Regional Risk Factors for Stomach Cancer in the FRG

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A multicentric, hospital-based, case-control study was conducted in high- and low-risk areas for stomach cancer in the Federal Republic of Germany, by which means a low intake of dietary vitamin C (relative risk [RR] = 2.32, 95% confidence interval [CI] 1.22–4.43 for lowest against highest quintile), noncentralized water supply (RR = 2.17, CI 1.14–4.13 against central water supply), refrigerator use for less than 25 years (RR = 1.33, CI 0.82–2.15 against more than 30 years), and the use of spruce for smoking meat at home (RR = 3.33, CI 1.56–7.12 against not smoking meat at home), were identified as factors potentially causally related to stomach cancer occurrence. The attributable risk for gastric carcinoma among the population (AR) was 37.5% for low vitamin C intake, 37.2% for noncentralized water supply, 10.6% for late refrigerator use, and 4.15% for use of spruce for smoking meat at home in this analysis. The overall AR amounted to 68.3%. These personally linked factors also showed a strong regional distribution, in that the low-risk area had more favorable categories of exposure.

Traditional nutritional habits around 1910 were recorded during a survey by ethnologists in 1965. This material was used to contrast those in high and low stomach cancer risk areas with the habits in the south of Germany in general. Vegetable use was most common in the low-risk area, whereas mashed potatoes, cabbage, and farinaceous dishes dominated in the high-risk area. Tomatoes were introduced several years later into the high-risk area, both in terms of consumption and cultivation. Mostly beech wood had been used for smoking meat in the low-risk area, whereas in the other areas different kinds of wood were used, including spruce.

Introduction

Dietary factors are considered as potentially important in the carcinogenesis of some neoplastic malignancy sites (1). Special interest has been concentrated on the organs that are lined along the epithelial tube of the digestive system. Here the relationship between the ingested food items and pathophysiological mechanisms in surrounding tissues is more obvious and is consequently thought to be of particular importance in most types of gastrointestinal cancer (2).

Notwithstanding the ongoing decline of the mortality and incidence of stomach cancer in Europe, there are important differences of incidence between different countries. In order to identify specific risk factors, several epidemiological case-control studies for stomach cancer have either already been terminated or are underway in countries with differing stomach cancer mortality (3–8).

Compared with the rest of Germany, high rates of mortality from stomach cancer prevail in southeast Bavaria, whereas in some regions of the centrally located state of Hesse the lowest rates were found (9) (Fig. 1). This pattern has been stable since the 1950s (10). It is also noteworthy that age-adjusted mortality for stomach cancer is declining similar to other industrialized countries and that the declining trend has been linked to birth cohorts, especially in Bavaria, where younger cohorts showed half the risk within 20 years seen for both males and females (11).

A case-control study was performed simultaneously in both Bavaria and Hesse. Besides investigating risk factors on an individual level, the study aimed at explaining the regional differences in stomach cancer mortality. This was accomplished by calculating the preventable proportion based on the differences in prevalences of exposure between high- and low-risk area.

In addition to the material collected within the case-control study, we had the opportunity to analyze data that had been collected in 1965 about traditional habits by a detailed questionnaire. Going back to the situation in 1910, some of these data referred to issues being of potential importance in the case of stomach cancer. These data were also useful to contrast high- and low-risk areas for stomach cancer.

Materials and Methods

The multicentric, hospital-based, case-control study was performed in four areas of Germany: three in a region typical for high stomach cancer mortality in the southeast of the Federal Republic (Deggendorf, Straubing, Ingolstadt) and one in an area in the midst of Hesse (Giessen) showing a notoriously low mortality from this malignancy (10). During the study periods from 1985 to 1987, 143 stomach cancer cases and 579 controls contributed a complete interview. The control group consisted of other hospital patients and visitors coming to these hospitals. A detailed description of the study design and the distribution of cases and controls by region and age group is given elsewhere (12; Boeing and Frentzel-Beyme, in preparation).

