Nutrition and gastric cancer

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Gastric cancer (Gc) has been linked for many decades to nutritional factors (Sigiura, 1951; Doll, 1956; Wynder *et al.* 1963). Since then many hypotheses have been brought forward to explain the aetiology of gastric cancer, making it almost impossible to sort the important factors out of the available ones and to find pathways for further research with a reasonable chance of success.

Different epidemiological techniques have been used over the years to study the aetiology of Gc. Studies of mortalities between and within countries, between social classes, mortality trends, case control studies and migrant studies have been used to trace possible aetiological factors.

The possible aetiological factors resulting from those studies are given in Table 1. More recent literature charges nitrates or nitrites or both, either added to food or from other sources and salty, pickled foods (Weisburger, 1979). Vitamin C

Table 1. *Aetiology of gastric cancer*

Genetic factors:	
Blood group A has higher prevalence than B	
Male sex (2 to 2·5 times higher prevalence)	
Soil factors:	
Trace elements, e.g. Zn:Cu value, cobalt and chromium	
Peaty soil	
Amount of NO_3 used as fertilizer	
Nitrates in drinking water	
Nutrition:	
High Starch*	Low protein*
Soybean sauce*	Smoked foods*
Added salt*	Lard*
Pickled vegetables*	Talcum (in rice)
Lack of fresh fruit and vegetables*	
Dried and salted fish or meat*	
Nitrates or nitrites or both added to food	
High temperature of food and drinks	
Low social class (higher prevalence)*	
Protective factors:	
High fat**	Milk**
Vitamin C	Selenium
High fresh fruit and vegetables intake**	
Refrigeration of food**	

*Factors related directly or indirectly to salt.
**Factors negatively related to salt.

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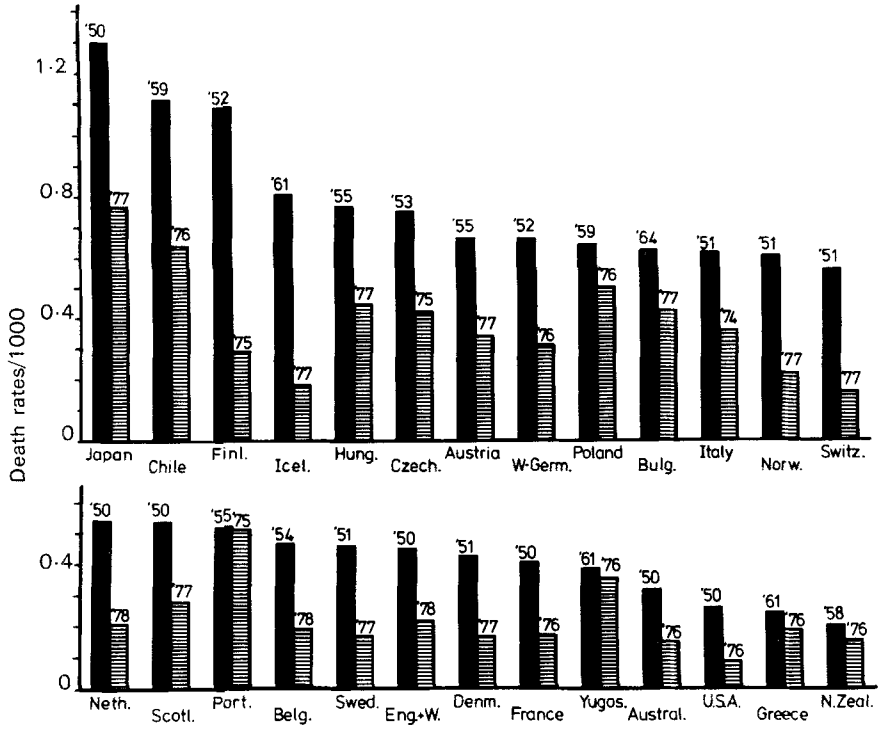

Fig. 1. Geographical distribution and time variation for stomach cancer death rates in twenty-six countries. Values are death rates/thousand and are the average of both sexes age adjusted between 45 and 64 years. The numbers on top of each double column indicate respectively the first and the last available year for the given country. (Source of basic data: WHO, Geneva).

is generally considered as favourable (Mirvish, 1975; Weisburger, 1979) as are fresh fruits and fresh vegetables and refrigeration techniques. The beneficial influence of cold storage has been ascribed to its mould inhibiting properties (Avery Jones, 1967), to the inhibition of nitrite formation in preserved food (Weisburger & Raineri, 1975) and to the possibility to preserve food without using salt (Joossens, 1965 *et seq.*).

