Colon cancer: investigating the roles of diet and hormones

Studies of migrants from low-risk countries can help identify risk factors.

One price that we inhabitants of Western countries pay for our affluence is an increased risk of getting the diseases associated with a fat-rich, high-kilojoule diet. As well as atherosclerosis and heart attacks, these include large-bowel cancer, which accounts for about 6% of all deaths in Australia.

By looking at the pattern of incidence of bowel cancer around the world, scientists have identified fibre and fat as important factors in the disease. In some low-risk countries such as Greece, the normal diet is relatively high in fibre, but this is not so in other low-risk countries like Japan. In both those countries, the diet is low in fats. Migrants from the low-risk areas settling in high-risk countries — like the United States and Australia — become increasingly more likely to develop the disease in their new environment than their non-migrating compatriots — strongly suggesting that aspects of the environment and diet are related to risk of colorectal cancer.

Case-control study

But the solution to the problem of colon cancer in high-risk countries is not as simple as encouraging people to cut down on fats and eat lots of bran. Indeed, scientists at the CSIRO Division of Human Nutrition in Adelaide believe that a host of factors apart from fats and fibre are involved, and that cancers of different sections of the intestinal tract may have different origins.

The bowel comprises the proximal (ascending or right) colon, the distal (descending or left) colon, and the rectum. In his study of the global epidemiology of bowel cancer, Dr William Haenszel, then of the United States National Cancer Institute, found that, in countries with higher rates of occurrence, the excess tumours occurred in the distal colon.

Few studies have looked at factors such as the age and sex of people at risk of the disease, or possible differences in the causes of cancers at the different bowel 'subsites'. Further, dietary studies have come up with contradictory findings.

It was into this arena that Dr John Potter and Dr Tony McMichael, of the Division of Human Nutrition, stepped to take up the challenge of identifying risk factors for the disease among a large sample of people from the Adelaide adult population. Their studies began in 1979, when Dr Potter carried out a case-control study of the disease — that is, he surveyed a group of 400 people who had been diagnosed as having colon or rectal cancer, and matched them with 700 other people (controls).

The most consistent risk factor found was a high dietary protein intake.

He contacted the cancer patients, aged between 30 and 74, through the South Australian Central Cancer Registry and their doctors, and selected the controls — individually age- and sex-matched to cancer cases — from the Adelaide electoral roll.

After receiving permission from the people selected for the study, interviewers visited their homes and asked a series of questions regarding their diet and, for women, their reproductive history. After Dr Potter and Dr McMichael analysed the huge body of data, they were able to identify a number of risk factors, some of which fitted in with the current 'model' of how large-bowel cancer originates, while others indicated that the theory was incomplete.

Bile acids and cancer

This model proposes that the amount, composition, and subsequent bacterial degradation of bile acids entering the gut influence cancer development in the colon. Bile acids are known to have a number of effects on the mucosal (lining) cells of the bowel, including altering cell metabolism, disrupting cell membranes, stimulating DNA synthesis, and causing cell proliferation.

Experimental evidence for the bile-acid model comes from studies on animals, particularly rats. These have confirmed the idea that increased bile-acid flux through the colon enhances cell proliferation and

tumour development. In the gut, bacteria act on bile acids secreted through the bile duct to produce secondary bile acids. The concentrations of these — particularly that of a substance known as deoxycholic acid — in the colon influence the rate of progression of cancer there.

The relation between risk of colon cancer and alcohol consumption was stronger for women than men.

The exposure time of bowel-wall cells to secondary bile acids is important. In the proximal colon, undigested dietary fibre and other dietary constituents from the small intestine undergo prolonged fermentation and degradation. As faecal — and bile acid — contact with the cells of the bowel wall is prolonged, the amount and types of bile acid entering the gut here are important. It appears that faecal bile acid concentration and rate of transit have more impact on tumour development in the proximal than in the distal colon; dietary factors may have a different influence on cancers of the distal colon. Most of the bile acid in the proximal colon is reabsorbed before the gut contents enter the distal colon.

