

Does subclinical malabsorption of carbohydrates prevent colorectal cancer? A hypothesis

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The incidence of colorectal cancer (CRC) is high in the western world and low in Asia and Africa. Fibre and starch are thought to be important protective factors, with a strong inverse relationship between starch consumption and CRC incidence. Whether this is true in Asia, particularly, and Africa is debatable. Because rice is the most easily absorbed of carbohydrates, a mechanism whereby there is an increased starch load in the colon in the Asian population needs to be identified. One possible cause is subclinical malabsorption. This is linked to increased mucosal permeability and low gross domestic product (GDP) per capita, which reflects poor sanitation and water supplies with increased risk for small bowel bacterial overgrowth leading to mucosal cell damage. A potential cause of the dramatic rise in CRC incidence in Japan may relate to its equally dramatic increase in GDP per capita of 600% over 50 years. This correlation appears to be stronger than with other dietary factors including fruit, vegetables and meat. Worldwide, a close correlation exists among low GDP per capita, low CRC incidence and presumed subclinical malabsorption. All these factors combine to maintain a low incidence of CRC in poorly developed countries.

Key Words: *Colorectal cancer; GDP; Malabsorption; Mucosal permeability*

The incidence of colorectal cancer (CRC) is high in the western world and low in Asia and Africa. There is no obvious genetic basis for this and, presumably, the differences relate to diet. Starch is the most important carbohydrate linked to CRC. Evidence is needed to link the incidence of starch consumption and the dramatic increase in CRC incidence in countries such as Japan over the past five decades. Dietary factors are estimated to account for 80% to 90% of this common malignancy (1,2), with the two dietary hypotheses of high intake of animal fat and low intake of dietary fibre being responsible for the increased risk (3). While this may be true in the western world, it appears not to apply in Asia and Africa, where starch is the most important dietary component. Because rice is the most digestible type of carbohydrate, it does not account for the low incidence of CRC, unless a mechanism is found to increase the amount of starch in the colon, thereby leading to an improvement in colonic health.

La malabsorption subclinique des glucides prévient-elle le cancer colorectal ? Une hypothèse

L'incidence de cancer colorectal (CCR) est élevée dans le monde occidental et faible en Asie et en Afrique. On pense que les fibres et l'amidon sont des facteurs protecteurs importants, avec un rapport inverse solide entre la consommation d'amidon et l'incidence de CCR. On peut toutefois se demander si cette notion se vérifie en Asie, notamment, et en Afrique. Puisque le riz est le glucide le plus facile à absorber, il faut établir s'il existe un mécanisme selon lequel il y aurait une charge d'amidon plus élevée dans le côlon de la population asiatique. La malabsorption subclinique en serait une cause possible. Elle est reliée à une augmentation de la perméabilité muqueuse et à un faible produit intérieur brut (PIB) *per capita*, reflété par des mauvaises conditions d'hygiène et de mauvais approvisionnements en eau, le risque accru de prolifération bactérienne dans l'intestin grêle étant responsable de dommages cellulaires des muqueuses. L'augmentation spectaculaire de l'incidence de CCR au Japon pourrait s'expliquer par l'augmentation tout aussi spectaculaire du PIB *per capita* de 600 % sur 50 ans. Cette corrélation semble plus solide qu'avec tout autre facteur diététique, y compris la consommation de fruits, de légumes et de viande. Sur la scène mondiale, il existe une étroite corrélation entre un faible PIB *per capita*, une faible incidence de CCR et une malabsorption subclinique présumée. Tous ces facteurs s'associent pour maintenir une faible incidence de CCR dans les pays en voie de développement.

Giovanucci and Willett (2) believed that there was accumulating evidence that the consumption of red meat, but not other sources of fat, increased the risk of CRC. This led to a reconsideration of the simple fat-colon cancer hypothesis, which is based on the premise that dietary fat induces excretion of bile acids that can be converted to carcinogens or promoters. They further believed that environmental factors, including physical inactivity or excess energy intake relative to requirements, increases risk. They proposed that a large body of data supported recommendations to substitute chicken and fish for red meat, to include a high consumption of vegetables and fruits, and to avoid highly refined sucrose-containing foods in the diet. Alcohol, particularly when consumed with a diet that is low in methionine and folate, may also increase the risk for CRC, as do nondietary factors such as smoking. They argued strongly against the fibre hypothesis, particularly because their long-term nurse study (4) showed no benefit of a high-fibre diet, although, those

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in the highest quintile consumed a relatively low-fibre diet compared with many other countries.

