



**Dr Stephen Heggie – The Second WCRF/AICR Expert Report, *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective***

I want to start by showing you some recent nutrition headlines, from the past month or so. “Ginkgo Biloba may help fight against cancer.”; “Red meat may increase risk for non-cardio gastric cancer.”; “Cabbage may protect against pancreas cancer.”; “Phyto oestrogen rich foods protect against cancer.” This one was from yesterday, “Peanuts may prevent cancer.”; and I got up early this morning to look on the Internet and in Sydney there was a headline, “Fish oil may benefit bowel cancer patients.”

Now some of these may actually be true. The problem is how do we know which ones are true and how do we know which ones are not true. And that’s really the focus of my talk today.

Non-communicable diseases are a problem worldwide and while we’ve been able to reduce the cause of death by accidents or communicable disease in the developed world we’ve had very little impact on non-communicable disease. And if we look at the cause of death in the UK by far the biggest cause, major cause is cardiovascular disease but a very close second is cancer, 28% of deaths in men from cancer and 24% of deaths in women.

There have been a number of studies that have shown about one-third of all cancers can be avoided through an improved diet. The question is, what is an improved diet? In 1997 the World Cancer Research Fund published *Food Nutrition and the Prevention of Cancer, a Global Perspective*. This book reviewed all the literature up until that date on food, nutrition and cancer, and it came up with some guidelines and estimated that if you follow these guidelines we could reduce the incidence of cancer by 30-40%. The guidelines are:

1. Choose a diet rich in a variety of plant-based foods
  2. Eat plenty of vegetables and fruit
  3. Maintain a healthy weight and be physically active
  4. Drink alcohol only in moderation if at all
  5. Select foods low in fat and salt
  6. Prepare and store food safely
- And remember don’t smoke or use tobacco in any form.*

We know that our report was very well received by the scientific community from the citation records. The Doll and Peto paper published in 1981 was the seminal paper that really set the scene for the association between nutrition and cancer. And that is currently cited about 100 times a year. The COMA report, Committee on Medical Aspects report, on cancer in the UK was published in 1998, the same time, more or less, as our ’97 report, and that’s currently cited about 25 times a year and our report is cited very close to 200 times a year. So it’s still going strong.

In order to fully understand the complexities of the field we need to ask the question what is cancer? Everybody knows cancer results from faulty DNA and that it’s a disease of the genes. The DNA damage, the mutations, can be either somatic, spontaneous or germline inherited. We also know that very few cancers are inherited and most of them are affected by the environment.



There are many causes of cancer. It's not just one thing. You've got radiation, nutrition, chemicals, toxicity, lack of physical activity, obesity, hormones, ionising radiation, sunlight, viruses, bacteria etc.

So we know there are lots of causes of cancer. Cancer has a long latent period. It doesn't take one or two years, it takes a lifetime to develop. Very often decades before it's even detected. There's no one single event that causes cancer, it's a multi-hit process.

Throughout our lifetime we're exposed to various insults to our DNA, which causes damage. Through a process of repair and cell death that damaged DNA is removed from the body. But eventually at some stage, if there are enough insults to the DNA, the genes that are responsible for repair and for cell death are damaged themselves and there's nothing to stop that damaged DNA resulting in to unregulated cell growth and becoming cancerous.

So there have been six hallmarks or six things that a cell needs to achieve in order to become cancerous:

1. Self-sufficiency in growth signals – that is it shouldn't be reliant on other cells to tell it when to grow.
2. Insensitivity to anti-growth signals – it shouldn't respond to other cells telling it to stop growing.
3. Evasion of apoptosis – the cell shouldn't self-destruct when it gets out of control.
4. Limitless replicative potential – the cell should be able to undergo cell division indefinitely.
5. Sustained angiogenesis – the cell needs to be able to secure the nutrients it needs to grow.
6. Tissue invasion and metastasis – that's where a cancer cell can spread to other parts of the body.

The other important thing to consider are the complexities associated with diet. Firstly, foods are a mixture of different components. Diets are a mixture of different foods. Diet is just one component of lifestyle and food and diet and lifestyle components are correlated. And to give you an example of a lifestyle component when it's correlated with food is we know that smokers tend to eat fewer fruits and vegetables than non-smokers. Also another example would be people who watch a lot of television are more likely to be obese than people who don't watch a lot of television.

We need to consider the types of evidence. There are three broad categories of evidence that are used in this field. Randomised clinical trials are very often considered the best kind of evidence but we also have observational cohort studies and case control studies. And randomised clinical trials are robust but there's a question about how generalisable they are. Observation cohort studies are generalisable but confounding can be a problem, that issue of smoking and fruits and vegetables. Are you measuring whether a person is a smoker or are you measuring whether they eat fruits and vegetables? Case control studies are good for rare cancers and adverse effects but recall bias is a serious problem with case control studies.