Protein and fibre

The most consistent risk factor that the CSIRO scientists found among their study population was a high dietary protein intake. This appeared to be more associated with risk than a high fat intake, and the relation was particularly strong in women. We know that fats affect bile-acid production (as noted above), but most human and animal studies in the past have given little attention to the possible role of protein in cancer of the lower digestive tract.

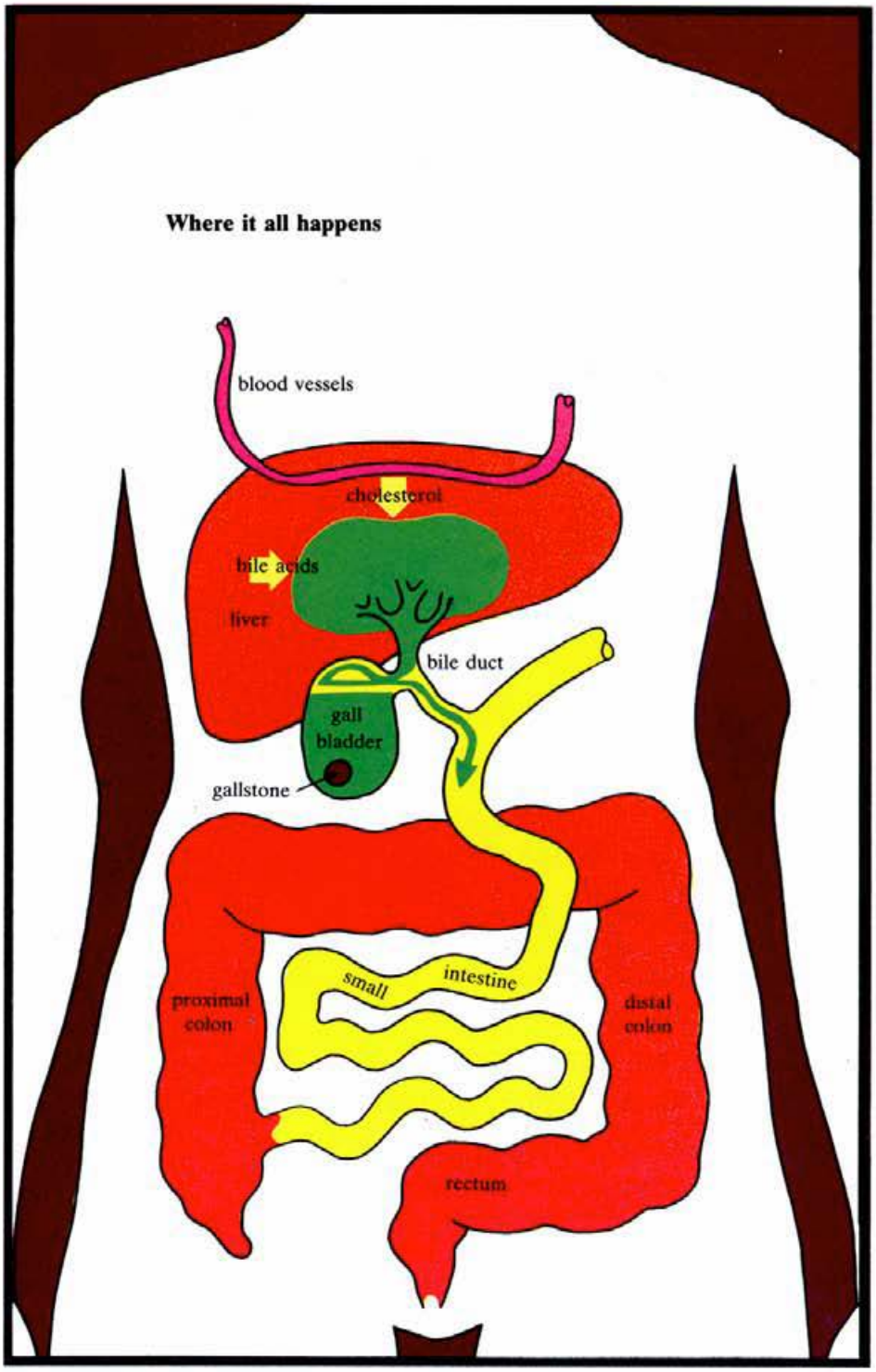
Dr Potter and Dr McMichael point out that dietary protein levels are known to influence, in a manner similar to dietary fat, the activity of several of the bacterial enzymes associated with bowel cancer.