In contrast, a comprehensive review of the literature led Hill (5) to support Burkitt's proposal (6) that fibre is protective against CRC. The mechanism whereby fibre reaching the colon reduces CRC risk is multifactorial. It increases stool bulk, thereby diluting the carcinogens and promoters present in the gut lumen, and speeds transit. Its fermentation by colonic bacteria also has a number of effects. Not only is there an increase in bacterial mass, but there is a modification in the physiology, in which there is lowered pH and a greater production of short-chain fatty acids, such as butyrate, which reduce the risk of malignant change in colonic epithelial cells. There is a reduction in the conversion from primary to secondary bile acids and also in phenols, which could, potentially, act as tumour promoters.

Hill (5) further believed that the amount of carbohydrate reaching the colon for fermentation was considerably underestimated. Based on calculations by Cummings (7) and Stephen et al (8), it was believed that the rate of bacterial synthesis in the colon required at least 60 g to 70 g per day.

In further support of the fibre hypothesis, Cummings et al (9) examined bowel habit data for normal individuals in the United Kingdom and compared them with stool weight in other countries. They calculated that there was an association between stool weight and cancer risk. Individuals with large stools had low cancer risk, and their fecal output was increased by dietary nonstarch polysaccharides (NSPs). Diets characterized by high NSP intake were associated with stool weights of at least 150 g per day; this may reduce CRC risk.

Cassidy et al (10) then compared the intake of starch, NSPs, protein and fat among 12 populations worldwide. They found strong inverse relationships between starch consumption and large bowel cancer incidence (large bowel, $r=-0.70$; colon, $r=-0.76$). Relationships among starch, resistant starch and NSPs remain statistically significant after adjusting for fat and protein intake. They proposed that the strong inverse relationship between starch and CRC corresponded to the hypothesis that fermentation in the colon is a mechanism for the prevention of CRC.

Where does all this starch come from? A number of authors have previously demonstrated that carbohydrates, which were previously believed to be readily absorbed, are, in fact, incompletely absorbed in the small bowel (8,11-13). They showed that this malabsorption of carbohydrates was not an artefact of intestinal intubation techniques. Levine and Levitt (14) demonstrated appreciable malabsorption of flour carbohydrate derived from corn, potatoes, oats and wheat. Ravich et al (15) also demonstrated incomplete absorption of large amounts of sucrose. These studies provided evidence that, in healthy subjects, carbohydrates reach the colon from a dietary source and that starch may be one source. On the other hand, rice flour carbohydrate was shown to be well absorbed by healthy individuals, with minimal generation of hydrogen on breath testing (15,16), whereas large breath hydrogen increases were reported in adult patients with small intestinal and pancreatic disease (16). Of particular interest was the study by Levitt et al (17), which assessed absorption of fermentable carbohydrate in a variety of foods by breath hydrogen testing. Breath hydrogen increased well above fasting concentrations after ingestion of 100 g of carbohydrates from oats, whole wheat, potatoes, corn or baked beans. However, rice caused only a minimal

increase in hydrogen excretion and is, presumably, the most efficiently digested carbohydrate. Rice remains the primary dietary constituent in most Asian countries, where it may constitute 75% of their caloric intake (18). It is difficult to understand how this source of carbohydrate could contribute to the nutritional well-being of the colon if it is more effectively absorbed than other carbohydrates and has the lowest fibre content of comparable cereals (5).

Using rice breath hydrogen tests, Khin-Maung-U et al (18) demonstrated that malabsorption of rice occurred in two-thirds of adults and children in Burma, raising the possibility that this malabsorption had an impact on child growth. This was most likely linked to small bowel bacterial overgrowth, which is related to an abnormality of small intestinal morphology and increased intestinal permeability (19-23). The findings were consistent with the hypothesis of tropical enteropathy proposed by Baker and Mathan (24), and Rosenberg and Scrimshaw (25). These findings were also confirmed in Gambia by Behrens et al (26) and Lunn et al (27), with markedly increased intestinal permeability as measured by the lactulose/mannitol test in infants. These studies suggested that damage to the small intestine played an important role in the development of infant malnutrition. The abnormalities have been confirmed elsewhere in Africa, as well as in South America (28). They are likely universal to all developing countries where there is poor sanitation and water supply. As a consequence, there is a greatly increased starch load in the colon of individuals within these countries, almost all of whom have low rates of CRC.

