New evidence emerges on diet–cancer links

Well-done meat appears to pose risks, and new findings confirm the virtues of vegetables, fruit and fibre

Robert Kerton

Diet is recognised as an important factor in the cause of cancer. Now new research indicates that to maintain a healthy diet we need to do more than avoid fatty or protein-rich foods; we also need to consider the way we cook some foods and the role of food in preventing cancer.

In recent months, scientists at the CSIRO Division of Human Nutrition in Adelaide have found that the temperature at which beef is cooked and the duration of cooking appear to affect the extent of cell damage caused in the body when the meat is eaten. The CSIRO scientists have also confirmed links between dietary factors and the body's ability to protect itself against two major types of cancer — breast and pancreas.

Illustration: Ian Sharpe

Incidence, and possible causes

cancer type	new cases, Victoria 1987*	known or suspected link#
breast	1786	hormones, lack of fibre
lung	1721	tobacco
colon	1493	animal fat, lack of fibre
prostate	1117	hormones
rectum	758	animal fat, lack of fibre
leukemia	695	X-rays
bladder	663	tobacco
stomach	534	salty food, tobacco
melanoma	523	ultraviolet light
oral cavity and pharynx	517	tobacco, alcohol
non-Hodgkin's lymphoma	509	AIDS virus
pancreas	334	tobacco, animal fat, sugar

* from: Anti-Cancer Council of Victoria
\# from: CSIRO Division of Human Nutrition and National Institutes of Health, U.S.A.

The table lists factors that research has linked strongly with the initiation or promotion of various cancer types. Some of the links, such as tobacco with lung cancer, are firmly established. The evidence for others, while strong, is not fully conclusive.

Cancer kills more than 30 000 women and men a year in Australia today, and its share of deaths is growing. Only heart disease kills a greater number. Cancer is already the leading cause of mortality among American women and according to research by the Health Department of Western Australia, if death from heart disease continues its current relative decline, will become the biggest killer of Australians within the next 2–3 years.

Cancer trends, however, are not uniformly dismal. Over the last 20 years, changes in life-style and improved medical practice have sharply reduced the incidence of, and risk of death from, a number of major types. Cancer of the stomach and the cervix, for example, appear to be in decline — assumed to be due, respectively, to the consumption of less salted and pickled food, and the early detection and treatment of pre-cancerous cells. In the United States, the death rate from cancer of the testis has been more than halved since 1973.

But some types of cancer continue to increase steadily, either in incidence (for example, prostate and breast) or mortality (bone marrow) or both (lung). The rises have varying explanations. The reported incidence of melanoma in Victoria, for example, has jumped 20% since the early 1980s, largely due to greater public awareness of it and the risks of sunburning. Reports of breast cancer are becoming more common possibly because of a greater use of mammography for early detection of the disease, while the emergence of the AIDS virus may explain the increasing prevalence of certain cancers of the lymphatic system.

Tobacco use remains the chief known cause, with studies linking it to the initiation or promotion of cancers of the lung, bladder, mouth, pancreas, kidney, stomach, larynx and possibly the liver.

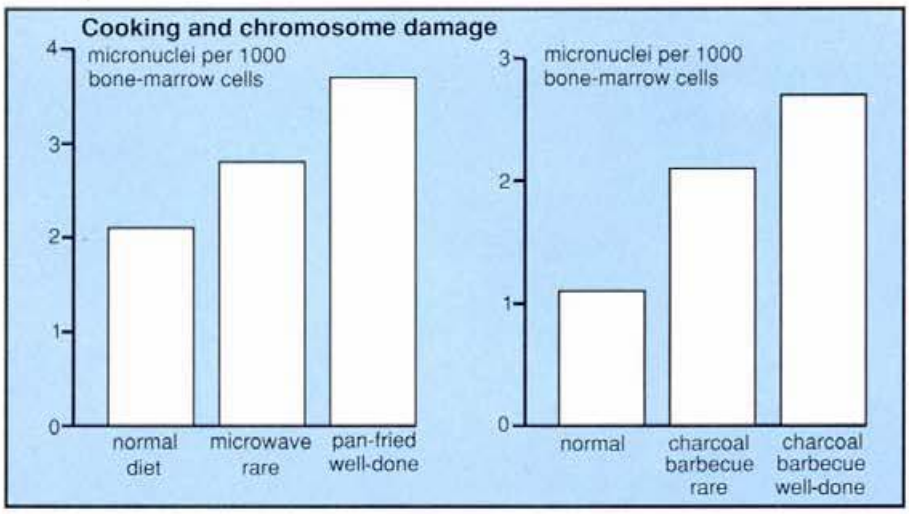
While agents like tobacco and man-made chemicals in the environment have received much attention as potential causes, the significance of eating habits in the incidence of major cancers is less well appreciated. In five of the top 12 types in Australia — accounting for about one-third of all new cancer cases — scientists know of or suspect a link with the presence or absence of natural dietary constituents (see the table for Victorian data).