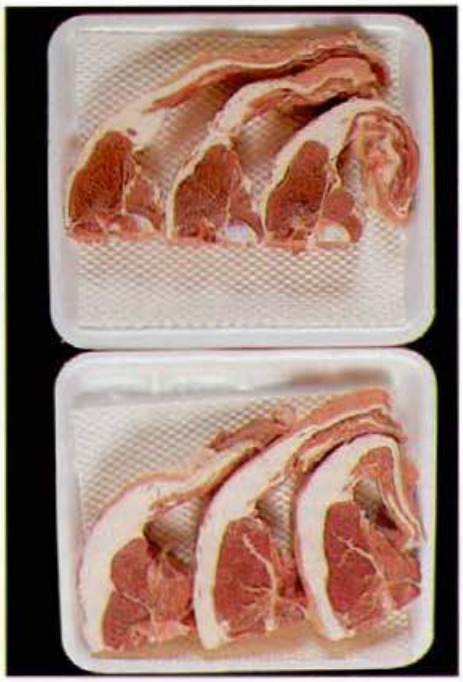
Other considerations are that people who eat more protein also eat more fat and, in addition, are likely to have a higher food energy intake — and eat more frequently — than those with a low-protein pattern. Indeed these two factors — high total kilojoule intake and meal frequency — were also associated with an increased risk of bowel cancer in the Adelaide study.

Dr Potter's and Dr McMichael's explanation is in two parts: that higher food intakes increase the rate of cell turnover and the workload of mucosal cells in the gut epithelium; and frequent eating continually triggers the gall bladder to empty, increasing the bile turnover rate and the ratio of secondary to primary bile acids in the proximal colon.

The relation of fibre to cancer of the bowel is a complex one. One finding of the Adelaide study that appeared to run counter to conventional wisdom concerning colon cancer prevention was that, other things being equal, a high cereal fibre intake increased the risk of women contracting the disease. However, a much stronger correlation showed up, for both men and women, between low-fibre/high-fat diets and increased cancer risk.

Dr Lucien Jacobs of the University of California at Davis, U.S.A., has found that high fibre intake may increase the turnover rate of cells in the proximal colon, but not the distal colon, of rats. If the same thing happens in the human gut, this could be a factor tending to promote colon cancer development. On the other hand, fibre promotes more rapid movement of faecal matter through the colon, which should reduce cancer risk. High-fibre/low-fat dietary patterns also increase the production of volatile fatty acids, which lower the pH of





The study has thrown light on links between diet and colon cancer risk.

the gut, reducing the effectiveness of bile-acid-degrading bacterial enzymes. The result should be reduced exposure of the mucosal cells lining the colon to secondary bile acids, and a reduced cancer risk.

Vitamin C and alcohol

The CSIRO study included two other aspects of diet in the questionnaire — micronutrients, such as vitamins, and alcohol intake. Analysis of the answers revealed that vitamin C seemed to act as a protective agent against rectal cancer. Vitamin C is known to be an antioxidant and can reduce the absorption of the carcinogenic substances known as nitrosamines, sometimes found in preserved meats and other foods.