The problems which occur when trying to validate a possible aetiological factor are increased when one compares what is found in one country to what is found in others. For example, smoked food was considered a causal factor of Gc in Iceland (Dungal & Sigurjohnsson, 1967) but is irrelevant in Japan where the smoking of food is unusual. In the Netherlands lard has been connected with Gc (Meinsma, 1964) but cannot be considered a causal factor of Gc in Japan or Korea. Rice (Merliss, 1971), and talcum adhering to it, were incriminated in Japan, but this cannot explain Gc incidence in Portugal or eastern European countries for example. Milk was found to be protective (Hirayama, 1967), but a much higher consumption of milk in Finland was associated with high rates of Gc (Saxen, 1967). Cereals have a strong positive relationship with Gc all over the world (Saxen & Hakema, 1967) except certain parts of Africa (Higginson, 1967). The

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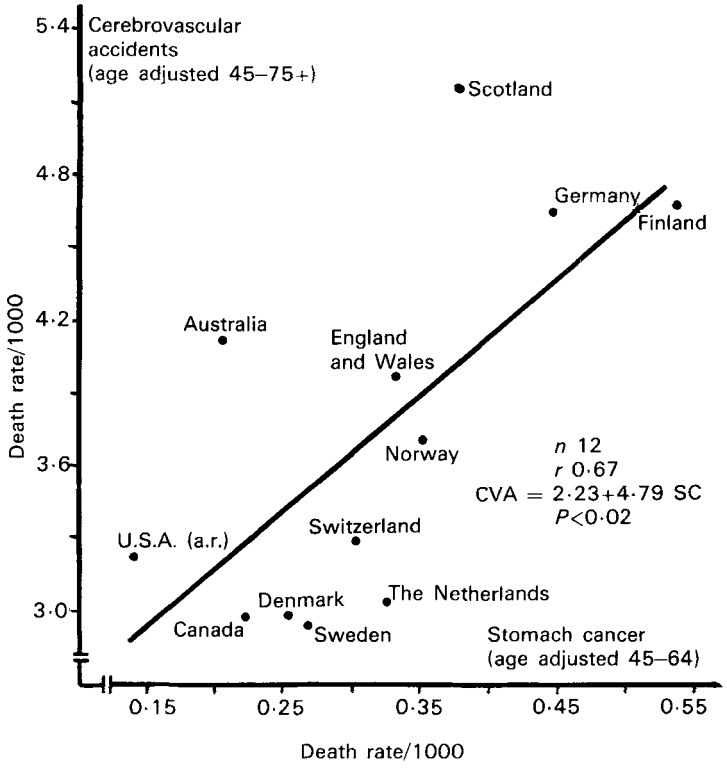

Fig. 2. The geographical gradient for gastric cancer and stroke is illustrated with results from twelve standard countries. Each point is the average of 21 years from 1955 to 1975. Values are death rates/thousand and are the average of both sexes. Reproduced from: *Essential Hypertension* (1979). [R. H. Thurm, editor]. Miami: Symposia Specialists and Chicago: Year book Medical Publishers. (Source of basic data: WHO, Geneva).

situation is even more paradoxical when one looks at mortality trends. There is no real treatment for Gc and the five year survival is now as low as in 1930. Gc is nevertheless decreasing in all countries from Chile, the USA, western and eastern Europe to Japan. The decrease started only in approximately 1960 in Japan but had been observed since at least 1930 in the USA (Haenszel, 1961).