Some natural food constituents may have the potential to trigger cancer. Various plants have evolved the ability to produce toxic chemicals as protection against being eaten. Of about 100 naturally occurring pesticides they have so far studied, toxicologists suspect 25% are potentially carcinogenic, on the basis of their chemical structure — a similar proportion to that found among synthetic chemicals and pharmaceuticals.

Food may also contain contaminants such as the toxins produced by microorganisms. For example, a group of chemicals known as aflatoxins, produced by a mould, have been strongly linked with the incidence of liver cancer in parts of China.

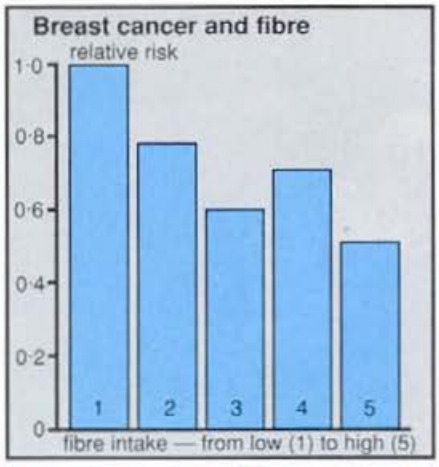
Evidence is growing that the way food is prepared may also play a part in determining the level of exposure to carcinogenic chemicals. Animal experiments by various overseas researchers in the 1980s suggest a link between tumours of the liver, lung and stomach and a class of compounds known as aminoimidazoazaarenes (abbreviated to AIAs) that are produced when meat is cooked. In bacterial tests, AIAs have proved highly mutagenic — that is, they cause mutations in the chromosomes of cells. They are readily formed in beef and pork (and to a lesser extent in chicken and fish) during high-temperature cooking such as frying and grilling, and research has shown that a well-done piece of meat has more than 10 times the concentration of AIAs in a piece of rare meat cooked by the same method.

Two American scientists, Mark Schiffman at the National Cancer Institute in Maryland and James Felton at the Lawrence Livermore Laboratory in California, have advanced the theory that low AIA intake may be linked to a



Mice fed well-done pan-fried meat, and both well-done and rare meat from a charcoal barbecue, showed significantly increased levels of chromosome damage — as measured by micronuclei — compared with normal diet groups.

lower risk of cancer of the colon and rectum. In a comparison of 50 colorectal cancer patients with a control group of hospital patients, they found that 46% of the cancer patients ate well-done red meat, compared with just 19% of the controls. They also found that the cancer patients were more likely to excrete certain mutagens in their faeces than the control patients. An Australian researcher, Dr Michael McManus at Flinders University in South Australia, is currently investigating a metabolic pathway within the human body that leads to the formation of carcinogens.



A high-fibre diet seems to be linked with a substantially reduced risk of breast cancer.

In an effort to assess the carcinogenic potential of cooked meat, Dr Michael Fenech and Ms Sonia Neville, at the Division of Human Nutrition, have carried out some preliminary experiments using mice. Dr Fenech is also conducting a major study among 300 human volunteers, comparing vegetarians with meat-eaters.

In the mouse experiments, the researchers used a genetic technique known as the cytokinesis-block micronuclei assay, a method for measuring chromosomal damage. The technique, developed by Dr Fenech, is now widely used in laboratories worldwide for studying the biological impact of pollution accidents.

