Future Inquiries into the Epidemiology of Gastric Cancer†

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Summary

The fact that gastric cancer has been shown in many studies to be strongly related to a large number of social factors, ethnic background, occupation, socioeconomic status, and the like, suggests the importance of exogenous factors in its etiology. Past studies show a variety of relationships that furnish leads requiring elucidation to further understanding of this disease, e.g., higher risks related to exposures to asbestos, metals dusts, purgatives, and poor dental hygiene. Diet inquiries have steadily improved and negative relationships have been discovered with ingestion of vegetables in studies in Wales, Liverpool, Buffalo, Honolulu, Japan, and Norway. Positive relationships with starch have been found in many of these same places as well as in Israel. These leads need further investigation, as do better methods of diet research, studies of diet and histological type of gastric cancer, diet in its relationship to familial aggregation of gastric cancer, and studies of consistencies in relationships among the various sites in the digestive tract. Because diet is so heterogeneous in modern societies, multivariate analysis is needed in addition to simpler traditional modes.

With the possible exception of cervical and lung cancer, there probably exists no other neoplasm for which so many social relationships have been discovered as cancer of the stomach. The presence of these clearly suggests the operation of some exogenous factor. Thus, the incidence rate has fallen precipitously over time (17), incidence increases with decreases in social class status (4), the foreign-born in the United States appear to have higher rates (5, 9), and there is some indication that Polish Americans have a higher risk than other foreign-born (9).

International comparisons suggest rates for Chile and Japan that are roughly 6 times those of whites in the United States, and rates in Austria, Finland, Germany, Italy, and Belgium, which are approximately 3 times the United States rate (21). Rates among the Japanese of Hawaii are lower than those in Japan, and among the Japanese on the West coast of the United States the rates are still lower (23). These relationships are suggestive of a response in disease incidence to a change in cultural surroundings. To be sure, the decreasing rate among Japanese as they move from Japan to Hawaii to the United States could be a product of differential selection of migrants because of genetic characteristics. This possibility becomes less attractive when one considers the results of studies of other migrants indicating that, in the 2nd generation away from the homeland, the risk of stomach cancer appears to become similar to that in the country receiving the migrants.

The fact that the 1st generation, the migrants themselves, retain the high rates current in their country of origin may suggest that youthful exposures to an exogenous agent are the crucial ones or that dietary or other folkways learned in the country of origin are maintained in the new country even in the presence of the differences in the receiving culture. Dietary habits, for example, may be difficult to change and may be maintained in fairly similar fashion throughout life. Thus, the factor maintaining the high risk of migrants in a low-risk-receiving society could be related to the fact that the migrants retain some of their old customs. It would be instructive to examine the extent to which dietary folkways persist under conditions of migration.

The ethnic investigations of Haenszel et al. (9, 10) have been particularly rewarding. This model of inquiry can be applied to other ethnic groups of particular interest. Almost 20 years ago, it was noted that the "native Hawaiians" had an extremely high rate of gastric cancer as compared with other ethnic groups in their polyglot islands (18). Although there can be no certainty as to the degree to which the term, native Hawaiian, includes genes of the indigenous islanders and those of recent arrivals, it may be significant that (as statistician Richard Rose of Wellington has written to me privately) other members of their Polynesian subrace and culture living in New Zealand similarly have high rates as compared with Caucasians. There is some evidence, too, that the Maori of New Zealand, like the native Hawaiians, have similar dietary characteristics: high in starch, low in protein, low in vitamin C, eating from 1 to 2 meals per day. Certainly, further inquiry into diet as related to gastric cancer should be mounted among the Polynesians as compared with other populations.

Alimentary Carcinogens

A likely area of investigation to explain these social relationships with gastric cancer may be the possibility of carcinogens that can enter the alimentary tract. These should be considered broadly, to include not only diet, but other substances as well. Recall that Kraus et al. (11) found...
an increasing risk of gastric cancer with an increase in duration and intensity of occupational exposure to iron dust. Similarly, Matolo et al. (14) find substantially higher rates of gastric cancer in Utah populations living in coal mining as compared to nonmining counties. Again, Selikoff et al. (22) found a larger than expected number of gastric cancers in asbestos workers, and we found a higher rate of gastric cancer among residents of asbestos-mining counties in Quebec than in nonasbestos-mining counties. In addition, Winkelstein (25) discovered a higher rate of gastric cancer in residential areas containing high air pollution, particularly in the neighborhoods of metals-manufacturing plants. One can only speculate that individuals with such occupational and residential characteristics may be exposed to a pathogen that enters the alimentary system. Inquiries to explain these relationships should be mounted.