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The information about exposure was obtained by an interview employing a standardized questionnaire with preformulated questions and lasted 55 min on average, covering sociodemographic characteristics, residential, occupational, medical, and smoking histories, water supply, food conservation methods, and the intake of food before onset of the disease. Dietary intake was assessed as usual intake in the last 5 years before signs of onset of a severe disease. Constant training of the interviewers ensured a uniform performance of the interviews.

All interviews were centrally coded by one person, the data entered into a data bank, and data checks were performed to identify coding and punching errors.

Risk estimates were obtained by unconditional logistic regression methods (13). All estimates were adjusted for age (continuous), sex, and hospital. The relative risk estimates were calculated for the pooled group of controls and separately by comparison with both hospital and visitor controls. Results of both subgroup analyses were, in most instances, in agreement and, therefore, only the results for the total group are presented.

The calculation of the attributable risk among the population was derived from the cases or the controls by considering each individual as separate strata. The AR, was, derived from the controls as $\text{AR}_c = \frac{\sum p_j (RR_j - 1)}{\sum p_j (RR_j - 1)} + 1$ (14) and from the cases as $\text{AR}_c = \frac{\sum p_j (RR_j - 1)}{RR_j}$ (15).

First, the AR, was calculated for each risk factor separately. In addition, an overall AR, was also derived based on the suggestions of Bruzzi et al. (16). In practice this was accomplished by generating an overall relative risk by multiplying for each participant the single risks obtained from a logistic model with his or her exposure categories ($RR_0 = RR_1 \times RR_2 \times \ldots \times RR_j$). The RR, obtained in this way was treated as presented above.

The proportion of stomach cancer cases possibly preventable (PP) by changing exposure were calculated using the formula of Wahrendorf (17). Here also each individual was considered as separate strata.

A second source of data for a regional comparison between high- and low-risk areas for stomach cancer was created by a national survey that was conducted in 1965 by a group of ethnologists who contacted several hundred individuals who participated in earlier surveys on traditions. These individuals (usually ministers or teachers) filled in a detailed questionnaire about traditional habits prevailing or having prevailed in their village, town, or quarter. Most of the questions referred to nondietary aspects of daily life and festivities. However, three complexes referred to issues being of interest in the case of stomach cancer etiology. One question concerned traditional dishes during weekdays and weekends in 1910. Other questions referred to the vegetable tomato, when it was eaten the first time in the respective area, and when the tomato was first planted locally. Also, in a series of questions referring to meat conservation, information on the kind of wood used for smoking meat was obtained. The original, completed questionnaires are currently stored at the Seminar of Ethnology in Bonn (H. L. Koks). Up to now only selected aspects of this enquiry had been processed and presented. Therefore, the written responses to the questions mentioned above had to be abstracted from the original questionnaires. Old German writing was still in use at the time of the survey, hence, deciphering the information required a specialist trained in reading this old style of writing. The abstraction of material, therefore, was restricted to particular areas in the south of Germany including Hesse as the low-risk area and Bavaria as the high-risk area for stomach cancer (Fig. 2).

Altogether, 644 questionnaires were found reporting on traditions in this defined area. Sometimes the particular questions of interest had been skipped by the respondent. Thus, different sample sizes occur for different questions. From the question regarding usual dishes, only the information of weekday dishes was used. The dishes were first categorized into 31 different food items. Later these items were combined to 15 food groups.

The area from which questionnaires had been abstracted was divided into four regions. The first region is located in the low-risk area and contains also Giessen (one site of the case-control study). The second area constitutes the areas of high stomach cancer mortality in lower Bavaria (Niederbayern) and upper Palatinate (Oberpfalz) including Deggendorf, Straubing, and Ingolstadt (further sites of the case-control study). A third region around the Alpes was contrasted with this Bavarian region. The remaining areas formed the fourth region. The prevalences of particular habits were calculated for each region.