Geographical differences and variations in rate of incidence of Gc with time are well known (Fig. 1). Japan, Korea (Hirayama, 1967), Portugal, Iceland, Finland, Chile and the eastern European countries are or have been areas with high Gc incidence. Low stomach cancer rates are found in the USA, Greece and in the western world generally, with the exception of Portugal. There is a definite east–west gradient for Gc (Doll, 1967).

It is almost impossible to decide which factors from Table 1 are operative when trying to explain the geographical differences and the remarkable decreasing with time trend. A chance finding in 1964 (Joossens, 1965), namely that Gc mortality was strongly related to cerebrovascular mortality, and the subsequent study of this

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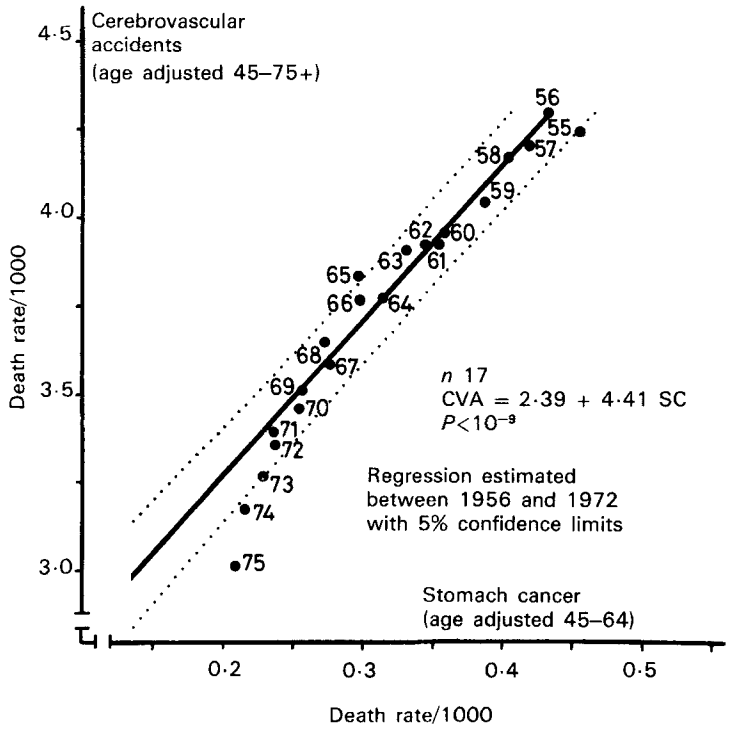

Fig. 3 The time gradient from 1955 to 1975 for gastric cancer and stroke. Each point is the average of the twelve countries from Fig. 2 for one given year. Values are death rates/thousand and are the average of both sexes. Two remarks can be made: first the linear part is not significantly different from the regression line observed under totally different conditions in Fig. 2. Secondly, the linear part goes from 1955–1956 to 1972. Since gastric cancer is not influenced by the gradually improving treatment of hypertension, it follows that there is no visible impact on stroke mortality by the latter up to 1972. From 1973 on, however, a marked deviation from linearity can be seen, suggesting that treatment of hypertension is now effective at the population level. Similar observations can be made in the USA, England and Wales, Switzerland and Japan (Joossens, 1980*c*) and in West Germany (Fig. 4). (Source of basic data: WHO, Geneva).

phenomenon over many decades and in many totally different countries offered the possibility to get a better idea about the aetiology and prevention of Gc.

