Developments in the Epidemiology of Stomach Cancer over the Past Decade

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Summary

The history of stomach cancer epidemiology is reviewed. The introduction of migrant population studies in the 1960 decade that described the critical role of exposures to this disease in early life was a key event. Companion pathology studies have indicated different epidemiological patterns for 2 histological entities, intestinal and diffuse type carcinomas, and confirmed an excess of intestinal metaplasia in populations at high risk to stomach cancer. Recent results suggest that epidemiology of stomach cancer can be transformed into the epidemiology of precursor lesions, and introduction of the fiberoptic gastroscope makes technically feasible detailed studies of the relationship of precursor lesions to suspect factors, including diet, in selected geographic areas. Nitroso compounds have been identified as candidate carcinogens and the epidemiological, pathological, and chemical data display signs of internal consistency. Feeding experiments with N-methyl-N'-nitro-N-nitrosoguanidine have led to animal models that permit a coordinated epidemiological-experimental approach to stomach cancer.

The epidemiology of stomach cancer has been the subject of several reviews. Barrett's (2) comprehensive review, published in 1946, summarized the information available up to that time. Later reviews by Doll (8) in 1956 and by Haenszel (15) in 1958 utilized the more extensive and reliable data on cancer mortality and incidence accumulated in the years following World War II. A survey of the literature appearing after Barrett's publication was included in the 1963 report by Wynder et al. (40) on case-control studies of stomach cancer in Japan, Iceland, Slovenia, and the United States. The most recent compilation and appraisal of the relevant epidemiological data on gastrointestinal cancers was carried out by Bjelke (3).

This paper will attempt to place in perspective developments of the past decade, and for this purpose the summary by a panel of experts assembled under the auspices of the World Organization of Gastroenterology in 1964 provides a useful benchmark and point of departure (4). The characteristics of stomach cancer epidemiology established beyond dispute at that time were as follows.

1. There was marked intercountry variation in stomach cancer mortality, the rates in high-risk countries being approximately 5 times those in low-risk areas. Japan, Chile, Costa Rica, Iceland, and Finland had been identified as high-risk populations, while United States whites and Commonwealth countries, particularly Australia and New Zealand, were at the opposite end of the risk spectrum.

2. The marked intercountry variation in risk was accompanied by variation within countries, the general rule being that northern and/or colder regions had the higher risks, one well-known example being the higher stomach cancer rates in the mountainous region of Slovenia (Yugoslavia) as contrasted with the lower risks in the Adriatic coastal zone.

3. A rather stable male:female ratio of risks had been observed to prevail within all populations, the overall female rate being roughly one-half to two-thirds of the corresponding male rate.

4. A marked inverse socioeconomic gradient in risk was a prominent characteristic of this disease, the risks for the lower classes being roughly 2.5 times those for the highest socioeconomic class.

5. No consistent gradient in risk between urban and rural populations was demonstrable, and this did not appear to be an important epidemiological characteristic.

6. Within the United States the foreign-born displayed higher mortality than the native-born, the excess being most pronounced among migrants from Japan and certain European countries.

7. A steady downward trend in stomach cancer mortality had been underway for many years, a feature noticed first in the United States and later in several European countries.

8. Observations on the high risk of stomach cancer patients with pernicious anemia had firmly established the premalignant role of pernicious anemia.

These undisputed facts were accompanied by other pieces of evidence of more uncertain pedigree, the interpretation of which was subject to discussion and caveats. The latter included the following.

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1 Presented at the Conference on Nutrition in the Causation of Cancer, May 19 to 22, 1975, Key Biscayne, Fla.
2 Presenter.
1. A role for genetic factors was suggested by the familial clustering of disease and by the excess number of patients in Blood Group A. Since familial aggregation is a necessary, but not sufficient, condition for a genetic factor, familial aggregation could also reflect exposure to a common environment. The excess stomach cancer risk of patients in Blood Group A was small (a risk of 1.2 relative to Blood Group O was suggested by the composite evidence). What seemed clear was the inability of a genetic factor to account for a substantial portion of the interpopulation variation in stomach cancer risk.

2. While several authorities were of the opinion that chronic atrophic gastritis and intestinal metaplasia were precancerous conditions, the information in hand seemed inconclusive and more epidemiological studies were needed to clarify the issue.

3. The social class gradient in risk was not accompanied by consistent patterns of excess risks in specific occupations. Miners, fishermen, and agricultural workers were implicated by several studies, but the evidence was anecdotal in character.

