

# Antioxidants in cereals and in food preservatives and declining gastric cancer mortality

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Statistics on cancer mortality by site were published in the United States for the first time in 1930. Since then the death rates from cancer in various sites have shown different trends. Forty years ago, cancer of the stomach was the leading cause of cancer mortality in men, and was second only to uterine cancer in women. The incidence and death rates from stomach cancer have decreased steadily in both sexes until today it is only the fifth leading cause of cancer deaths in men and the eighth most common cause in women. Mortality from stomach cancer is now less than one third of the 1930 death rate in men and less than one fourth of the 1930 death rate in women. The reason for the continuing decline is not known.

Recent evidence indicates that antioxidants prevent carcinogenesis,<sup>1, 2</sup> possibly by decreasing the attachment of the carcinogen to deoxyribonucleic acid (DNA).<sup>3</sup> The potent food additive antioxidants, butylated hydroxyanisole and butylated hydroxytoluene, recently have been shown to decrease the incidence of stomach cancer in mice;<sup>4, 5</sup> and an inverse relationship has been observed between the potent antioxidant, selenium, and human cancer mortality.<sup>6</sup>



Two factors may contribute to the decline of gastric cancer mortality in Americans: the widespread consumption of wheat cereals rich in antioxidants which began in the late 1920's, and the extensive use of the food antioxidant preservatives which began in the late 1940's.

### Antioxidants in cereals

The word "cereal" is derived from *Cerealia*, the name given ancient Roman rites held in honor of Ceres, the goddess of grain. Cereals are members of the grass family grown for their edible seeds; they include wheat, oats, rye, barley, corn, millet, and rice.

The manufacture of modern breakfast cereals began in the late 19th century. Although oatmeal, porridge, and mush had been eaten since colonial days, oat cereals were invented first by Ferdinand Schumacher of Akron, Ohio, in about 1880, when he learned to roll the grains flat instead of grinding them into flour. It was then possible to cook them into a less pasty and more appetizing product. In 1881 Schumacher's factory was destroyed by fire, but Quaker Oats bought the process and introduced the cereal in 1887. Cracked and rolled wheat cereals soon followed. In the 1890's the discovery by Henry Perky, that boiled whole wheat prescribed for his health could be made more palatable by pressing it into long filaments, led to a product called shredded wheat.

Puffed wheat and puffed rice were developed in the early 1900's as the result of experiments on starch grains conducted by the chemist, Alexander Anderson. He was searching for a new type of cooked cereal. Two kernels of rice exploded accidentally in his test tubes. This new dry cereal "shot from

guns" was displayed at the 1904 World's Fair. Puffing is done now by placing the grains in a puffing chamber or puffing gun, heating them, and opening the gun when the desired pressure has been reached. The expansion of water vapor and air results in enlargement of the grains.

Wheat flakes and corn flakes were first developed as a health food by John H. Kellogg at the Battle Creek Sanitarium, Battle Creek, Michigan, where a vegetarian diet was part of the treatment. In 1906 a younger brother, Will Kellogg, incorporated the Battle Creek Toasted Corn Flake Company, and in a few years many brands of corn flakes appeared on the market. Charles W. Post, a former patient at the sanitarium, invented a ready to eat cereal by baking wheat and barley into loaves, which were then dried and ground into small bits. The product was called Grape Nuts and was first marketed about 1900.

American wheat germ oils are especially rich in the antioxidant,  $\alpha$ -tocopherol, and in addition contain some  $\beta$ -tocopherol.<sup>7</sup> Wheat bran contains as many as eight different tocopherols. In an early study Jaffe<sup>8</sup> reported that rats fed a diet including wheat germ oil had fewer mixed tumors resulting from intraperitoneal injection of 3-methylcholanthrene (MC) than rats fed a control diet. Haber and Wissler<sup>9</sup> have observed that a tocopherol supplemented diet had an inhibitory effect on subcutaneous sarcoma formation from MC injection in the mouse.

Until the late 1920's cereals were consumed mainly by food faddists and vegetarians, but by the early 1930's cereals had received wide acceptance in the United States. Consumption of breakfast cereals in the United States



is about 3 kg per person per year; cold cereal accounts for about 65% of this amount.

In contrast, breakfast cereal is not widely used in Europe. A typical European breakfast consists of hard crusted rolls (without preservatives), jam and butter, and coffee and milk, or hot chocolate.