In addition to dust and fibers of various sorts, other potential carcinogens can enter the alimentary system. Purgatives must be considered. Boyd and Doll (2, 7) and later we discovered a relationship between frequent use of cathartics and gastric cancer. This association has not been pursued further to any great degree. Nevertheless, the relative risks associated with use of purgation were substantial enough to warrant further inquiry.

Oral hygiene comprises another set of factors that can condition exposures of the alimentary canal. Wynder (27) shows a relationship between edentia and gastric cancer, and preliminary examination of our data suggests that various indices of poor oral hygiene, the presence of decayed teeth, calculus and staining, and poor mastication are associated with gastric cancer.

Diet

Partly because of large ethnic differences in rates of gastric cancer and because of what appear to be substantial variations in styles of eating in different ethnic groups, diet has been of considerable interest. A couple of decades ago, there was considerable doubt among epidemiologists that diet could be studied in any meaningful way. Methodological difficulties were all too apparent. There was doubt that dietary diaries would be adhered to by subjects so as to obtain information concerning behavior, and a number of investigators experimented with approaches in obtaining dietary information. They found that this cannot be done by asking simple questions about what one ate on any recent day or what one usually has for dinner. Rather, interviews become complex, often lasting a couple of hours, and utilize a number of approaches. Requesting individuals to state how often they eat given items of food and how it is prepared, asking them to compare the size of portions that they usually eat with those in photographic representations, and asking them to describe changes in their dietary habits for each item of food throughout life was 1 method that seemed potentially useful. A variety of methods are available and several should probably be used in any diet inquiry. Whatever the difficulties with dietary interviewing, and the cautions to be observed in interpreting such results, the number and variety of strong social relationships with gastric cancer demanded that some steps be taken to ascertain dietary and other alimentary characteristics as they might relate to the disease. Should relationships be discovered and should these be replicated in a number of studies, useful leads could be uncovered.

Of course, replication may produce replicated error. However, a few relationships are beginning to appear with some consistency in the few interview studies carried out among different populations living in different cultures or different geographic areas and using different languages. There is a similarity, for example, in the high risk associated with a high-starch diet in studies of foods in Tel Aviv, of rice in Honolulu, and of potatoes in New York and Buffalo (2, 7, 10, 15).

Similarly, the diet of gastric cancer patients as compared to controls has been found less often to include vegetables in Wales, Buffalo, Hawaii, and Japan and among Norwegian Americans (1, 8, 10, 24). If there has been bias in generating these results, it has worked in the same ways in very different places, at very different times, and using different languages. This suggests the need for several lines of inquiry, such as examination of the whole range of vegetables as related to this disease in a number of different places and a quantitative analysis of the nutritional constituents such as vitamin C and A and fiber in the diet of gastric cancer cases and controls as deduced from interviews. In addition, future inquiries should deal to a greater degree with ingestion of fruits, particularly citrus fruits.

J. H. Weisburger (unpublished data) has shown that food nitrates can alter to form nitrites when food is stored at room temperature. Obviously, inquiries should be made into the methods of food storage, preparation, and handling. Is the decline in gastric cancer associated in some way to the growing use of electric refrigerators?

We should not expect too much of diet studies. They cannot provide detailed information on ingestion of foods; they cannot be used to detect small differences. We must use them only to detect large differences. We can use them to search for consistencies between their findings and those of animal studies or of biochemical, endocrine, or other studies of cases and controls.

Thus, the self-reports of smoking behavior, based as they were on imperfect interview data, convinced few until consistent findings from animal and autopsy studies were obtained. Reporting by individuals as to their own past behavior is fraught with recall error and sometimes fabrication. Still, it has been useful in the past, as in the smoking
studies, and it is necessary in some way to establish the differences between human cases and controls in types of behavior that could have increased their risk of disease.