The evidence linking Gc and cerebrovascular accidents (CVA or stroke), has been described (Joossens, 1968, 1973, 1980*a*, 1980*b*, 1980*c*; Joossens *et al.* 1972; Joossens & Brems-Heyns, 1975; Joossens *et al.* 1980) and will be summarized here. (1) There is a strong positive relation between CVA and Gc between countries (Fig. 2). Both are high in eastern Europe and Portugal, both are low in the USA, both are medium in England and Wales. The same is true between regions in England and Wales (Joossens, 1980*b*). (2) There is an even stronger positive relation between CVA and Gc within a given country or within a group of countries (Fig. 3). This relation is quantitatively very similar in Germany (Fig. 4), Japan, Switzerland and England and Wales (Joossens, 1980*c*). (3) The between countries relation described in (1) is not significantly different from the within

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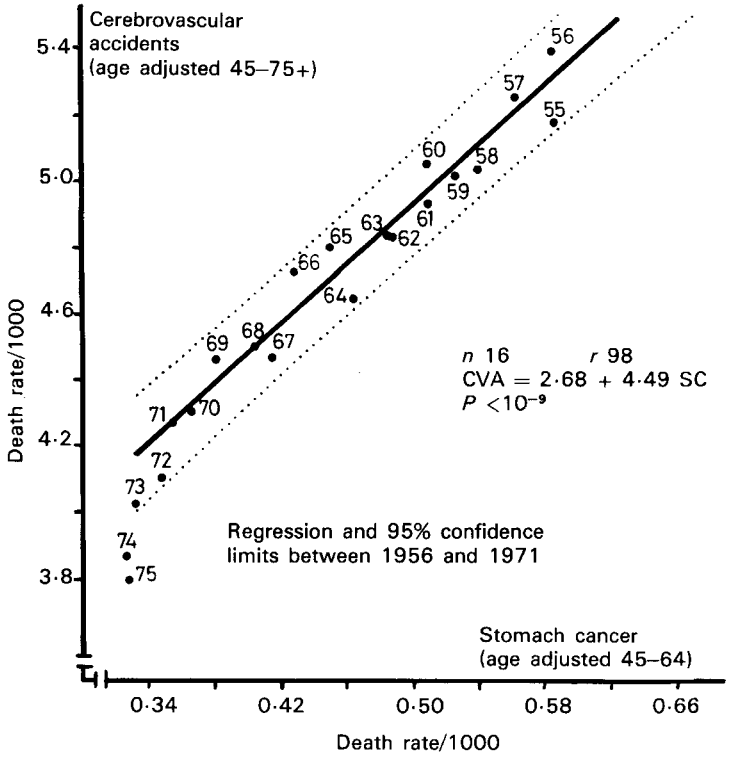

Fig. 4. The time gradient from 1955 to 1975 for gastric cancer and stroke in West Germany. Values are death rates/thousand and are the average of both sexes. See Fig. 3 for comments. (Source of basic data: WHO, Geneva).

country relation described in (2) making it possible to estimate CVA from Gc in Japan, Portugal and Bulgaria using a relation obtained between, for example, twelve western countries or just that obtained in England and Wales. (4) Gc is more common among lower social classes (Clemessen, 1965), as is CVA.

All these relationships hold for males and females separately and for the average of both sexes.

Gc is therefore a good predictor of CVA. In fact Gc is sometimes a better predictor of CVA than the officially reported values of CVA, particularly in countries where vital statistics were less than standard, as in Belgium up to 1968, in Czechoslovakia until about 1973 and Japan up to 1960 (Joossens, 1980*c*). The reported CVA mortality in Poland and Chile is still markedly below the value estimated from Gc. The predicted values for CVA from Gc in Poland and Chile are more in accordance with the reported mortality from all causes than the officially reported CVA values.

The relationship between CVA and Gc is so strong, so linear over a wide interval of values, so consistent in countries as different as England and Japan and so predictable that a spurious origin can be ruled out with certainty. This was

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found to be of great help in the search for the linking factor or factors between both diseases.

First of all a complex multifactorial linking factor can be dismissed. Although both CVA and Gc are determined by many genetic and environmental factors, the linking factor must be unique or at least predominant. This follows from observations (1), (2) and (3). The more factors influencing both diseases, the less the probability to get identical regression values between countries and within countries. A unique factor must give identical relations under those conditions. A good example of a complex, multifactorial linking factor is shown in the relation between CVA and lung cancer. The between countries relation is also strongly positive but the within country relation is not only significantly different from the between countries relation, but it is actually negative. When lung cancer in a given country is high, CVA in general will be high also, but an increasing lung cancer death rate in the same country will go together with a decreasing CVA rate.