4. The belief that occupations involving close contact with the soil carried higher risks was widely held. Some studies had associated soil composition with gastric cancer risk, although the nature of the relationship varied from place to place. Most of the findings were based on a search for coincidences in maps of geological formation and soil contents and maps of stomach cancer risks. Soils with a high content of peat and other organic matter were in clustering of disease and by the excess number of patients in Blood Group A was suggested by the composite evidence). What seemed clear was the inability of a genetic factor to account for a substantial portion of the interpopulation variation in stomach cancer risk.

5. The observations on diet and gastric cancer assembled prior to 1964 were varied in nature. Some represented observations of unusual customs in high-risk populations, others were based on contrasts in food practices between high- and low-risk populations, and a few were derived from case-control studies. Rice was suspected in Japan, fried foods in Wales, potatoes in Slovenia, grain products in Finland, spices in Java, and smoked fish in Iceland. Some epidemiologists viewed starchy foods as a potential common pathway, since the stomach is a digestive organ in immediate contact with ingested food, and the absence of simple protective factors in some foods (14). None of the 3 alternatives had been elaborated into well-structured etiological hypotheses as of 1964, and their development was probably inhibited by the lack of suitable animal models to test hunches or impressions. The glandular mucosa of the stomachs of experimental animals was resistant to methylcholanthrene and the other potent carcinogens then available for feeding experiments.

Recent History

We now turn to recent developments. New data on cancer incidence and mortality from many areas throughout the world have elaborated and refined earlier reports (9) on intercountry and regional variation in stomach cancer risks. The high risks in the altiplano of Costa Rica have been confirmed (36). Certain cities in the tropical zone of Latin America, Bogota, Cali, Guatemala, and Lima, were described to have elevated risks for stomach cancer (30). The pattern that emerged indicated populations in the central Andean region to be at high risk while residents of the tropical coastal zones in Latin America tended to be at low risk. The latter feature was suggested by observations on migrants to Cali, Colombia, which has received an influx of population from both low-lying and mountainous areas of Colombia (6).

The decline in stomach cancer risks has continued unabated in the United States and western Europe. A recent downturn in stomach cancer mortality has been suggested by the vital statistics from Japan (32), and examination of the age-specific rates indicates this feature to be most pronounced in the age group under 65 years.

The male:female ratio for stomach cancer has been investigated in depth by Griffith (13) and has been shown to be age dependent. The ratio is close to unity at ages under 35, reaches a peak of about 2:1 around age 55, and thereafter declines to about 1.3 to 1.5:1 at the oldest ages. It
was suggested that this specific pattern might be linked to sex differences in food and caloric intake. However, as noted later, the findings may be better reconciled with histological-type differences in age- and sex-specific rates. The behavior of the sex ratios provides support for the thesis that gastric carcinoma is not a homogeneous entity but is composed of at least 2 distinctive etiological components.

Migrant Studies

The major advances in stomach cancer epidemiology over the past 10 to 15 years have come from utilization of the natural experiment of human migration. The migrant population approach dates from the observation (15) that the United States foreign-born coming from countries with high risks for stomach cancer continued to experience the risks characteristic of the population of origin. The presentation of risks characteristic of the host population of United States whites was delayed to the succeeding generation of United States-born offspring. This phenomenon was general and not peculiar to any single migrant group, nor was it a feature common to all cancer sites. For example, the risks for large bowel cancer among these same migrants rose during their lifetime to approximate the risk characteristic of the United States white host population. The observations on stomach cancer are not confined to the United States and similar findings have been reported from Australia (33). Nor does the stream of migration need to cross national boundaries. The cancer registry in Cali, Colombia, has described a marked excess of stomach cancer cases among migrants born in the department of Nariño, a mountainous region bordering Ecuador (6).

The strong correlation of stomach cancer with birthplace found in the migrant studies offers a possible explanation for the absence of striking urban-rural differentials in risk. Large-scale farm to city migration means that urban populations represent a mixture of individuals with different birthplaces and exposures; when the decisive events occur elsewhere, the urban rates will represent a weighted average of risks for its constituent migrant and native-born groups.

Histology

Investigations of migrant populations benefited from close coordination in the collection of epidemiological and pathological observations. The need for companion pathology studies had been suggested by the work of Järvi (22), Lauren (25), and Muñoz et al. (29) who had applied the Järvi-Lauren type criteria to stomach cancers in Latin American populations at high and low risk to the disease. They reported the intestinal type to constitute the greater proportion of cases in high-risk areas from which they inferred the intestinal type to be an "epidemic" component of stomach cancer responsible for much of the difference between high- and low-risk areas. Typing of stomach cancers in Cali indicated that the intestinal-type tumors accounted for most of the excess incidence in the subpopulations of migrants at highest risk (6), and the Cali results appeared consistent with the earlier, broadly based geographic comparisons within Latin America.