Dr Potter and Dr McMichael found, as they had with most of the other dietary variables, that the relation between risk of colon cancer and alcohol consumption was stronger for women than men. In their sample, women who consumed one glass of spirits per day had a risk of getting bowel cancer twice that of non-regular drinkers; for men, this doubling of risk was associated with about two glasses per day. No consistent relation between beer-drinking and bowel cancer showed up.

The CSIRO study indicated that the incidence of cancer of the proximal colon is about 10 to 20% higher in women than in men at all ages. In contrast, the incidence of cancers of the distal colon increases progressively with age in men, relative to women of the same age.

Metabolic studies have shown that women, compared with men on similar diets, have a higher gut pH, more secondary bile acids within their bile, lower faecal

The liver–bile–gall bladder connection

Among the many functions of the liver is that of regulating blood cholesterol. It picks up protein-coated cholesterol particles from the blood, stores the cholesterol, and releases it as needed — packaged in new lipoprotein carriers. It also synthesizes cholesterol if necessary.

The liver also produces bile, and it secretes some of the cholesterol in this digestive liquid.

Bile is a mixture of salts that, like laundry detergents, emulsify fats, breaking them into droplets. In this form, they can be attacked by enzymes called lipases.

After leaving the liver, bile is stored in the gall bladder. In some cases, the bile may become supersaturated with cholesterol, which then crystallizes as gallstones.

Cholecystectomy — surgical removal of the gall bladder — increases the risk of colon cancer. Obviously, this would alter the pattern of bile-acid secretion into the bowel: secretion would be more continuous, because the concentrating effect of the gall bladder is absent. This operation also causes an increase in the ratio of secondary to primary acids in the bowel, particularly increasing deoxycholic acid. The reason may be that daily secretions of bile can occur without food being in the intestine.

With doctors from the Queen Elizabeth Hospital and Flinders Medical Centre, Dr McMichael and Dr Robert Scragg, of the Division, conducted a large-scale study of gallstone disease in Adelaide. Until this study, not much was known about the causes of gallstones. Patients with the disease had been characterized as 'female, fair, fat, forty, and fertile'!

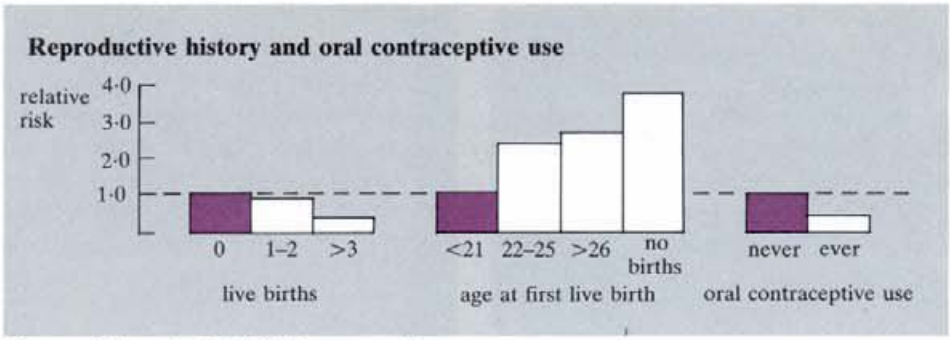
The results of the Adelaide study showed that gallstones were, indeed, prevalent among women, especially those who had recently used contraceptive pills or who had had several children. Both men and women who eat diets high in calories and simple (fibre-depleted) sugars, and who abstain totally from drinking alcohol, are also more likely to develop the disease. In fact, the CSIRO results indicated that people with a moderate intake of alcohol — two glasses of wine a day, for example — appear to be more 'protected' against gallstones than those who abstain.

This protective effect of alcohol may partly explain why women, who usually consume much less alcohol than men, have a higher incidence of gallstones. Reproductive factors are also clearly very important.

For women, too, obesity was a factor that could trigger the disease, although this appears not to be a risk factor in men.