**FIGURE 1.** Mortality from stomach cancer among males in the Federal Republic of Germany, 1976-1980. Age-adjusted rates by administrative district (county) classified by quintiles.
REGIONAL FACTORS AND STOMACH CANCER

Results

General Risk Model and Attributable Risk

In this paper a risk model is presented considering simultaneously those factors identified by the case-control study in low- and high-risk areas for stomach cancer in the FRG from a series of variables being associated with and most likely causally related to stomach cancer. Out of the array of variables, vitamin C, the type of water supply, years of refrigerator use, and type of wood used for smoking meat were selected for this presentation. Other factors found to be associated with stomach cancer in this study such as particular food items or food groups, tobacco smoking, or the consumption of particular alcoholic beverages were not considered in this analysis because of their uncertain mode of action or the possibility of spurious associations. A description of the complete results and a discussion in relation to the outcome of other studies is beyond the scope of this paper and can be found elsewhere (12).

In Table 1, the relative risk estimates are presented for the selected variables. These relative risks can deviate from previous estimates because here all factors are considered simultaneously. It is also important to note that the low-risk category was selected as baseline to facilitate the calculation of the attributable risk.

Table 2 presents the attributable risk among the population (ARp) for the four risk factors. Attributable risks were calculated from the prevalences of exposure among the controls as described in "Materials and Methods." In addition to these calculations based on the prevalences among the controls, the approach, based on the prevalences of exposure among the cases, is also presented showing slightly different estimates. These differences may be caused by the effect of confounder variables such as age, sex, and hospital.
Table 1. Relative risk estimates* for water supply, food conservation practices, and dietary provision with vitamin C (case-control study, Bavaria, and Hesse).

| Variable                          | Cases | Controls | RR (95% CI) | x²test |
|----------------------------------|-------|----------|-------------|--------|
| Water supply                     |       |          |             |        |
| Central water supply only        | 43    | 294      | 1           | 9.54b |
| Well water and central water supply | 75   | 223      | 2.18 (1.39–3.42) |        |
| Only well water                  | 21    | 55       | 2.17 (1.14–4.13) |        |
| No information                   | 4     | 7        |             |        |
| Smoking meat at home             |       |          |             |        |
| No                               | 68    | 321      | 1           |        |
| Yes, with other wood             | 57    | 239      | 0.92 (0.61–1.40) |        |
| Yes, specifying spruce           | 18    | 19       | 3.33 (1.56–7.12) |        |
| Years of refrigerator at home    |       |          |             |        |
| 30+ or always                    | 58    | 281      | 1           | 1.46a |
| 25 to 29                         | 37    | 159      | 1.12 (0.70–1.80) |        |
| 24 or less                       | 41    | 127      | 1.33 (0.82–2.15) |        |
| Information missing              | 7     | 12       |             |        |
| Vitamin C                        |       |          |             |        |
| I quintile (highest)             | 19    | 116      | 1           | 6.63   |
| II quintile                      | 25    | 116      | 1.40 (0.71–2.73) |        |
| III quintile                     | 28    | 116      | 1.60 (0.82–3.30) |        |
| IV quintile                      | 31    | 116      | 1.69 (0.88–3.26) |        |
| V quintile (lowest)              | 40    | 115      | 2.32 (1.22–4.43) |        |

*Mutually adjusted and for age, sex, and hospital.

*First three categories.

The overall AR,p combining the effects of vitamin C, type of water supply, years of use of a refrigerator, and kind of wood used for smoking meat at home amounted to 68.3% for these four factors.

Regional Differences in Risk Factors Based on Data from the Case-Control Study

The regional distribution of the exposure categories for the four risk factors is shown in Table 3. All risk factors show a gradient between low- and high-risk area in respect to lower prevalence of categories associated with high risk in the low-risk area.

The differences in exposure prevalences between high- and low-risk areas were used to calculate the preventable proportion (Table 4). For this calculation, the relative risk estimates obtained for the total group were used because of the small numbers appearing in each region. When the exposure prevalences of the high-risk area for stomach cancer shifted to the exposure prevalences of the low-risk areas the preventable proportion of stomach cancer in Bavaria was highest for the type of water supply (15.4%), followed by use of spruce for smoking meat at home (10.8%), vitamin C intake (10.6%), and period of refrigerator use (4.1%). By using the overall relative risk estimate approach, the preventable proportion amounted to 38.8%.