The typing of cases in Miyagi prefecture and Hawaii by 3 collaborating pathologists has elaborated previous findings (7). Tumor registries provided incidence data for Japanese populations in both localities, and the substantial number of cases typed permitted estimation of type- and age-specific incidence rates. The incidence for diffuse carcinomas differed little between the 2 areas and the disparity in overall incidence was concentrated in the intestinal, mixed, and other types, thus providing additional documentation for the conjecture of Muñoz et al. The age detail in the Miyagi-Hawaii comparisons represents the most substantial body of evidence now available on type-specific differences in incidence among populations at varying levels of risk. The data suggest the age curves of log incidence to have distinctive slopes for the diffuse and intestinal types, the risk for the diffuse type rising more slowly with age in both Japan and Hawaii. A steeper gradient in log incidence for the intestinal type appeared in both areas, the difference between Miyagi and Hawaii being expressed as a lateral displacement of the curve to the right (to older ages) in Hawaii. For both areas the rise in the female curves for intestinal type occurred at older ages than for males, and this feature could account for the characteristic peak in the male:female ratio of stomach cancer risk around age 55 noted by Griffith.

The constant slope values for the intestinal type suggest that the forces contributing to the rise in incidence with age are of the same magnitude once a critical age has been attained in each population. The displacement of the Hawaii curves could reflect either a later exposure to carcinogens or a longer latent period. Given the evidence for the close link between intestinal metaplasia and intestinal-type tumors, the latter appears more plausible.

The differences in type distribution have been more clearly expressed for the more extreme contrasts in stomach cancer risks represented by intercountry comparisons. While Kubo (24) has reported data that cast doubt on the hypothesis that the intestinal type is the variable component in contrasts of high- and low-risk populations, his classification criteria are not identical with those of Correa et al.; further checks and standardization of criteria for use in interpopulation comparisons are needed. For the smaller risk differentials encountered in intracountry comparisons, the use of typing in studies of time trends and case-control analyses has been less informative and the findings more equivocal (16, 27, 28).

Precursor Lesions

Epidemiology-pathology studies in migrant populations have strengthened the case for intestinal metaplasia as a precursor lesion. In Cali, Colombia, autopsy studies have demonstrated a greater prevalence of intestinal metaplasia among migrants from Nariño (6). Also, among the several...
migrant groups in Cali, the prevalence of intestinal metaplasia appeared more closely correlated with the incidence of intestinal-type stomach cancer than with incidence of the diffuse type. Review of autopsy materials collected in several localities have confirmed an excess of intestinal metaplasia in populations at high risk to stomach cancer (5). Other observations (coincidence in sites of maximal intestinalization and gastric cancer, description of transitional states between metaplasia and cancer, etc.) provide corroboration detail implicating intestinal metaplasia as a precursor lesion (34).

Introduction of the fiber-optic gastrocamera has added another dimension to the study of intestinal metaplasia. The cancer registry and autopsy observations on the Nariño-born in Cali indicated the need for field work in the place of origin. Although the risks in Nariño are exceptionally high, equal to or exceeding those in Japan and the altiplano of Costa Rica, preliminary inquiries suggested clustering of cases in certain localities. Review of hospital admissions and discharges confirmed the clinical impressions of local physicians on clustering (C. Cuello, personal communication) and this information was taken into account in the survey design. Samples of apparently well individuals were gastroscoped to identify individuals with IM and/or CAG and to determine the prevalence of these lesions. All persons examined were asked to report on residence history, food history, and sources of water supply. When the population was classified by birthplace, the distribution of IM and/or CAG coincided closely with the distribution previously delineated for stomach cancer cases (C. Cuello, P. Correa, W. Haenszel, et al., unpublished data). The prevalence of IM and/or CAG for stomach cancer was under 25% in low-risk communities and close to 50% in high-risk communities. The excess prevalence of intestinal metaplasia persisted among individuals born in high-risk (by Nariño standards) communities who had later moved to low-risk areas, a feature that reinforced the pervasive epidemiological theme on the important role for exposures in early life for stomach cancer. The comparison of findings on Nariño residents and Nariño migrants to Cali raises the possibility that the prevalence of CAG may be diminished, and hence reversible, by removal to a different environment, but this possibility does not extend to the later stage of intestinal metaplasia. The consistency between the survey findings and earlier autopsy studies enhances the case for IM and CAG as precursor lesions.