Before a living cell divides, each chromosome in the nucleus is duplicated. Then, in a process called mitosis, the pairs of chromosomes separate and move on spindles towards one or other of two 'poles' known as centrioles. In the final phase of mitosis, new daughter nuclei form. Any damaged chromosome, however, tends to lag behind in this movement towards the poles; if the chromosome is broken, the fragment lags behind.

These lagging sections of DNA sometimes form small nuclei of their own, called micronuclei. By counting the number of micronuclei in a sample of red blood cells, scientists can measure the level of chromosomal loss or damage, and therefore quickly estimate a compound's potential for affecting the genes in an organism.

In their first experiment, Dr Fenech and Ms Neville maintained three groups of mice for 21 days on differing diets: a normal, largely vegetarian laboratory diet based on cereals, soybeans and meat and fish meal; a diet comprising (in equal proportions) rare meat cooked in a microwave oven and the normal laboratory food; and one comprising (in equal proportions) well-done fried meat and the normal laboratory food.

The key differences between the two experimental diets (designated 'MWR' for 'microwaved rare meat' and 'PFWD' for 'pan-fried well-done meat) were the temperatures at which the meat was cooked and the cooking time. The MWR meat was microwaved in an oven at a core temperature of 62°C for 10 minutes, while the PFWD meat was fried on an electric hotplate at a core temperature of 166°C for 20 minutes (10 minutes each side). In both diets, the cooked beef was milled, mixed with the normal diet and oven-dried before feeding.

After 21 days, the mice were sacrificed and their red blood cells (taken from the bone marrow and the peripheral blood vessels) analysed for numbers of micronuclei. A minimum of 1000 bone-marrow cells and 4000 peripheral blood cells from each animal were examined.

In the normal diet group, the number of micronuclei per 1000 bone-marrow cells averaged 2·09. By comparison, the numbers of micronuclei per 1000 cells averaged 2·72 in the MWR group and 3·63 in the PFWD group. Only the difference between the normal diet group and the PFWD group — more than 50% higher — was statistically significant. Similar trends emerged with the peripheral blood cells.

The researchers concede that dietary factors or changes in metabolism could have confounded the findings. The MWR and PFWD diets were substantially richer in fat and protein than the normal one. However, it is worth noting that the addition of microwaved rare meat did not produce a statistically significant change in the number of micronuclei. This, they claim, suggests that meat in the diet does not necessarily contribute to the genotoxicity of food unless the chemical changes induced by cooking significantly alter the concentration and combination of toxic substances within the meat.

The roles of temperature and duration of cooking in the formation of toxic chemicals in meat are not well understood, largely due to the complexity of the chemical reactions involved. We do know, however, that speedy cooking — as exemplified by microwaving — causes a rapid loss of water from a piece of meat. The water contains many of the chemicals that react to form compounds such as the AIAs. If these chemicals are lost before they have time to combine and react, the genotoxicity of the meat may be lowered.

Another important factor is the temperature required for certain complex reactions involving the proteins and carbohydrates in meat. Known as browning reactions, these chemical changes produce the characteristic flavour and appearance of fried or grilled meat. Browning reactions occur only at high temperatures, generally above 150°C, typical of frying, broiling and most baking methods. In contrast, boiling and its variants, braising and stewing, can only occur at or below the temperature of boiling water — 100°C — well short of the temperatures needed for browning. Microwaving too is not hot enough and — as any cook will tell you — does not brown meat.

In a second experiment, Dr Fenech and Ms Neville fed groups of mice a diet of beef cooked over a charcoal barbecue. The burning of animal fat on the hot coals produces smoke containing chemicals called polycyclic aromatic hydrocarbons (PAHs), some of which are known to be powerful carcinogens.

The meat was cooked at a temperature of 265°C, at a height of 12 cm above the coals, for 13 minutes (rare) or 25 minutes (well done). It was fed (unmixed with the normal diet) to the mice on alternate days. A control group received only the normal diet.

After 21 days, the micronuclei frequencies averaged 1·1 per 1000 bone-marrow cells for the control group, 2·1 for the mice given rare meat and 2·6 for those on well-done meat. Statistical tests found the two groups fed meat had significantly more micronuclei in their cells than the

normal group, although the difference between the two experimental groups was not statistically significant.