Table 2. Attributable risks for stomach cancer derived from the exposure prevalences among controls and cases (case-control study, Bavaria, and Hesse).

| Variable                        | Population attributable risk |
|---------------------------------|------------------------------|
|                                 | From controls, % | From cases, % |
| Vitamin C                       | 37.5             | 37.1           |
| Water supply                    | 37.2             | 38.2           |
| Refrigeration of food           | 10.6             | 11.8           |
| Smoking meat at home            | 4.1              | 5.3            |
| Overall*                        | 68.3             | 67.2           |

*All four variables combined.

Regional Comparison of Dietary Habits in 1910

The eating profiles around 1910 of four regions with distinct stomach cancer risk were investigated for differences in these areas (Fig. 3). Region 1 (Hesse) represents the habits in the low-risk area, and region 2 (southeast Bavaria) represents the habits in the high-risk area for stomach cancer. The eating pattern of other regions (3 = south Bavaria with intermediate stomach cancer risk, and region 4 = remaining areas [Fig. 2]) are not shown but referred to in the text. The most impressive differences between high- and low-risk area for stomach cancer (region 1 against region 2) were seen in regard to the consumption of vegetables, legumes, vegetable soup, farinaceous dishes, and
mashed potatoes. For vegetable soup, vegetables, legumes, and potatoes, the low-risk area stood out. The use of farinaceous dishes was low compared to the other regions. The high-risk region (region 2) was lowest in the consumption of vegetables, legumes, conserved fruit, and bacon.

The eating profiles of the four regions in 1910 can be described as follows (the items listed were mentioned in more than 65% of the reports from each region): in the low-risk area (Hesse): vegetables, legumes, vegetable soup, potatoes, meat; in the high-risk area (southeast Bavaria): potatoes, mashed potatoes, farinaceous dishes; in the region near the Alpes, not being particularly high in risk for stomach cancer (south Bavaria): milk products, farinaceous dishes, and meat; and in the remaining areas: farinaceous dishes, potatoes, and meat.

The mean year in which tomatoes had first been consumed and cultivated locally was analyzed for the four regions. The use and planting of tomatoes began in the high-risk area on the average 5 years later than in the other regions (1933 for region 2 against 1928 for region 1, 1926 for region 3, and 1925 for region 4 for tomato consumption and 1934 against 1929, 1930, and 1927 for tomato cultivation). Tomato use and growing in the low-risk area, showed no particular differences compared with the other regions.

Information in the survey regarding the use of wood for smoking meat is presented in Figure 4, which lists all the different possibilities and also considers the combined use of wood. The region in Hesse was linked with the use of beechwood, whereas in the other regions, different kinds of wood were in use, including spruce. However, it has to be considered that individual households can deviate from this pattern. The inquiry in the case-control study revealed that in the low-risk area spruce was not being used.

Discussion

Stomach cancer still ranks as the leading cancer site in the world by number for both sexes combined (8). Epidemiological research on risk factors for stomach cancer is supposed to generate evidence for mechanisms most likely to explain the high occurrence of this type of cancer in particular regions in the world. Simultaneous studies on risk factors in high- and low-risk areas in culturally similar environments may, therefore, not only identify risk factors for individuals but also generate hypotheses for reasons and even causes of regional differences (6,8,12).

The results from the case-control study in high- and low-risk areas for stomach cancer in the FRG clearly revealed that factors associated with stomach cancer in individuals also showed a risk gradient between high- and low-risk area. When differences in exposure between high- and low-risk areas were quantified and combined with risk estimates obtained from individuals, it was found that these differences can explain a major part of the regional differences in cancer occurrence. In the situation described here, personally linked factors and regional factors supplemented each other, whereas by theory, personal and regional risk factors may deviate.

"Regional" risk factors being commonly adopted by the entire local population may not appear as risk factors in regionally conducted studies and are therefore difficult to identify. By contrasting high- and low-risk areas alone, causally relevant factors cannot be differentiated from cultural differences.

This difficulty of interpretation of contrasting regions appeared when high- and low-risk areas were contrasted according to prevalences of "habits in 1910." The authors were not able to conclude whether discernible differences were of etiological importance. Nevertheless, to make use of such additional information has its worth in that certain consistencies with current knowledge and concepts may be observed.