It would be difficult to overemphasize the importance of the fiber-optic gastroscope for epidemiologically oriented studies of the gastric mucosa. More indirect measures of intestinalization of the gastric mucosa, gastrin, parietal cell antibodies, and pepsigogen I and II, have been made in studies of the Hawaiian Japanese, but the sensitivity and specificity of the latter tests do not permit an adequate classification of individuals by presence and degree of intestinal metaplasia (G. N. Stemmermann, personal communication). Direct visual and histological surveillance of the gastric mucosa via endoscopy seems required.

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4 The abbreviations used are: IM, intestinal metaplasia; CAG, chronic atrophic gastritis; MNNG, N-methyl-N′-nitro-N′-nitrosoguanidine.

Geochemistry

The major new impetus in geochemical studies has come from the discovery of the mutagenic and carcinogenic properties of nitroso compounds. Hill et al. (20) have reported an association between high nitrate ingestion and high gastric cancer in Worsnop, England. This clue is being pursued in Colombia (Nariño) where samples of well water have been collected and analyzed for nitrate and nitrite content (18). The local surface water supplies have negligible nitrate and nitrite content. Wells with nitrate-rich water are a distinctive feature of several of the high-risk communities in Nariño. However, the finding that nonusers and users of nitrate-rich wells in these same communities have the same prevalence of precursor lesions raises questions about the meaning of this observation (C. Cuello, personal communication). A modified hypothesis that well water is an index of local soil content, implying that locally grown foods are the source of nitrates, may still be viable, since elevated urinary nitrate levels (an index of nitrate intake) have been reported for residents of high-risk areas who do not use well water (C. Cuello, personal communication). While elevated nitrate intake may prove to be correlated with precursor lesions and stomach ulcer in Nariño, additional studies must be carried out before accepting this conclusion.

A case-control study in Japan describing an elevated risk of stomach cancer for well water users, particularly among farmers in Miyagi prefecture, provides another indication that associations with nitrates are worth pursuing. Studies of nitrates are attractive since they offer plausible pathways for production of carcinogenic effects. Weisburger (39) has pointed out that bacterial conversion of nitrates in foods stored at room temperatures to nitrites opens the way to the synthesis of nitrosamines in stored foods. MNNG has been shown to induce cancer of the glandular stomach in rats (38), and Sugimura has stated that administration of low dosages of MNNG produces intestinal metaplasia.

Foods

The findings on diet from case-control studies of stomach cancer have been reviewed by Bjelke (3), and Table 1 draws on this source for the summary of results for nonmigrant populations published since 1964. Japanese and Norwegian migrants to the United States have been the most intensively studied and a brief recapitulation of the findings follows.

The Hawaiian Japanese study revealed that migrants from the Japanese prefectures with highest stomach cancer risks continued to exhibit higher risks in Hawaii, a relationship that did not persist for their Nisei offspring (16). Lower risks were also suggested for the Nisei but not for the original migrants (Issei), who had adopted Western-style diets. These nativity distinctions were consistent with other evidence on the critical nature of exposures in early life.

The favorable observational situation presented by the
Hawaiian Japanese, distinctive Japanese and Western foods, heterogeneity in food habits arising from variation in timing, and degree of transition from Japanese to Western-style customs, facilitated detection of case-control differences for some food items. Elevated stomach cancer risks were described for users of pickled vegetables and dried, salted fish, and a rise in risks with increased frequency of use was suggested. In the absence of similar associations for raw fish and unprocessed vegetables, suspicion is directed to methods of preparation. Low risks were described for several Western-type vegetables (lettuce, celery, corn, etc.), and the latter effects appeared to be independent of the associations with pickled Japanese foods, suggesting possible protective effects. The companion case-control studies conducted in Japan (Hiroshima and Miyagi prefectures) did not reproduce the associations with pickled vegetables and salted, dried fish reported for the Hawaiian Japanese. A homogeneous background of food habits in early life prior to World War II may have operated against their detection. The greater use of lettuce and celery reported by controls in Japan reinforced the Hawaiian Japanese results on possible protective effects.

The Norwegian migrant studies included collection of diet data by mail questionnaires from representative samples of Norwegian-born men in the United States and Norway. Case-control studies of stomach cancer using a common protocol were also conducted in Norway and in Minnesota (for persons mostly of Scandinavian descent). Bjelke's findings are quoted below.