Alcohol and Tobacco

The results with regard to ingestion of alcohol are equivocal. Some investigators find high risk and others do not (7, 20). The fact, however, that some do suggests the need to investigate this factor further and in greater detail. Thus, there is a need to look into the specifics of alcohol consumption, such as the type. Are wine, distilled spirits, or beer related in different ways? We need to examine different levels of dilution. Does the diluted drink carry less risk than spirits on ice or in cocktails? Similarly, some additional risk has been associated with the use of tobacco. This needs to be examined in some detail, as well, including variations not only in amount smoked but in ways in which smoking is done. For example, do the variety of habits evinced by smokers vary in risk; smoking before breakfast, smoking on an empty stomach, cigar smoking versus cigarette smoking, etc. Research is needed to establish whether there is a greater than additive risk for smokers who drink, as in the synergy discovered for buccal cancer.

Research on Methodology

The discovery of a few dietary relationships via interview studies further emphasizes the necessity of conducting inquiries in addition to those already done, usually by nutritionists, to develop better dietary research methods tailored to epidemiological requirements. Because gastric cancer is likely to be of long latency, we should be interested in the long-term characterization of diet. Intensive interviewing needs to be done concerning people's dietary habits and the changes in diet that occur throughout their lives. To what extent is there consistency in preferences from adolescence through later years? Is there consistency of diet across generations and in sibships in a given family.

Special problems inhere in obtaining reliable data in sensitive areas such as alcohol ingestion. Inquiries should be made of the degree to which that ingestion reported by subjects is also reported by people they live with, work with, take recreation with, and drink with. We need to know the degree of underestimation, if that is what is found, of drinkers of various amounts and types of beverages.

Studies of the above questions could be used to assess methodology. Only in the comparison of observations with interview data would we obtain actual measures of validity, and the observation may alter usual behavior to produce another kind of bias. It may not be possible. Comparisons of answers given by subjects and their associates, however, can indicate questions on which there is little agreement and those that are more reliable.

Equally useful would be the comparison of gastric cancer patients and controls, not only on their own statements, but also on the statements of the various sources of corroboration described above. If the dietary differences between cases and controls were the same when reported by subjects themselves as by individuals well acquainted with their behavior, more confidence would be engendered in the results.

Diet and Histology

Lauren (12), Correa et al. (3), Múnoz et al. (16) and others have noted 2 broad kinds of gastric cancer, an intestinal and a diffuse type. They suggest that the intestinal type may be responsive to environmental characteristics. These authors would agree that findings are equivocal. Further work needs to be done to ascertain any possible relationships between diet and type of gastric cancer. Bjelke (1), for example, finds a negative relationship between vegetables, and particularly vitamin C, and diffuse gastric cancer. Similarly, Haenszel et al. (10) find essentially no difference in the risk associated with use of vegetables for either intestinal (0.46) or diffuse (0.44) cancer. In the Hawaiian Japanese they observed identical (1.7) positive risk for the large use of rice in both types of cancer and a significantly high risk for both diffuse (3.2) and intestinal (2.6) types associated with frequent eating of dried fish (9). Indeed, this food carried a higher risk for diffuse cancer. Of 8 items of alimentation they studied, ranging from milk and saki to pickled vegetables and Western vegetables, 5 showed no difference or a larger difference for diffuse cancer and 3 showed a more substantial difference for intestinal types of cancer. Clearly, much more work has to be done on the relationship between gastric cancer pathology and diet. We would suggest that the intestinal-diffuse typology of gastric cancer should be examined in relation not only to diet but also to other alimentary characteristics.

Diet and Familial Aggregation

In the several studies of the incidence of gastric cancer among the relatives of patients as compared to the relatives of controls or various other sorts of control proband, the risk of kin of patients is about twice that of the kin of controls (6). It is apparent that such familial aggregation could occur for a variety of reasons, among them genetic. Also to be considered, however, is the possibility that carcinogenic dietary folkways are found in some families more than in others. It would be instructive, therefore, to examine the diet of patients and their kin as compared with the diet of controls and their kin. If it were found that diet of controls and their kin were similar and if patients and their kin were like each other but in different fashion, we would have some evidence of the aggregation of similar dietary habits within kin groups. If it were shown that the diets of patients and their kin were different from those of controls in the same way that gastric cancer and control diets have been shown to be different in the past, we would have some further evidence of the relationship between diet and gastric cancer and a partial explanation of the familial aggregation already observed.