While the findings can only be regarded as suggestive, Dr Fenech's advice, at this early stage of the research, is that people should minimise the amount of well-done meat they consume, use low-temperature cooking methods such as steaming where possible and consider using the microwave to partly cook meat before browning it on the barbecue.

The thorough investigation of dietary factors in the induction of cancer is complicated by the presence of anti-mutagenic or anti-carcinogenic agents in food. For example, in the mouse experiments described above, it is not possible to exclude the possibility that a cut in the vegetarian component of the diet had reduced the consumption of unknown compounds that lower the risk of chromosomal damage.

Research by the Division of Human Nutrition, in conjunction with the University of Adelaide, the Queen Elizabeth Hospital in South Australia and scientists in France and the United States, has provided more information on the importance of certain nutrients in preventing cancer of the pancreas.

Pancreatic cancer is a major form in Australia, accounting for about 3% of all new cancer cases (according to Victorian data) and 5% of cancer deaths. Cigarette-smoking is a well-established risk factor for the disease, but the association with dietary factors has seldom been studied.

In a study of 104 men and women in Adelaide with cancer of the pancreas, the researchers found strong inverse correlations between the disease and consumption of a range of so-called micronutrients found principally in plant foods. These are generally vitamins and minerals that the body needs for metabolism and other processes.

By comparing the diets of the cancer patients with those of healthy control subjects, the scientists found a significantly reduced apparent risk of disease among people who consumed more of the vitamins, B6, C, E, folic acid and ß-carotene (a metabolic precursor of vitamin A) and the minerals, potassium, magnesium and manganese.

For example, those subjects in the top 25% of consumers of folic acid were found to have a relative risk of pancreatic cancer almost one-third of those in the bottom 25%. Foods high in folic acid include asparagus, lentils, spinach, wheat bran and liver.

Australian Overseas Information Service

New evidence confirms the health-giving virtues of fruit and vegetables.

Similarly, the analysis suggests — after correcting for total energy intake — that high consumption of vitamin C or ß-carotene is associated with a halving of the risk of pancreatic cancer, and high intakes of manganese, vitamin B6 or vitamin E with a reduction of more than 60%. High consumption of potassium or magnesium was associated with a reduction of almost 80%.

Among the women, those with cancer ate less lettuce, broccoli, currants, raisins, Vegemite, potatoes and tomatoes than those without the disease, while the men with cancer consumed less currants, raisins, wine, fish and tomatoes. According to the CSIRO researchers, the study suggests that those with pancreatic cancer consume significantly less of their nutrients from plant sources as opposed to animal sources. For example, although magnesium, potassium and folic acid — all positively associated with lower risk of cancer — occur in milk, the chief source of these nutrients in the Australian diet is fruit and vegetables. The observed difference in manganese consumption also appears to reflect a lower intake of plant-based nutrients (from bread, wine and fruit) among the cancer sufferers.

The mechanism of how certain nutrients in fruit and vegetables may protect the body against cancer is unknown, although one view is that they operate as anti-oxidants, 'mopping up' the highly reactive chemicals produced in the body when oxygen interacts with organic compounds.

Food's role in preventing cancer is highlighted by the preliminary findings of a major CSIRO study of breast cancer in women. This is Australia's most common form, accounting for one-quarter of the cancer cases among women and 12% of all new cancer cases. The disease is linked to the effect of the ovarian hormones, oestrogen and progesterone, on the body. The two hormones help regulate cell growth and division in the breast, and an imbalance may promote the formation and growth of tumours.

Evidence is growing, however, that diet may also be involved in breast cancer. Some researchers believe that

obesity during childhood is a risk factor, while a number have claimed a strong relationship with fat consumption.

Recent research by the American Health Foundation, using 62 women, has shown that a high-fibre diet (supplemented with wheat bran) can reduce oestrogen levels in premenopausal women. The scientists concluded that dietary fibre may provide some protection against breast cancer. The much-bigger 4-year study (using 451 women with breast cancer) by the Division of Human Nutrition in Adelaide now appears to confirm this conclusion.

The unpublished CSIRO study claims to have found a strong link between the proportion of fibre-rich foods in the diet and incidence of the disease — stronger in fact than previously studied links with fats and total energy intake.