The advice given by the Adelaide researchers to people concerned about developing gallstones is: cut down on sugar, drink a little alcohol regularly, and keep slim. Eat moderate, regular meals and, for women on the pill, use a low-dose one.

Aetiology of gallstone disease. A.J. McMichael and J. McK. Watts. *The Medical Journal of Australia*, 1984, September 1, 270–2.



Some of the scientists' findings on colon cancer risk in women. In each group of bars, the standard for comparison is the coloured one. Higher numbers of children and use of oral contraception are associated with declining risk of colon cancer, while a later age when a woman has her first child is associated with an increased risk.

output, and longer faecal transit time. According to Dr Potter and Dr McMichael, some of these sex differences may be caused by female hormones. All are liable to increase the risk of bowel cancer.

Hormones and bile production

Variations in levels of circulating oestrogens are known to affect lipoprotein metabolism, bile-acid synthesis, and bile composition of the female digestive system. Before menopause, women have shown lower total plasma cholesterol than men, with higher levels of high-density-lipoprotein-cholesterol (HDL-cholesterol). This type of cholesterol, found at low levels in heart disease sufferers, is cleared from the blood by the liver.

After returning to the liver, HDL-cholesterol seems to be preferred over other cholesterols for incorporation into bile — it may even be the primary precursor of bile-acid synthesis. Women, therefore, would have a higher rate of bile-acid synthesis and 'richer' bile than men.

Women who had borne a number of children had a higher degree of protection.

Another sex difference, mentioned earlier, is the ratio of secondary to primary bile acids, which is higher in women than men. This increased ratio in women may be a result of their higher intra-colonic pH. Both this higher pH and the longer time taken for bowel contents to pass through in women than men would accelerate the production and reabsorption of secondary bile acids, deoxycholic acid being particularly important. This substance not only increases the cholesterol saturation of the bile, it is also known to encourage colon cancer in rats.

In the Adelaide case-control study, the researchers asked women questions about their pregnancies and oral contraceptive use. The results showed that women who had borne a number of children had a higher degree of protection from cancer of the bowel than women who had not had children. The explanation may be the long-term change in oestrogen profile that women experience after their first pregnancy.

The pill

Oral contraceptives, too, are associated with reduced risk of colon cancer in women. The parallel effects of reproduction and oral contraceptive use are due to changes in circulating hormones that are associated with lower total plasma cholesterol and increased bile-acid production. Pregnancy and oral contraceptives lower plasma HDL-cholesterol, thus reducing the rate of plasma cholesterol clearance by the liver and reducing bile-acid production.

Dr Potter is currently undertaking a study of the occurrence of large-bowel cancer among southern European migrants who have settled in Australia. In particular, he will be looking at dietary and circulatory lipids and aspects of reproduction, and their possible relation to the low incidence of bowel cancer among people of Italian and Greek descent.

Mary Lou Considine

Diet and colon cancer risk

These tables compare the top 80% of protein, fat, and calorie consumers in the study sample with the lowest 20%. The numbers denote relative risk of contracting colon cancer; those greater than one indicate that the higher-intake group is at greater risk.

It seems that substantial differences in the diet-related risks of colon cancer exist in men and women. The tables indicate that diet has a greater impact on the risk in younger than in older women, while among men the impact is greater in the older than in the younger group. In women, diet appears to have a greater impact on risk of cancer of the proximal than of the distal colon. In men, the reverse seems to apply.

In general, the tables indicate that the effects of diet on colon cancer risk are greater in women than men.

	protein		fat		calorie intake	
age (years)	<55	>55	<55	>55	<55	>55
male	1·5	2·2	0·2	1·3	0·2	1·7
female	3·4	2·1	8·4	1·2	7·3	4·0

	protein		fat		calorie intake	
colon 'subsite'	proximal	distal	proximal	distal	proximal	distal
male	1·4	2·8	1·0	1·3	1·0	1·9
female	2·3	2·9	5·0	1·4	6·7	4·1

More about the topic

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