



# Diet, Lifestyle and Cancer Symposium Report

In May 2006, the Sydney University Nutrition Research Foundation conducted a symposium about the role played by diet and lifestyle in the aetiology of cancer. This report summarises the three lectures presented at the symposium.



## Obesity, physical activity and cancer: the new frontier?

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In 2002 the International Agency for Cancer Research (IARC) reviewed the associations between overweight, obesity and cancer and concluded there was sufficient evidence for a link with cancers of the colon, breast (post-menopausal), endometrium, kidney and oesophagus. At the time there was some evidence for increased risk of cancer of the pancreas though it was inconclusive. Using estimates for the prevalence of overweight and obesity in Europe, IARC's estimates of the population attributable risk for these cancers due to overweight and obesity were: colon cancer 11%, post-menopausal breast cancer 9%, endometrial cancer 39%, kidney cancer 25% and oesophageal cancer 37%. As the prevalence of overweight and obesity in Australia is similar to that in Europe, similar attributable risks could be expected in this country.

### American Cancer Society Study

The range of cancers thought to be associated with overweight and obesity was increased considerably with the publication in 2003 of a large cohort study conducted by the American Cancer Society (1). The prospectively studied population of more than 900,000 United States men and women had been followed up over 16 years and experienced over 57,000 cancer deaths. In addition to the cancers identified by IARC, non-Hodgkin's lymphoma, multiple myeloma and cancers of the liver and pancreas were associated with higher body mass index (BMI) values. On the basis of the associations observed in this study, current patterns of overweight and obesity in the United States were estimated to account for 14 percent of all deaths from cancer in men and 20 percent of those in women.

Since the publication of the American Cancer Society study additional cohort studies have been published allowing a meta-analysis of the data relating to the cancers newly under scrutiny. Fortunately, consistent cut-offs for overweight and obesity have been used in these studies which simplifies the process. The preliminary

data suggest obesity is associated with increased risks for pancreatic cancer by 40%, non-Hodgkin's lymphoma by 50% and multiple myeloma by 60%.

### Lifestyle and colon cancer

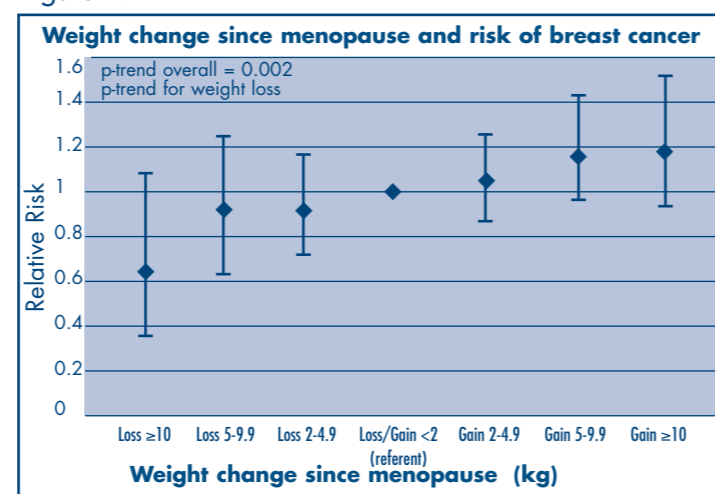
Support for a role for overweight in the aetiology of colon cancer has come from the Pooling Project of Prospective Studies in which data from different cohort studies in different countries are pooled for analysis at Harvard. In men, a significant 64% increase in colon cancer risk was observed as BMI increased from 23 to 30. Although the effect was substantially reduced in women, it remained significant. In the Framingham Study waist circumference was a stronger predictor of colon cancer risk than BMI, suggesting that central obesity is related to increased risk of colon cancer (2). These findings are consistent with the hypothesis proposed by Giovannucci in 1995 that the increased risk of colon cancer in Western countries is linked to high levels of insulin in the blood (3).