### Antioxidants as food preservatives

Antioxidants were introduced as food preservatives about 1947. Most popular are butylated hydroxytoluene (2,4,6-Ditertbutyl-p-cresol) (BHT) and butylated hydroxyanisole (Phenol, tert-butyl-4-methoxy) (BHA). Nearly 6.2 million pounds of BHT were added to food in 1969.<sup>10</sup> Other antioxidants used to a lesser extent are nordihydroguaiaretic acid (Pyrocatechol, 4-4'-2,3-dimethyltetramethylene) and propyl gallate (gallic acid, propyl ester), lecithin, and the tocopherols. In some instances synergists are added to the antioxidant to enhance the effect of the antioxidant. Synergists added to food are citric acid, phosphoric acid, tartaric acid, monoglyceride citrate, stearyl citrate, monoisopropyl citrate, and thiodipropionate.

Usually, primary antioxidants like BHA or BHT are substituted phenolic-type compounds, and act as free radical scavengers to terminate the propagation of chain reactions which accelerate the oxidation process. On the other hand, synergists or secondary antioxidants such as thiodipropionates break down hydroperoxides, which normally decompose to form additional free radicals into relatively stable products.

After introduction of antioxidants to food in 1947, the use of these substances increased rapidly. They are

added to cod-liver oil, margarine, lard, breakfast cereals, vitamin A and D preparations, corn oil, safflower oil, orange oil, peanut oil, pork fat, salted fish, maple syrup, butter, butter fat, and bakery products.

Our dietary habits are similar to those of the Canadians. In Europe the dietary habits are much different. The Europeans use few preservatives and, because of a general lack of refrigeration, shop each day for fresh foods. Their breads are not sliced and are baked with thick crusts which preserve the moisture and fresh quality of the bread. In America bread is sliced, is spongy and has a thin crust, and contains antioxidants.

### Antioxidants and mortality

The trends of the cancer death rate by site in men for the last 40 years are shown in *Figure 1*. Cancer death rates in most sites such as esophagus, pancreas, prostate, colon, and rectum have been increasing or remaining steady. Deaths from lung cancer in men have been rising precipitously. This increase is generally associated with the great increase in smoking in the early 1940's. In contrast, there has been an almost equally dramatic de-

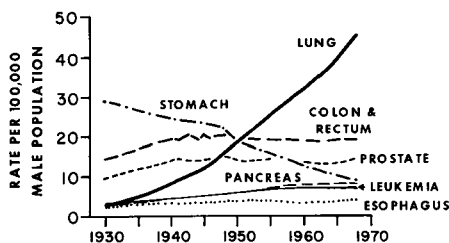


Fig. 1. Cancer death rates in men by site, United States, 1930-1968. The male population is standardized for age on the 1940 United States population. (Adapted from American Cancer Society, 1972 Cancer Facts, p. 10.)



cline in the death rate from stomach carcinoma.

Only the death rate from gastric carcinoma is shown in *Figure 2*. Note the inflection in the curve in about 1947 when the death rate from gastric carcinoma started to decline at an even higher rate.

*Table 1* shows the marked difference in mortality from stomach cancer in several different countries.<sup>11</sup> The United States had the lowest death rate from gastric carcinoma followed by Australia, Canada, and New Zealand. The eating habits and methods of food preservation in these countries parallel ours. Western European countries had intermediate death rates from gastric carcinoma. Other European countries such as Austria, Bulgaria, Czechoslovakia, Finland, Hungary, Italy, Poland, and West Germany had the highest death rates from gastric carcinoma.

The ratio of the observed to the expected cancer death rate by site for men in 17 paired large cities in high and low selenium areas is shown in *Table 2*. The sites which come into contact with dietary selenium such as the pharynx, esophagus, stomach, small and large intestine, and the bladder had substantially lower expected mortality in the high selenium

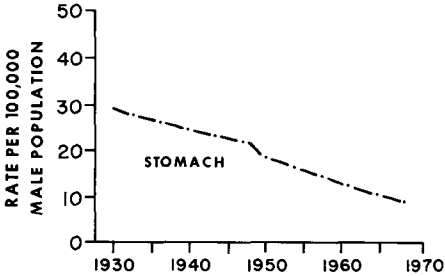
**Table 1.**—Age-adjusted death rates per 100,000 for stomach cancer 1964–1965<sup>11</sup>