The properties of the linking factor 'X' between Gc and CVA can be derived from the observations (1) to (4). 'X' is a typical environmental factor affecting the stomach mucosa and the cerebral arteries and therefore almost certainly of nutritional origin. 'X' must be identical in the western world, in east European countries and in Japan. It must be found in decreasing amounts in food in almost all countries with time. In the USA it must have been decreasing since 1925–1930 (Haenszel, 1961; Acheson, 1966) and in Japan since 1960. 'X' is a factor with a great impact on public health. This is consistent with the observation that total mortality over the age of 45 years is decreasing when stomach cancer is decreasing in a given country. By calculating the regression between mortality from all causes except gastric cancer and Gc, it follows that each death from Gc is linked to twenty-four deaths from all causes except Gc. This quantitative relation is about four times higher than the one found for lung cancer (Joossens & Geboers, 1981).

'X' must be present in high amounts in the food of Japanese, Koreans, Portuguese and of inhabitants of east european countries, Columbia and Chile. In Finland it must have been very high years ago, decreasing to 'normal' levels in recent years. All those properties make it possible to rule out certain factors listed in Table 1, among them genetic and soil factors, since they cannot explain the observed time trends.

The identification of 'X' is made easier by the fact that it influences CVA. The risk factors of CVA are well known. They include high blood pressure (Shurtleff, 1974), high alcohol intake and obesity. Smoking and high serum cholesterol levels have no or only a marginal effect on CVA. Stress and trace elements like cadmium, lead or mercury are also of secondary importance. In fact all the risk factors of CVA are acting directly or indirectly through high blood pressure. Factor 'X' must therefore have an influence on the stomach mucosa and on blood pressure. In 1965 Joossens presented the working hypothesis making 'X' equal to salt (sodium chloride) intake. Looking again at Table 1, it can be seen that all items with one asterisk are directly or indirectly related to salt, those with two asterisks are negatively related. These findings did not exclude the protective

influence of vitamin C against Gc and the Gc enhancing influence of nitrites and nitrates; it only states that it is improbable that either vitamin C or nitrite/nitrate is the linking factor. There is no known influence of vitamin C on CVA and the amount of sodium in nitrites and nitrates is too small to affect blood pressure. Also the distribution of these factors among different countries and over time is not known. Nitrates from the use of fertilizer and from fresh vegetables are probably found more extensively now than years ago and nitrites have a hypotensive rather than a hypertensive action.

If salt added to food is the linking factor it could act on CVA by increasing blood pressure (Dahl, 1972; Joossens, 1973, 1980*b*; Freis, 1976) but it could also irritate the stomach mucosa by its osmotic properties. Salt has the highest osmotic activity of all substances found in nutrition in quantities greater than 1 g and delays emptying of the stomach through its influence on osmotic receptors in the duodenum (Hunt & Pathak, 1960), thereby prolonging the contact of the gastric mucosa with carcinogenic substances from food. High salt intake produces gastritis in animals (Sato *et al.* 1959) and is associated in humans with a high prevalence of atrophic gastritis, such as found in Japan (Yoshitoshi, 1967). Gastritis is common in areas where Gc is prevalent, such as Finland (Siurala *et al.* 1968) and Columbia (Correa *et al.* 1976). Atrophic gastritis produces the optimal condition for nitrite formation (Ruddell *et al.* 1976) and hence for the formation of potent carcinogenic nitrosamides (Sugimura & Kawachi, 1973). The delaying action of salt on the emptying of the stomach may enhance the carcinogenic activity of those compounds. This was shown under experimental conditions in animals (Tatematsu *et al.* 1975).

The salt hypothesis gives an explanation for the contradictions mentioned at the beginning of this article. Lard in the Netherlands, smoked food in Iceland and rice in Japan are all heavily salted. Cereals are also salted in most parts of the world but not by primitive populations in Africa (e.g. Kung Bushmen of Truswell *et al.* 1972).