Geographical variation exists in intestinal mucosal morphology in many tropical countries. Studies from Thailand and other countries in Asia (29), Pakistan (30), Haiti (31,32), Puerto Rico (33), Nigeria (34) and the Caribbean (34) showed a high prevalence of villous atrophy. Long-term travellers visiting countries such as Pakistan (35) and Vietnam (35-37) develop the same mucosal abnormality and subnormal xylose absorption. Conversely, subnormal xylose absorption and jejunal villous architecture in subjects emigrating from the Caribbean (38), India and Pakistan (39) have been reported to be reversible with increased length of residence in the temperate climate of New York City (New York, USA). This suggests an impact of environmental factors that could reverse subclinical malabsorption.

Similar geographical variations in mucosal permeability, using a urinary lactose/rhamnose ratio, have been demonstrated (40) in healthy residents of most tropical areas, indicating increased intestinal permeability and reduced absorptive capacity. Menzies et al (40) believed that this variation in intestinal permeability corresponded to the condition described as tropical enteropathy.

They used a measure of gross domestic product (GDP) per capita for each country to determine whether GDP was associated with absorptive capacity and permeability. A lower GDP per capita was associated with increased mucosal permeability and decreased absorptive capacity.

This concept indicates that subclinical malabsorption will result in an increased carbohydrate load in the colon, which may be protective against CRC. If intestinal permeability is used as a marker for a disturbance in morphology and function, as proposed by Menzies et al (40), the geographical areas involved are those associated with low rates of CRC and low GDP per capita.

In contrast, more developed countries have a GDP per capita that is substantially greater and associated with much higher rates of CRC (55.2 in 100,000 in more developed countries versus 7.3 in 100,000 in less developed countries). The great variation in CRC incidence worldwide correlates well with GDP value.

This hypothesis may go some way to explain the epidemiological dilemma of the distribution of CRC and may be a partial explanation for the rapidly rising CRC risk in countries such as Japan. It has become dramatically more urbanized and westernized, with better sanitation and water supply in the past 50 years. This is mirrored by an equally dramatic improvement in the GDP of 600% over the past 50 years; much of this occurred between 1955 and 1985 (Table 1). Using a predominantly Japanese population who migrated from Japan to Hawaii, Le Marchand et al (41) analyzed data that supported a protective role for vegetable fibre but not for fibre from other sources. The protective effect was limited to those in the highest quartile of fibre intake. This indicates that, although diet has had some impact on CRC incidence in the Japanese population migrating to an area with a high GDP per capita, it is probably not of a high enough magnitude to account for the rise in prevalence.

There has been quite an extraordinary rise in the incidence and mortality rates of colon cancer in Japan. It increased in almost logarithmic fashion until the early 1990s, when the increasing incidence of colon cancer ceased (42).

The incidence of CRC in the Japanese population during the 1950s was approximately nine in 100,000 in both males and females. By 1990, this had increased to approximately 65 in 100,000 males and 40 in 100,000 females (43).

The cumulative risk of CRC in 2006 was such that the rate in Japanese men equalled or exceeded that of American men and male Japanese immigrants living in Hawaii, with

TABLE 1
Gross domestic product (GDP) of Japan per capita at market prices estimated by the International Monetary Fund, 1955 to 2005

Year	GDP (yen)	Currency exchange (US\$)
1955	8,369,500	360.00
1960	16,009,700	360.00
1965	32,866,000	360.00
1970	73,344,900	360.00
1975	148,327,100	297.26
1980	240,707,315	225.82
1985	323,541,300	236.79
1990	440,124,900	144.15
1995	493,271,700	93.52
2000	501,068,100	107.73
2005	502,905,400	110.01

Data from reference 45

similar findings in women (44). These rates apply to both colon and rectal cancers. Cereal consumption has decreased continuously after the 1970s, with a gradual rise in the consumption of vegetables and fish. Meat intake markedly increased from 1950 until the early 1970s. Thereafter, the intake has remained nearly constant, with red meat accounting for approximately 70% of meat intake (42). The impact of these various dietary constituents remains a moot point and it is difficult to envisage that they would have been responsible for such an explosion in colorectal cancer incidence over a period of three decades.

Therefore, the concept of subclinical enteropathy with malabsorption of carbohydrates may be at least one important factor in the prevention of CRC in Asia and Africa.

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