According to this hypothesis, both overweight and lack of physical activity increase colon cancer risk by increasing insulin resistance, acting fairly late in the process as adenomas progress to carcinomas. Investigation of this hypothesis has been facilitated by the development of C-peptide as a biomarker for insulin secretion. When proinsulin is cleaved it releases insulin and C-peptide into the bloodstream in equimolar amounts, making C-peptide a valid indicator of insulin production.

Several studies have now found elevated plasma C-peptide concentrations to be associated with increased colon cancer risk, even after controlling for BMI. In the combined data from the Nurses Health Study and the Health Professionals Follow-up Study plasma C-peptide was also associated with increased risk for pancreatic cancer, again suggesting a link through the insulin pathway.

showing that activity lowers hormone levels. The oestrogen-related mechanism linking obesity and physical activity with breast (and endometrial) cancer stands in contrast to the insulin-related pathway to colon and pancreatic cancer. Women with higher physical activity also have lower recurrence of breast cancer. Importantly, these relationships are determined by activity levels after diagnosis and not to prior activity levels. So the arguments for intervention with patients with respect to both body weight and physical activity appear strong.

Figure 1:



#### References

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3. Giovannucci E. Cancer Causes Control 1995;6:164-79.
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Physical activity also plays into this mechanism through its effect on glucose metabolism. In both the Nurses Health Study and the Health Professionals Follow-up Study there were significant inverse associations between increasing physical activity and colon cancer risk(4). Importantly, walking was sufficient to generate this benefit. Three MET-hours of activity per day, equivalent to about a one hour walk at a casual pace, was associated with a halving of colon cancer risk in both men and women. The beneficial effect of physical activity on the risk of colon cancer is probably the second most consistent finding in the literature after smoking and smoking-related cancers. However, physical activity does not appear to affect the risk of rectal cancer.

### Can cancer risk be reduced?

From a public health point of view a key question is whether reducing excess weight and increasing physical activity can reduce cancer risk. With respect to breast cancer there is some encouraging evidence. Figure 1 shows the change in breast cancer risk with weight change after menopause in the Nurses Health Study. While weight gain of 10 kg or more was associated with a 20% increase in risk of breast cancer, weight loss of 10kg or more was associated with a reduction in risk of nearly 40%. The trend across these relationships is statistically significant. Increased physical activity after diagnosis with breast cancer also appears to be beneficial(5). Women who walked three to five hours a week reduced the risk of death from breast cancer by half. Benefits of physical activity were particularly apparent among women with hormone-responsive tumours, consistent with trial data

### Key points

- ▲ Excess body weight is associated with increased risk of cancers of the colon, breast, endometrium, kidney and oesophagus. Recent evidence suggests non-Hodgkin's lymphoma, multiple myeloma and cancers of the liver and pancreas can now be added to this list. Several mechanisms appear to be at play. Currently 14-20% of all cancer deaths are attributable to overweight and obesity and these figures can be expected to rise in line with the upward trends in body weight.
- ▲ Physical activity is associated with lower risk of cancer of the colon and breast, and with better survival and less recurrence after diagnosis with breast cancer.
- ▲ The association between the consumption of meat and colorectal cancer remains weak and inconsistent. Nevertheless, the high rate of colorectal cancer and the potential public health opportunity demand further research into this issue. Current evidence suggests any risk associated with the consumption of meat is more likely to be associated with the way it is cooked and preserved than with meat per se.
- ▲ Recent findings from prospective cohort studies cast considerable doubt on the notion that consumption of fruits and vegetables may help prevent cancer. The earlier studies suggesting benefit were primarily case-control studies and prone to bias.

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## Meat and colorectal cancer: a critical appraisal

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When examining relationships between diet and disease, the epidemiologist asks a number of questions: How strong is the association? How consistent is the finding across different study designs and populations? Is there a dose-response gradient? Does exposure to the food in question precede the emergence of the disease? Are there plausible mechanisms to explain the association?

