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 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. 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. When individual nutritional elements of the diet are taken separately, the association with reduced cancer risk remains strong for vitamin C 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. 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, 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. Secondly they demonstrated that infection with *Helicobacter pylori*, considered by many to be a risk factor for gastric cancer, greatly depletes gastric juice ascorbic acid. 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. 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. 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 and can act in synergy with vitamin E, which has similar functions in the lipid phase, 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. The ROMs generated by the phagocytic activity of neutrophils and macrophages in *H pylori* infected mucosa may be of particular importance. Oxidative stress has been implicated not only in the acute mucosal injury produced by these agents but also in gastric carcinogenesis 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).

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. 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 and is unlikely to penetrate the gastric mucus layer, which is itself an effective ROM scavenger. Perhaps the high concentration of vitamin C within the mucosa itself 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. The importance of iron in mediating ROM damage to gastric cells has been amply shown in vitro culture. The availability of iron within cells is limited by sequestration into ferritin where it is unable to participate in ROM generating reactions. However, ascorbic acid may be capable of liberating iron from ferritin. How the gastric...
The development of iron deficiency in prolonged hypocholesterinaemia or post-gastrectomy may be related to loss of ascorbic acid as a chelator rather than loss of gastric acid.
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