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Leading article

Vitamin C and gastric cancer: supplements for some or fruit for all?

The concept that vitamin C can prevent disease has an enduring appeal. This is perhaps not surprising given the variety of different metabolic functions with which the vitamin is involved[1] and the observations that *Homo sapiens* is one of the few mammalian species unable to synthesise it de novo. Present interest is focused on its possible role in cancer prevention and in particular, the prevention of gastric cancer.

The epidemiological evidence concerning vitamin C and gastric cancer has been the subject of several excellent reviews.[2–4] The link between high fruit consumption and a low gastric cancer incidence seems well founded. But fruit contains many substances in addition to vitamin C that may be relevant to cancer prevention, in particular β-carotene which may be an anti-carcinogen in its own right.[5] When individual nutritional elements of the diet are taken separately, the association with reduced cancer risk remains strong for vitamin C[2 6] but proof that it is the 'active ingredient' is difficult because even plasma ascorbic acid concentrations are at best a modest indication of whole body vitamin C status.[7] Epidemiological correlations do not always translate into successful disease prevention strategies. The failure of a number of vitamin supplementation studies, most notably the Finnish lung cancer prevention study,[8] shows the dangers of drawing simplistic conclusions from epidemiological data in diseases with complex aetiologies.

Justification for pursuing the vitamin C hypothesis in relation to gastric cancer was supported by two important reports from the gastroenterology group at Leeds. They showed that, provided plasma values are above a certain threshold, the normal stomach is able to concentrate vitamin C in gastric juice to values many times higher than those in plasma and that most of this is in the reduced form ascorbic acid.[9 10] Secondly they demonstrated that infection with *Helicobacter pylori*, considered by many to be a risk factor for gastric cancer,[11–13] greatly depletes gastric juice ascorbic acid.[14 15] Similar low values are seen in other conditions that predispose to gastric cancer such as the post-surgical stomach or extensive gastric atrophy or intestinal metaplasia.[16] Normal gastric juice seems to be endowed with a protective vitamin, which is lost in conditions of pre-malignant potential.

The remarkable activity of ascorbic acid as an antioxidant is most often quoted as the key function in cancer prevention.[17] This derives from its ability to trap reactive oxygen metabolites (ROMs) and prevent propagation of the damaging chain reactions that result. Ascorbic acid is probably the most efficient ROM scavenger in biological fluids[18] and can act in synergy with vitamin E, which has similar functions in the lipid phase,[19] reducing oxidised tocopherol back to its active form. The stomach is exposed to considerable oxidative stress, with ROMs arising from many sources, such as cigarette smoke and ingested toxins.[20] The ROMs generated by the phagocytic activity of neutrophils and macrophages in *H pylori* infected mucosa may be of particular importance.[21] Oxidative stress has been implicated not only in the acute mucosal injury produced by these agents[20 22 23] but also in gastric carcinogenesis,[23–25] where ROMs can act directly to produce DNA strand breaks, point mutations, and sister chromatid exchanges which, if not adequately repaired, may result in activation of oncogenes (or inactivation of tumour suppressor genes).[26]

How relevant is the presence of a ROM scavenger in the gastric juice? Most damaging radicals are generated within the mucosa and probably act locally. Those occurring in the juice are unlikely to exert much effect on the epithelial cells.[27] The hydroxyl radical, the most reactive and damaging of the radicals that vitamin C is able to scavenge, can act over very short (nanometer) distances[28] and is unlikely to penetrate the gastric mucus layer, which is itself an effective ROM scavenger.[29] Perhaps the high concentration of vitamin C within the mucosa itself[9 30] is more relevant to protection against oxidative damage than that in the surrounding gastric juice.

The interactions of vitamin C and transition metals are also complex. In aqueous solution a combination of ascorbic acid and even trace amounts of iron, leads to the production of ROMs rather than their removal.[28] The importance of iron in mediating ROM damage to gastric cells has been amply shown in in vitro culture.[20] The availability of iron within cells is limited by sequestration into ferritin where it is unable to participate in ROM generating reactions.[31] However, ascorbic acid may be capable of liberating iron from ferritin.[32] How the gastric

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epithelial cell with its high vitamin C content and susceptibility to iron mediated oxidative damage overcomes this problem is not known. The gastric mucosa seems different from other gastrointestinal epithelia by being uniquely impermeable to iron.[33]