According to one of the CSIRO team, Dr Peter Baghurst, women eating less than 14 grams of fibre a day are twice as likely to contract breast cancer as those eating 28 g or more a day.

Theories on how fibre could affect breast cancer suggest that it may simply inhibit the absorption of oestrogen from the intestine (thereby lowering hormone levels in the blood) or fibre-rich foods may contain compounds that block certain effects of oestrogen.

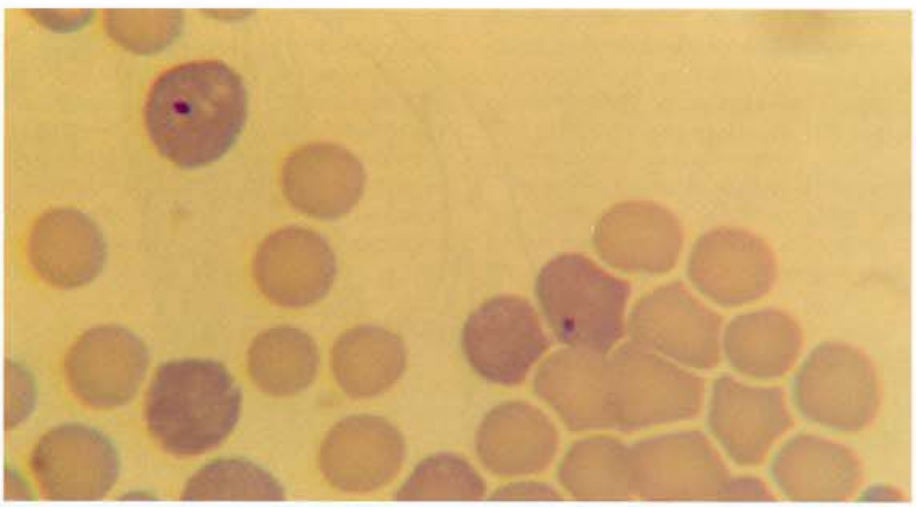
Whatever the mechanism, the claimed link may provide a very effective solution to one of the chief causes of mortality in Australia. 'Some women may be able to reduce their risk as much as 50% simply by increasing the proportion of fibre-rich food in their diet', Dr Baghurst said.

Fibre-rich foods, which are derived solely from plants, include wheat bran (about 45% fibre by weight), wholemeal bread (6.5% fibre) and legumes (more than 7%).

Brett Wright

Australian Overseas Information Service

Too much barbecued meat may be a health risk.



The prominent dark spots in two of the red blood cells pictured are micronuclei. Counting micronuclei provides a measure of chromosomal loss or damage.

More about the topic

Cancer mortality trends in Australia. II: 1910-1984. C.D.J. Holman,W.M. Hatton, B.K. Armstrong and D.R. English. *Health Department of Western Australia: Occasional Paper* No.18, Perth, 1987.

'Victorian Cancer Registry — 1987 Statistical Report.' G.G. Giles, H. Farrugla and B. Silver. (Anti-Cancer Council of Victoria: Melbourne 1991.)

Micronucleus induction in bone-marrow cells following consumption of cooked beef in mice — preliminary investigations M. Fenech and S. Neville. *Mutation Research*, 1992, **281**, 3–10.

A case-control study of diet and cancer of the pancreas. P.A. Baghurst, A.J. McMichael, A.H. Slavotinek, K.I. Baghurst, P. Boyle and A.M. Walker. *American Journal of Epidemiology*, 1991, **134**, 167–79.

Fried foods and the risk of colon cancer. M.H. Sciffman and J.S. Felton. *American Journal of Epidemiology*, 1990, **131**, 376–8.

Diet, body mass and colorectal cancer: a case-referent study in Stockholm. M. Gerhardsson de Verdier, U. Hagman, G. Steineck, A. Reiger and S.E. Norell. *International Journal of Cancer*, 1990, **46**, 832–8.

Towards the primary prevention of cancer. B.E. Henderson, R.K. Ross and M.C. Pike. *Science*, 1991, **254**, 1131–8.

High-fibre diet reduces serum estrogen concentrations in premenopausal women. D.P. Rose, M. Goldman, J.M. Connolly and L.E. Strong. *American Journal of Clinical Nutrition*, 1991, **54**, 1–6.