Country	Death rate	
	M	F
United States	10.45	5.13
Canada	17.56	8.13
Australia	15.48	7.95
Austria	42.11	23.62
Bulgaria	40.56	26.67
Czechoslovakia	42.74	22.59
Denmark	21.76	13.39
England, Wales	23.42	11.46
Finland	39.66	20.38
France	21.44	10.63
Germany (F.R.)	37.09	20.69
Greece	16.49	10.04
Hungary	42.74	23.18
Ireland	23.88	15.94
Italy	33.61	17.81
Netherlands	28.26	15.18
New Zealand	16.54	8.33
Northern Ireland	21.87	13.59
Norway	26.01	14.63
Poland	44.18	21.17
Scotland	25.47	14.50
Sweden	22.04	12.03
Switzerland	26.04	14.90
Yugoslavia	21.10	11.95

cities than in the low selenium cities. A similar pattern can be observed in the case of the kidney, which can concentrate selenium. In contrast, carcinoma of the pancreas, lung, and prostate, organs which do not come into contact with selenium, showed little or no difference in mortality. Mortality from leukemia and lymphomas was also not significantly different in the high and low selenium areas.

**Discussion**

Antioxidants such as selenium and vitamin E applied to 7,12-dimethylbenzanthracene-treated mouse skin inhibited tumor production by croton oil.<sup>1, 2</sup> Ascorbic acid was also effective,



**Fig. 2.** Gastric cancer death rates in men in the United States, 1930–1968.



**Table 2.**—The ratio of the observed to the expected cancer death rate<sup>6</sup> by site for males in 17 paired large cities. Standard errors are indicated.

Cancer site	Low selenium area	High selenium area
Pharynx	1.86 ± 0.150	1.58 ± 0.128
Esophagus	1.51 ± 0.073	0.90 ± 0.065
Stomach	1.68 ± 0.100	0.99 ± 0.042
Small intestine*	1.05 ± 0.104	0.79 ± 0.082
Large intestine	1.08 ± 0.032	0.80 ± 0.077
Rectum	1.39 ± 0.060	0.89 ± 0.060
Liver	1.17 ± 0.068	1.07 ± 0.068
Pancreas	1.27 ± 0.092	1.27 ± 0.053
Bladder, urinary organs	1.65 ± 0.082	1.35 ± 0.063
Kidney	1.49 ± 0.084	1.23 ± 0.058
Bronchus, lung	1.78 ± 0.053	1.85 ± 0.082
Leukemia	1.23 ± 0.045	1.28 ± 0.028
Lymphatics	1.26 ± 0.031	1.22 ± 0.036
Prostate	2.09 ± 0.072	2.19 ± 0.068

\* Male and female.

but to a lesser extent than the other antioxidants. The antioxidants used as food preservatives, BHA, BHT, and ethoxyquin, when added to experimental diets markedly reduced the incidence of stomach cancer induced by DMBA in mice.<sup>4, 5</sup>

Antioxidants applied on or near the site of carcinogenesis may be preventing peroxidation and attachment of the carcinogen to DNA.<sup>3</sup> This attachment may be one of the rate-limiting steps of carcinogenesis. In unpublished experiments we have observed that the antioxidants selenium and BHT prevent chromosome breakage in tissue culture.

In two other experiments<sup>5, 12</sup> when tocopherol was added to experimental diets no effect on carcinogenesis was observed. Tocopherol is a very labile compound and is altered upon contact with the air. In both experiments it is possible that the tocopherol was destroyed by contact with the air.

The declining American death rate from gastric carcinoma appears to be

associated with the introduction of breakfast cereals, particularly wheat cereals rich in tocopherols. It is likely that the decline of mortality from gastric carcinoma in 1947 is associated with the introduction of the antioxidant preservatives BHT and BHA at that time. A parallel situation has been observed in Iceland. The high incidence of gastric carcinoma in Iceland may be related to a large intake of smoked food, perhaps in association with a low intake of the antioxidant, ascorbic acid.<sup>13</sup> In contrast, the European diet does not have much cereal, and Europeans do not use preservatives in their foods. Their average death rate from gastric carcinoma is about 30 per 100,000 which is similar to the American rate before the extensive use of wheat cereal and preservatives.

The lower incidence (*Table 2*) of carcinoma in all parts of the gastrointestinal tract in high selenium areas might indicate that selenium plays a protective role throughout the bowel.



In contrast, the organic antioxidants BHA, BHT, and ascorbic acid appear to be related to a decreased mortality from carcinoma of the stomach only. This difference may be explained by the fact that most of the organic antioxidants are absorbed from the stomach and do not reach the distal gastrointestinal tract, whereas selenium may be excreted unaltered. Lambs fed diets containing 1 ppm Se as  $\text{Na}_2\text{SeO}_3$  per day excrete 35% to 40% of their daily intake in the feces and 29% to 34% in the urine.<sup>14</sup> If humans metabolize selenium in the same way, selenium might be available to protect the rest of the gastrointestinal tract.

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