In the late 1990s a previous review of the association between meat and colorectal cancer found these criteria were only partly satisfied<sup>(1)</sup>. While there were plausible mechanisms, the relation was not strong and the findings of studies were inconsistent. A dose-response relationship was evident in some studies but not others. Causality could not be inferred. Nevertheless, colorectal cancer is the commonest cause of cancer in Australia and results in approximately 13,000 deaths each year. If there were a weak causal relation between meat consumption and colorectal cancer the potential to reduce the number of cases may be considerable.

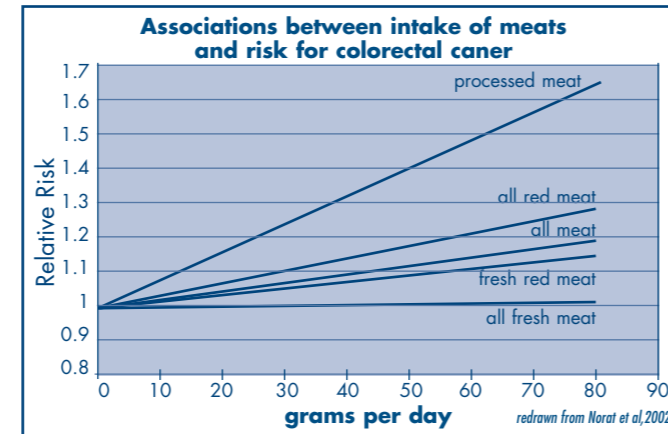
### IARC meta-analysis

In 2002 the International Agency for Research on Cancer (IARC) published a meta-analysis on the relation between meat consumption and colorectal cancer<sup>(2)</sup>. The technique of meta-analysis combines the data from several studies thereby increasing the likelihood that a weak association might find significance. For several reasons such studies are difficult in relation to meat. Firstly, definitions of what comprises 'red meat' and 'processed meat' differ widely in different countries and studies. Secondly, the comparisons conducted in different studies vary widely. Some studies may divide their cohort into three groups while others choose six groups, making the comparison of highest-to-lowest very different. Also, the average intake of meat is high in some populations and low in others. Notwithstanding these caveats, the overall picture provided by the IARC meta-analysis is shown in Figure 2. Total fresh meat intake appeared to be unrelated to the risk of colorectal cancer. With respect to fresh red meat, the risk appeared higher though the relative risk is small. The increase in the relative risk for colorectal cancer associated with increased consumption of processed meats appeared substantial.

### The EPIC study

The most recent findings in this field came from the large EPIC study<sup>(3)</sup>. In a sense this study is like a meta-analysis in its own right with the data derived from 10 European cohorts, though fortunately the data collection and classification have been consistent. The change in risk associated with a 100 g/day increase in red meat and processed meat (combined) was generally positive but

Figure 2:



failed to reach statistical significance, even when the data from all cohorts were combined. By contrast, increasing intake of fish was associated with a substantial and significant fall in the relative risk for colorectal cancer. The results of EPIC are generally consistent with that from the IARC meta-analysis but do little to move the debate about meat and colorectal cancer forward. Perhaps a clearer picture will emerge with further follow-up of this important study.

### Plausible mechanisms

One reason for persevering with the study of meat and colorectal cancer risk is the array of plausible mechanisms that might explain it. Polyaromatic hydrocarbons are produced when meat is cooked directly over a fire. Although thought to increase cancer risk in high concentration, these substances are ubiquitous in the diet – cereals, oils and fats being the major sources. High meat-eaters and vegetarians may have comparable intakes. The formation of heterocyclic amines when meats are subjected to high heat e.g. pan-frying, is another potential concern. N-nitroso compounds may be generated during the preservation of some meats. One of these, MDNA, is known to induce gastric cancer in animals at high doses, though its effect on colorectal cancer in these models is weak. Finally, it has been suggested that haem iron in red meat may catalyse the formation of N-nitroso compounds in the gut.