The salt hypothesis is also able to explain the decrease in stomach cancer over the years in practically all countries over the world and at the same time also explains why stroke mortality decreased long before any treatment for hypertension was available, e.g. in the USA since 1925 (Acheson, 1966). Salt excretion has decreased in Belgium (Joossens, 1980*b*), Switzerland (Société des Salines, 1980) and Japan (Komachi & Shimamoto, 1980). It is highly probable that salt consumption is decreasing unconsciously all over the world due to the introduction of refrigeration techniques in order to preserve food as the reason to use salt in food is not for the taste, but for preservation. In cold climates which are not the natural habitat of the human primate, salt was needed in order to avoid starvation. The more salt one uses the more one needs it in all kind of foods (e.g. bread, potatoes, etc.) due to the damaging effect of salt on taste-buds which may be irreversible in older people but is normally recoverable within a couple of months on a low-salt intake. This vicious circle has been broken by refrigerators and deep-freezers. Salted meat (smoked or unsmoked), salted fish, salted vegetables were

common food items 50 years ago and the intake of salted bread and salted potatoes was very high. They are now gradually disappearing from the average diet, except, for example, in Portugal, where they are still very common. Salt excretion/24 h has been measured in Portugal and in Korea. Standardized to 1·77 g of creatinine it was found to be equal to 304 mmol/24 h in Portugal (Forte *et al.* 1979) and to 489 mmol/24 h in Korea (Kesteloot *et al.* 1980). The high salt intake in Portugal was predicted at a session on epidemiology of the European Congress of Cardiology in Amsterdam in 1976. This prediction was based on the observed mortality from Gc and CVA in Portugal and was confirmed later on. The same prediction can now be made for certain parts of Chile and Columbia. The link between lower social classes and Gc can be explained by the higher salt intake in lower classes (Joossens *et al.* 1980) and is explained by the fact that cheap food generally contains more salt.

We have tried to test the salt hypothesis in Belgium. The mass media, in collaboration with the Ministry of Health, with all the Belgian medical faculties and other groups (Hypertension Committee, Belgian Cardiological League, nutrition societies such as Iban, etc.), have successfully influenced the behaviour of the whole population. The impact of the campaign was monitored by measuring the excretion of NaCl/24 h in the population. The 24 h excretion was then standardized through the simultaneously measured urinary creatinine, to a mean value of 1·77 g (15·7 mmol) creatinine. 5535 24 h urine collections have been made since 1966 in 2493 individuals (Joossens & Brems-Heyns, 1975; Joossens, 1980*b*). The standardized salt excretion fell gradually from 250 mmol/24 h in 1966 to 140–170 mmol/24 h in 1979 and a marked decrease in Gc and CVA was seen during this period. The decrease in Gc and CVA was more marked in Belgium than in the rest of the Common Market (Joossens, 1980*a*). Among thirty countries the decrease in incidence of Gc in middle-aged persons (45–64 years) since 1968 was greatest in Finland; Belgium had the second greatest decrease (Joossens, 1980*a*).

In conclusion it can be said that the linking factor 'X' between Gc and CVA is a typical environmental factor present in the food. Factor 'X' is very important in terms of public health, probably more hazardous than cigarette smoking. The available evidence points to salt as being factor 'X'. More epidemiological research is urgently needed to monitor salt intake, through 24 h urine excretion (standardized by urinary creatinine), at the population level all over the world and at regular intervals. More information is especially needed from Japan, Finland, Chile, Columbia, Iceland, Greece, Portugal and the east European countries. If the salt hypothesis is correct, it follows first that the introduction of the refrigeration technique was one of the major contributions to public health and secondly that a simple and inexpensive method is available to prevent not only gastric cancer, but also stroke mortality and hence to reduce total mortality.

The author thanks very sincerely Mrs J. Smisdom-Rongy and Mrs A. Menten-Mellaerts for their help in the preparation of the manuscript and of the Figures and is indebted to Mr L. Cooreman and Mr G. De Vadder for their most valuable aid in the bibliographic research.

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Printed in Great Britain