*Norway. (a) Recent use of cooked cereals, fruit, soup, and salted fish was somewhat higher among stomach cancer patients than among controls. The data for salted fish suggest greater case-control difference for former use, an observation consistent with the greater use of this item among siblings of index patients with stomach cancer compared to control siblings. (b) More pronounced case-control differences were shown by a number of vegetables and fruits, which were used less frequently by the stomach cancer patients. The greatest deviations from the controls were shown for the indices for total vegetables and vitamin C intakes, for which the relative deviations were greatest among young patients and women. (c) The negative associations with vegetables and, more clearly, with vitamin C were more pronounced for diffuse than for intestinal-type carcinoma. (d) The negative association with vitamin C was seen most strongly in the subsets of individuals whose risks otherwise were relatively low due to absence of previous gastric surgery, Blood Group O (women), or infrequent use of salted fish. Salted fish and vitamin C appeared to interact also with respect to the histological expression of the carcinomas. (e) As reported earlier, the 3 variables, ABO blood group, history with respect to gastric surgery, and intakes of fruits and vegetables as summed up in the vitamin C index, were all independently associated with case-control status and constituted the most powerful discriminators between cases and controls.

*United States. (a) Recent use of cooked cereals, smoked fish, and canned fruits was higher and intakes of lettuce and tomatoes were lower among stomach cancer patients than among controls. (b) While total intakes of cereal products and fish were only slightly higher than among the controls, the index for total vegetables was considerably lower and the vitamin C index was moderately lower among stomach cancer patients. (c) As in Norway, the lower vegetable and vitamin C intakes among stomach cancer patients had persisted over a long period, were more pronounced among women, and, in both sexes, were mainly a feature of the diffuse carcinomas.

The long interval between exposure and onset of disease complicates the collection of reliable and relevant histories of food practices. Two remedies are possible. One is to collect diet histories prospectively and to observe the subsequent disease experience of the cohort members. This approach has, in fact, been taken in ongoing studies of Hawaiian Japanese males, male residents of Norway, and insurance policyholders of Scandinavian descent in the United States. Another alternative is to reduce the interval between exposure and onset of disease by substituting a precursor lesion as an observational end point. The transformation of stomach cancer epidemiology into the epidemiology of intestinal metaplasia was 1 objective of the Hawaiian Japanese male cohort study. This objective has not been
The transformation to epidemiology of intestinal metaplasia is off to a more promising start in Nariño, where population screening with gastroscopy has opened the door to a contrast of diet histories between individuals with chronic atrophic gastritis and/or intestinal metaplasia. The results will be reported elsewhere (W. Haenszel et al., unpublished data) and we comment here on the findings for 2 foods, lettuce and corn. A negative association with lettuce described by the low prevalence of IM and/or CAG among regular users is the latest in a series of similar observations from many populations (1, 4, 16, 28) and the repeated detection of a “protective” effect warrants more attention to the chemical and nutritional properties of lettuce. Corn is of interest because it has been the most important staple food in high-risk communities. More than 80% of persons born in high-risk areas eat corn as a staple diet item versus 50% of natives of low-risk areas. While above-and below-average use of corn as a discriminant for prevalence of IM and/or CAG was weakened when birthplace was controlled in the analysis, the omission of information on methods of preparation may be responsible, since much of the corn in Nariño is prepared by the Indian technique of alkali cooking (with wood ashes) (23). This point will be investigated in later work.

The collective information from diet studies lends itself to some tentative generalizations. Given the diverse foodstuffs consumed in populations with a high risk of stomach cancer, no single food or class of foods displays a 1:1 correspondence with the geographic distribution of stomach cancer. A relationship, if it exists, seems more likely to be linked with the treatment of foods (salting or smoking of fishes, meats, and vegetables for preservation and storage; alkali cooking of corn to enhance the biological availability of certain amino acids).

Discussion

Reviews of stomach cancer epidemiology prior to 1964 leave the reader with the impression that work in populations sharing homogeneous backgrounds of exposures had come to a dead end. Migrant population studies emphasizing a combined epidemiology-pathology approach have infused new life into this subject. Their great virtue has been the ability to correlate observations over a wide spectrum of exposures in home and host populations, which has emphasized the critical role of exposures in early life and the search for etiological factors in places of origin. The results were achieved by straightforward epidemiological methods demanding no novel analytical techniques. The new elements were selection of observational settings that might be expected to yield fruitful leads. In turn, the stage has been set for transformation of the epidemiology of stomach cancer into the epidemiology of intestinal metaplasia and allied precursor lesions. While the latter will depend on direct observation of the gastric mucosa, it will make technically feasible studies of variability within small geographic areas and detailed consideration of suspect factors, including diet, in local environments.