Currently, none of these mechanisms sits neatly with the epidemiological data. However, most relate to the way meat is preserved or cooked and this may guide dietary advice until more conclusive evidence is available – avoid char-grilling; less high temperature cooking of meat; more roasting, stewing and microwaving; limit intake of processed meats.

#### References

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2. Norat T et al. Int J Cancer. 2002;98:241-56.
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## Fruit, vegetables and cancer: making sense of the evidence

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Two decades ago Walter Willett wrote a paper titled 'Diet and cancer: a whirlwind odyssey through a sea of inconsistency'. Those inconsistencies still arise today in relation to the association between the consumption of fruits and vegetables and the development of cancer. The perception that fruits and vegetables are protective which developed in the 1960s and 70s was largely based on the findings of early case-control studies. However, the results of recent large, prospective cohort studies have generally failed to provide support for this association, and cancer mortality among vegetarians and omnivores has been shown to be the same.

### The latest evidence

The most recent comprehensive review of the relationships between fruit, vegetables and cancer was conducted by a committee of experts under the auspices of the International Agency for Research on Cancer (IARC) and published in 2003<sup>(1)</sup>. All the good quality case-control and cohort studies available at the time were considered. Among the case-control studies, fruit consumption was found to be protective against cancer of the pancreas and bladder, but not cancer at other sites. However, the findings of the cohort studies show fruit to be protective against oesophageal cancer only. The cohort studies indicated vegetables are not protective against cancer at any site. A number of prospective cohort studies have been published since the IARC review and most provide no support to the notion that either fruits or vegetables are protective against cancer. Importantly, they also show no evidence of harm. Although the large EPIC study, conducted in 400,000 subjects in 10 European countries, failed to find an association between fruit and vegetables and cancer, a relation was observed between the consumption of dietary fibre from all sources and protection against bowel cancer<sup>(2)</sup>. However, findings on fibre in other studies have been very inconsistent and benefits of dietary fibre have not been observed in randomised controlled trials. If the consumption of dietary fibre has a beneficial effect on colorectal cancer risk a lot more research will be required to accurately describe it.

### Error and bias

Understanding the apparent disappearance of the relation between fruits, vegetables and cancer requires consideration of the problems of measurement error and the biases to which the case-control study is prone. Accurately measuring diet is very difficult at the best of times. The food frequency questionnaire is the preferred instrument but is far from perfect, even when

used in the context of a prospective cohort study. The case-control study, however, is retrospective in design – subjects are asked to recall what they were eating five, 10 or 15 years ago, and the recall bias is significant. Response bias is also a problem – response rates in case-control studies are typically low. And then there is 'rumination bias'. If someone has succumbed to a disease they tend to think about it, research it and consider what caused it. As a result they provide much different answers to questions compared to those of control subjects. Another significant source of bias is the Hawthorn effect i.e. the way people respond to questionnaires is pre-conditioned by their pre-conceived notion of what researchers are after. Responses to questions about fruit and vegetable intake can be predicted by education level, female gender and past disease history. Bias leads to estimates of risk that are not real. The overall result of the biases inherent in the early case-control studies may have been to inflate the apparent benefits of fruit and vegetables in relation to cancer risk.

Another possibility is that the protective effect of fruit and vegetables observed in case-control studies in the 1960s was real but driven by very low intakes in some population groups. One recent cohort study in the United States found those in the lowest six percent of vegetable intake had twice the colorectal cancer risk of those with higher intakes. This leaves open the possibility that there may be a threshold of fruit and vegetable intake below which cancer risk is increased. However, the fruit and vegetable consumption of virtually the whole population may now be above the threshold following increases in recent decades, so no association between intake and cancer risk is discernable.

There is a chance that by considering all fruits and all vegetables, then looking at the incidence of all cancers at a site something may have been missed. All tumours of breast and prostate are not the same. There is a possibility that specific foods and nutrients might affect the risk of specific cancer sub-types, though the public health implications of such a relationship would be at the margins. In addition, the relevant window of exposure may be early in life and therefore outside the stage of life studied thus far.

#### References

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