S. Graham
Multivariate Analysis

I have been discussing the interaction of diet and familial aggregation in gastric cancer. There are still other areas where multivariate studies of this disease are required. We need to assess whether the low use of raw vegetables among gastric cancer patients is a product of the edentia that has been shown to characterize them. We need to study whether the relationship between alcohol ingestion found by some investigators is associated closely with dietary deficiencies which in turn are related to gastric cancer. Is the higher risk connected with tobacco a product of poor dentition associated with tobacco? Do individuals with high levels of ingestion of raw vegetables have correspondingly low levels of ingestion of starchy foods; which accounts for the high risk of gastric cancer associated with starch and low risk associated with raw vegetables? For which type of food is the risk most highly correlated? There is a pressing need to find answers for a number of such questions. They can best be answered with retrospective studies utilizing large enough numbers of patients and controls to allow the detailed examination of the operation of one factor in the presence or absence of another.

Prospective Studies

The prospective study is the model that most closely conforms to the desirable scientific approach of experimentation. Nevertheless, short of a clearly prodigious expenditure of money and a lavish investment of the career-time of investigators, it is probably not warranted for upper gastrointestinal cancers at present. Because gastric cancer is of low incidence, about 10/100,000, and because the disease may be one of long latency, the scientist would have to ascertain diet or other habits of a cohort and follow them for long periods. If he started with 10,000 subjects in high-risk ages, for example, and assiduously retained contact with them for 10 years, truly a difficult feat, he could expect to have no more than 50 cases. To study the working of a potential carcinogen over a latent period of perhaps 30 years, the investment would be even greater and probably would not yield more than 100 cases. This is certainly not enough to do the kind of multivariate analysis that is required at this juncture. We could explore none of the questions described above. Thus, many tens of thousands of subjects would have to be followed to furnish ultimately the numbers of cases necessary for adequate analysis. It appears to me that, although the prospective design is very useful, the outlay of resources to use it in the study of a disease for which the leads are still so flimsy would be profligate.

Other Gastrointestinal Sites

Finally, let me suggest the value of conducting studies of factors impinging on all sites of the upper gastrointestinal system at once, if possible. If a custom or substance is found to be associated with gastric cancer and if it is also found to be associated with cancer of the esophagus, larynx, pharynx, or buccal cavity, we have additional evidence as to its possible carcinogenicity and of the need for further study of it. For this reason, I would suggest the need to carry on the above-mentioned studies in all sites of the upper gastrointestinal system. Inquiries to date suggest that these might be fruitful. Thus, a number of investigations, as well as our own unpublished data, suggest the relationship between tobacco, alcohol, and dentition and cancer of the esophagus, larynx, pharynx, and buccal cavity, as well as of the stomach (13, 19). Our own data, as well as those of Martinez (13) and Wynder (26) suggest a higher risk of buccal cancer for individuals who have diets characterized by low ingestion of vegetables. These are perhaps fortuitous findings in an area that has not been systematically studied. I submit, however, that systematic inquiries may be useful. We need to know more about how all upper gastrointestinal sites relate to each other epidemiologically.

What I have tried to suggest here is that a number of kinds of research urgently need doing in order to follow up on currently available leads. Considering the factors that impinge on the upper gastrointestinal system, we should know more about relationships with various kinds of dust and fibers such as coal, iron, and asbestos. We need to know about risks associated with frequent and long duration of use of cathartics; we need to know the relationship between various oral characteristics, including decay, edentia, and poor mastication, and this disease. We need studies of diet, including not only nutrients but also by-products of storage and preparation processes. We need to know the way the above-mentioned factors are associated with intestinal as compared with diffuse types of gastric cancer. It is apparent too that these many factors cannot be examined in themselves, that each needs to be studied utilizing a multivariate analytic technique to get at such questions as the relationship between raw vegetables, edentia, and gastric cancer, and diet and familial aggregation of gastric cancer. Most useful, finally, would be studies of all these factors in other adjacent sites in the upper gastrointestinal system to see the extent to which factors associated with one site are also associated with others. It is clear that the studies of diet and gastric cancer over the last 10 to 15 years have been fruitful indeed in suggesting new lines of inquiry.

References

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