Recent experimental advances make possible a coordinated epidemiological-experimental approach to stomach cancer. Sugimura’s (37) feeding experiment with MNNG has led to animal models that may yield information on how the chain of events culminating in stomach cancer may be interrupted.

To close this review we summarize our reading of the facts in hand bearing on the etiology of stomach cancer and propose a model that may fit the facts.

1. Environmental factors play an overriding role in gastric cancer etiology. The declining incidence and mortality rates observed in recent decades is the most eloquent evidence of this assertion.

2. The initiating event in the carcinogenic process occurs early in life. This is best indicated by the prevailing high incidence in migrants from high-risk countries to low-risk environments. Our studies in Colombia indicate that the experience of the 1st decade of life determines the magnitude of the risk at later years.

3. A long latent period, 30 to 50 years, corresponds to the natural evolution of precursor lesions in the gastric mucosa: chronic atrophic gastritis and its frequent companion, intestinal metaplasia. The process begins as an inflammatory change leading to atrophy of the normal gastric mucosal epithelium and its gradual replacement by cells that are foreign to the stomach but occur normally in the intestine: goblet cells, absorptive cells, Paneth cells, and argentaffine cells. These metaplastic cells show, with time, different degrees of atypia which gradually progress until they become autonomous.

4. The series of mutations or cell transformations from gastric to intestinal to atypical to invasive epithelial cell may be accomplished by a ubiquitous low-dose mutagen-carcinogen. The agent may be a nitrosamine synthesized somewhere between the oral and the gastric cavities from the nitrite normally found in the saliva and the amines present in food. In vivo formation of nitrosamines from nitrates and secondary amines has been well documented, and their intragastric synthesis and potential carcinogenic role have been suggested (17, 31). Endo and Takahashi (10) have shown that methylguanidine, a compound present in several foods, is converted into a potent mutagen after exposure to sodium nitrite in both simulated and real human gastric juice environment.

5. Synthesis of the agent is dependent on food intake. Correlations between some foods and gastric cancer risk have been reported, but no food can be identified that is common to all high-risk populations. More consistent results have been obtained for foods associated with a decrease risk, such as lettuce. A complex interaction of food items in the microenvironment of the stomach may be involved. The forces favoring induction may include abrasive or irritant items such as vegetables with hard cortex or fiber or items with a high salt concentration. On the protective side, we may have fresh vegetables and fruits rich, among other things, in vitamin C. Such foods may condition the effectiveness of a carcinogen.

6. Intercountry comparisons of autopsy series have de-
scribed 2 major types of stomach cancer, intestinal and diffuse. The risk of the diffuse type appears less variable among countries and it is the predominant type at younger ages. However, the intestinal-diffuse distinction apparent in interpopulation contrasts has not been well demonstrated in studies of time trends or by case-control studies of suspect factors conducted within a single population. We speculate that the different behavior of type distinctions in inter- and intrapopulation contrasts might arise in the following manner. Synthesis of suspect nitroso compound(s) may be promoted by a low-pH gastric environment, so that vulnerable individuals not developing the intestinalization response continue to have a low-pH-favoring synthesis and tend to present diffuse-type carcinoma at young ages, the experimental counterpart being early induction of carcinoma of the glandular stomach by high dosages of MNNG. Individuals manifesting intestinalization followed by an elevated pH may be exposed to lower doses over the longer term and tend to present intestinal-type carcinomas at older ages, the experimental counterpart being slower induction of intestinal metaplasia by low dosages of MNNG.

In this situation the intracountry findings would not discriminate well between intestinal and diffuse types because the same environmental factors underlie both types and the diffuse response at an early age would reflect primarily host characteristics. The intercountry differences in presentation of intestinal-type tumors would, on the contrary, be sensitive to interpopulation differences in dietary and nutritional factors that enhanced or retarded the formation and activity of a mutagen-carcinogen within the stomach. Variations in environmentally modulated effective exposures would be a major determinant of latent period (and age of expression) of extensive intestinalization and intestinal-type tumors.

The general subject of the rate of formation and stability of various nitroso compounds in different pH environments and the conditions that affect their biological activity within the stomach need investigation in suitable animal models.

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