No coincidence was seen between the results of the case-control study that revealed that high consumption of cheese, fruit, especially citrus fruit, and whole-meal bread was negatively related and high consumption of processed meat was positively related to stomach cancer risk (12) and the differences in habits around 1910 in high- and low-risk regions. These differences seen in 1910 referred in particular to the use of vegetables, which did not show a negative association with stomach cancer risk in the case-control study except (in tendency) for raw vegetables. However, in view of the results of many other individual-based studies, the finding of high vegetable consumption in the low-risk area fits well in the picture that in these studies showed a negative association of high vegetable intake with stomach cancer risk (3,7,19–22). It has to be taken into account that cabbage, which was consumed in higher amounts in the high-risk area, may usually be stored by processing to sauerkraut. This procedure may destroy most of the vitamins found in fresh cabbage. In the high-risk area, also, the habit of processing freshly cooked potatoes to mashed potatoes may diminish the provision of
vitamin C by destroying this vitamin by oxygen and heat.

One can only speculate about the particular role of legumes because this item did not appear particularly protective in individually based studies. In the case-control study, legumes had also been found to be consumed in higher amounts in the low-risk area (data not shown).

The regionally confined typical distribution of kinds of wood used for smoking meat is in line with the observation in the case-control study linking spruce use with stomach cancer in the high-risk area for stomach cancer; however, no particular observation can be reported for the region in the southeast of Bavaria based on the situation in 1910.

Not enough is known about dietary deficiencies of cohorts born around 1900 compared with those born around 1920 and thereafter clearly experiencing a decreased mortality risk (9,11). It is well known that during World War I and in the subsequent years (1916–1919), nutrition was very poor in wide areas of Germany. Furthermore, one of the rare sources of animal protein in the first decades of this century that was readily available in every region and low-priced was salt herring, preserved in brine. The availability of this well-preserved merchandise around the year even in places remote from the seacoast was one typical feature of the past, when meat, milk, and eggs were less affordable for low-income groups. This seems to be in contrast to the data from the survey about eating habits around 1910, which did not reveal that herring played an important role in the eating pattern at the beginning of the 20th century. However, the survey was completed usually by middle-class persons who may not have
considered the eating pattern of the part of the population with low income. Salted fish is considered as one source of nitrosamide precursors which form with nitrite direct-acting mutagens (23). Nitrate contents in private water sources, a precursor of nitrite, was described to be high in earlier periods (24). Private water sources lasted until recently in circumspect areas, included to some extent in the case-control study (Table 3).

The distribution of vegetable growing and the intake of certain types of fresh or processed greens have not been surveyed with the same coverage in the early years of this century as today. To our knowledge, roots such as turnips and cheap cabbage were, next to potatoes, often the only available food during war and post-war times. The contents of nitrites in these, as well as in the water supply of those years, can only be guessed.

The regional analysis of potential risk factors indicate that the higher risk for stomach cancer in southeast Bavaria can be partly explained by a low provision of dietary vitamin C through food such as vegetables and fruits that are able to block the formation of direct-acting mutagens in the stomach if consumed in higher amounts (25). In addition, particular regional habits such as smoking meat with spruce and possibly an increased intake of nitrate in connection with lack of vitamin C as it is when nitrate-rich water is consumed may also have been of importance.

We are indebted for the local support of the case-control study by M. Berger, V. Berndy, W. Göres, M. Körner, R. Lohmeier, H. F.K. Männl, M. Meinhardt, A. Menarcher, R. Müller, H. Osterniekr, F. Paul, K. Schwemmle, and K.H. Wagner. We also acknowledge the work of the interviewers and are grateful to the participants who shared their experience with us.

Professor H. L. Koks from the Seminar of Ethnology, Bonn, was so kind to allow the access to the survey data. We are also indebted to P. Bothien for abstracting the original questionnaires and for drawing the map with the use of wood. The efficient secretarial assistance of P. Berthold is gratefully acknowledged.

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