cells, (d) the diffuse and intestinal types of gastric cancers, which are different diseases, may have different causal factors, (e) the conditions of chronic atrophic gastritis and intestinal metaplasia are closely associated with gastric cancer, thereby facilitating risk analysis and elucidating the pathogenesis, but these conditions are not proven precursor conditions.

Table 1 outlines some of the most frequently confirmed environmental, dietary, or occupational situations which, in several countries, have been risk associated. Some of these factors, such as cigarette smoking and smoked foods contain well-established chemical carcinogens, but others, such as salt (NaCl), are not carcinogenic alone. Thus, ingestion of highly salted food probably creates a promotional condition, such as local osmotic damage to the gastric mucosa, which facilitates action or entry of another agent which is the proximate carcinogen or procarcinogen. As noted, a large number of the high risk occupations are those wherein mineral dust or chemical fumes are inhaled and thus, could also drain into the gastrointestinal tract. It remains unclear precisely what factors in these high risk occupations are operative. The types of foreign agents which might enter the gut in industrialized societies, and their complex interactions and absorption within the gut lumen have recently been reviewed by Pfeiffer [12].

The role of exogenous factors in gastric cancer causation has been supported by several of the classical methods of epidemiologic analysis, including migrant studies, time trend studies, differences in the sex ratio of incidence, dietary, and case control study. Different races residing in high risk zones (Japanese and Caucasians in Japan) or in low risk zones (same races in the United States) have approaching rates, and migration to zones of changed risk imparts changes in incidence similar to the recipient country. A decrease in gastric cancer incidence has been shown almost worldwide, and in both high risk (Japan, Chile) and lower risk countries (United States, Canada, European countries), suggesting life-style changes which alter exposure to exogenous factors. The generally twofold greater susceptibility of males than females is occasionally reversed in local regions, again showing that the inherent sex-related resistance is likely altered by external factors. Dietary studies have long been fraught with difficulties, accuracy and meaningful results, but most items in Table 1 have been well supported. Of particular note also is the accumulating evidence of possibly protective factors in the diet, including milk consumption, and ingestion of fresh vegetables [5, 7], perhaps indicating the protective role of vitamins A or C or other antioxidants, as has been demonstrated as well for cancer of other sites [7] in large scale prospective studies in Japan.

Recent International Findings

During the past 2–3 years, new occupational-risk analyses of gastric cancer patients have shown that rubber workers have a standardized mortality ratio of 183 (age 40–64) for stomach cancer, an elevated risk that was associated with compounding and mixing, milling, cementing, and other processes in this trade [9]. The high risk of stomach cancer for farmers was confirmed by Haenszel et al. [4] and by Hirayama [6] for Japanese farmers. Also, the high risk for fishermen, previously shown in England and Wales, was confirmed in Japan [6] and in Newfoundland, Canada, the triad of fishermen, fish processing plants, and seabirds also being interlinked with enhanced risk [15]. Further, in Japan, the differential patterns among male geographic distributions for gastric cancer

versus cerebrovascular disease was confirmed by Nagai [10], with the former disease favoring agricultural workers. Also in 1978 Gaudette et al. [3] reported an elevated gastric cancer incidence in Canadian Hutterites, a religious farming sect.

Reports on dietary factors associated with gastric cancer appearing during the past 3 years have largely confirmed earlier notions. East German case control studies revealed as risk factors, food intolerance, high alcohol consumption, and long use of tobacco [20]. This smoking-related risk, shown in earlier studies, was also associated in 1977 with intestinal metaplasia of the stomach in Hawaiian Japanese [18], and it has been reported that the nornicotine in tobacco smoke can be nitrosated to a small degree in gastric juice of humans to N-nitrosonornicotine [16]. Further, the possible protective effects of dietary milk consumption was supported by data from Chile, and the inverse relationship between gastric cancer mortality and animal protein consumption was shown in Chile and Costa Rica. Fish extracts subjected to nitrosation, but not beef or hot dog extracts were shown to be mutagenic in the Ames test and ascorbic acid prevented this carcinogen formation [8]. Also, recent descriptive epidemiologic reports on gastric cancer from Belgium, contrasting the incidence in Flemish versus Walloon provinces, and a report on gastric carcinoma in Rhodesian Africans [2] have suggested the importance of exogenous factors, such as diet, alcohol, and tobacco consumption.

Gastric Cancer in Newfoundland and Iceland

Iceland has long been characterized as a high incidence island for carcinoma of the stomach, and more recently, the island of Newfoundland has been shown to be the highest risk province in Canada for cancer of this site [15]. As with most countries or regions in the world in which gastric cancer shows a high or moderate incidence, Newfoundland and Iceland demonstrate marked geographic variance in risk throughout the islands. It has been shown in Newfoundland that ethnic differences do not account for the variation in gastric carcinoma mortality, and that environmental factors, such as the geochemical background [15] or occupation are associated with these differences. Analyses of drinking water trace elements in Newfoundland (and Japan) show a positive correlation between gastric cancer and lead content [13], which is of interest because lead is carcinogenic in animals, and was the only element elevated in major river basin water in the United States, as correlated with gastric cancer mortality, according to Berg and Burbank [1]. It has also been demonstrated that lead workers had increased risk of pulmonary carcinoma [19].

A further indication that exogenous factors are involved in gastric cancer is the close parallelism between the Standard Mortality Ratio for this disease in identical occupational groups in both Iceland and Newfoundland (Fig. 1), where the dietary and ethnic factors are different, suggesting common environmental factors.

Fishermen were at greatly enhanced risk in both Iceland and Newfoundland, and it should be noted that fishermen were also at very high risk for cancer of the