The other property of ascorbic acid, of particular relevance to gastric cancer, is its ability to inhibit nitrosation[34] and the production of potentially mutagenic *N*-nitroso compounds (NOCs) in the stomach when nitrites (reduced from dietary nitrate) combine with other dietary nitrogen compounds (amides and amines).[35] Ascorbic acid can inhibit NOC production in vivo[36 37] and reduces the in vitro mutagenicity of gastric juice in a standard *Salmonella typhimurium* test.[38] Direct measurement of NOCs in gastric juice has been beset by technical difficulties[39] but Reed *et al* in Wexham Park Hospital, have recently developed a reliable assay.[40] They have shown that although NOC formation can occur at the acidic pH found in the normal stomach, the highest concentrations are found in the stomach in hypochlorhydria where the reaction is catalysed in the presence of bacteria. The rate of acid catalysed nitrosation is dependent upon the nitrite concentration and may be more important in areas of the world with a high dietary nitrate intake.[41] In such regions, the fall in gastric juice ascorbic acid that results from *H pylori* infection might allow significant increases in NOC formation and contribute to the increased gastric cancer risk associated with the infection. Unfortunately, the only reliable measurements of gastric juice NOC are in patients from industrialised countries. Here, subjects with duodenal ulcers, in whom *H pylori* infection can be assumed, have normal levels of NOCs.[40] Bacteria catalysed nitrosation, associated with increased gastric juice pH, may be quantitatively more important in areas where *H pylori* prevalence is high, resulting in widespread gastric atrophy at an early age – and the source of excess NOC formation in patients from industrialised countries with an increased risk of gastric cancer because of gastric surgery or pernicious anaemia.[42] In theory, there should be less potential for inhibition of nitrosation by ascorbic acid under these circumstances because vitamin C becomes unstable at higher pH, being rapidly converted to the inactive oxidised form.[43] Concentrations of vitamin C in the hypochlorhydric stomach are very low[10] and ascorbic acid disappears rapidly during in vitro incubation with gastric juice from patients with hypochlorhydria.[10] Thus the stomach has largely lost its ability to maintain a high luminal concentration of ascorbic acid under those conditions most favourable for NOC formation. None the less, high dose vitamin C supplements and fruit juices still seem capable of inhibiting gastric *N*-nitrosation in human volunteers with intraluminal pH above.[4 41 44]

It seems unlikely that a mechanism for concentrating vitamin C in gastric juice has evolved solely to combat environmental agents to which humans have only been exposed for a short period of evolutionary history. The true evolutionary significance of the high vitamin C content of gastric juice could lie not in cancer prevention but in the promotion of iron absorption. Absroption of therapeutic iron is increased when taken with vitamin C,[45] provided the non-organic iron is in a soluble state and in its reduced (Fe^{2+}) form.[46] Solubility is readily achieved by the acid pH in the stomach but is lost as soon as the stomach contents reach the duodenum unless iron is chelated to a carrier molecule. Although other chelators are available,[47 48] ascorbic acid is ideally suited for this purpose and provides the added advantage of keeping the iron in a reduced state.[46] The development of iron deficiency in prolonged hypochlorhydria or post-gastrectomy[49] may be related to loss of ascorbic acid as a chelator rather than loss of gastric acid.

What are the prospects for ongoing studies of vitamin C supplementation in gastric cancer prevention? The results of the recently published Linxian projects[50] were disappointing for vitamin C enthusiasts. Despite the inclusion of 30 000 subjects in a region of very high gastric cancer prevalence and borderline nutritional deficiencies, vitamin C supplementation with twice the United States recommended daily allowance did not reduce the gastric cancer incidence or mortality. However, most cancers were of the diffuse type affecting the gastric cardia whose pathogenesis may be different.[51] Furthermore, no attempt was made to eradicate *H pylori* and it is known that vitamin C supplementation fails to increase gastric juice ascorbic acid concentrations to the same extent in the presence of persisting infection.[30]

Another possible explanation for the failure of this study is provided by a recent epidemiological study from Sweden.[52] High dietary intake of vitamin C correlated with a reduced gastric cancer risk but the correlation was much stronger when ascorbic acid intake 20 years previously was considered rather than present diet. The histopathological progression towards gastric cancer proposed by Correa[51] probably takes many years. If vitamin C plays a protective part it may do so at an early stage, perhaps before gastric pH has increased as a result of extensive atrophy. If this is correct, then treatment with vitamin C supplements in people already well advanced along the path to gastric cancer may be unsuccessful. A European multicentre study of vitamin C supplementation and *H pylori* eradication in patients with gastric intestinal metaplasia[53] is now in progress: its results are awaited with interest. In the meantime, rather than treating people with established risk factors with specific vitamin therapies, it might be better to follow the recommendations of the WHO[54] and encourage an increase in fruit and vegetable consumption in the general population.

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