So the question is which evidence is the best evidence. Well all types of evidence have advantages and disadvantages and a thorough evaluation looks at all the evidence put together. What do we know about nutrition and cancer? From the first report we know that fruits and vegetables are inversely associated with stomach, colorectal cancer and lung



cancer. Meat is associated with colorectal cancer, physical activity is inversely associated with colon cancer and obesity is associated with breast cancer, endometrial cancer, oesophagus, gall bladder and kidney cancer. And then, of course, alcohol is associated with breast cancer and cancer of the oropharynx. Since 1997, however, there have been some new developments and there are better designed studies. An example is the European Perspective Investigation into Cancer (EPIC), which actually looks at hundreds of thousands of people, asks them what they eat beforehand and then follows up and records what they die of and tries to look for associations. New developments in this area include better markers of cancer risk including the BRACA 1, BRACA 2 genes, better markers of dietary exposure, better evidence of mechanisms and better ways of synthesising the evidence. Fat and cancer are currently under scrutiny as is red meat and cancer. These are all things where we know there's a lot more evidence and there are a lot more studies showing things going one way or the other. Also included is dietary fibre and colorectal cancer, fruits and vegetables, and, of course, as we've heard this morning already, a lot on body shape composition and obesity and physical activity.

So what evidence is actually needed in order to be able to draw firm conclusions? Well evidence of an association in humans is important. It's not good enough only to have experimental evidence from animals. But equally evidence of mechanisms from experiments is important. You can't only have an association that doesn't have an explanation for why the association is there. We need to have a sufficient amount of evidence. One study on its own is not good enough and I think a lot of those headlines that I showed up front were from single studies. We need evidence from different types of study, we need evidence from different populations and from different geographical regions. There should be no substantial unexplained heterogeneity. So we can have some conflicting data but you need to be able to explain why that data is conflicting if you want to draw a conclusion. So a good example there would be an exposure may affect prostate cancer in men but not in women. At least you've got an explanation for why it doesn't occur in women. You need good quality data, well controlled studies, studies that account for confounding, that adjust for confounding, and you need supporting data such as a dose response. Most importantly, any assessment needs to be based on all of the evidence and not just focus on the one that proves the point that you're particularly fond of.

So our second report follows a very systematic approach. It follows a new methodology that wasn't used in the first report. We have a comprehensive literature search that covers all languages and all parts of the world and we look at both the epidemiology and the mechanisms that have been published. What's different about the second report from the first report is we include in physical activity. There wasn't a particular focus for the first report but there has been a lot more evidence that physical activity is associated with cancer so we've included that in the second report. We've also included people who have already had a diagnosis of cancer to see how food nutrition, physical activity affects their likelihood of developing a secondary cancer or their quality of life. We're looking at the determinants of food and activity patterns and the effectiveness of interventions. So we want to know what works and what is the evidence that we have for why it works. So if, for example, there's been an intervention to put cycle paths, does it actually mean that people increase their physical activity? And we've commissioned a separate review on the effectiveness of those interventions.

The process for conducting the report is conducted in three overlapping stages. In the first stage we assembled a group of experts to tell us how to do it. We developed a methodology



that included how to search the literature, how to collect the evidence, how to analyse the evidence, and we compiled that into a literature review specification manual. We took the manual and gave it to research review teams around the world and they're the teams that actually do the work. They collect the data, analyse it. But we specifically asked them not to draw any conclusions. So they just presented the evidence for assessment by a later group. The reports are reviewed both at the protocol stage and at the final report stage by an independent set of peer reviewers and we have an advisory group that advises us on technical or procedural issues during the process. The advisory group is made up of experts from both stage 1 and stage 3. And stage 3 is, of course, where the panel of 21 experts from around the world, take the evidence supplied by the research review teams and draw conclusions and make recommendations. And they're the group that are responsible for the content of the expert report.

The launch date is in autumn 2007 and currently we're about 4/5 years into the process. The Chairman of the panel is Professor Sir Michael Marmot and he's ably assisted by 20 experts from around the world in nutrition, epidemiology, systematic review, public health and cancer biology. Our observers are from the World Health Organisation, the Food and Agricultural Organisation, UNICEF, URCC. Annie Anderson is our observer from URCC, the International Union of Nutrition Sciences and the International Food Policy Research Institute. These observers attend the panel meetings and they participate fully in the panel meetings and make sure they represent the organisations that they serve. So, for example, we need to have an observer from UNICEF because all the people on the panel are adults and they're going to be focused on adults and we need somebody there who's making sure that the needs of children around the world are also considered in our recommendations.

The systematic literature reviews are divided up by cancer site but we also have a review on the determinants of obesity and that's the review that Caroline Summerbell's doing for us at Teesside. We already know that obesity is associated with cancer so we don't just want to be able to tell people don't become obese but we also want to be able to tell them this is what you need to do in order to reduce your risk of becoming obese. And we're looking at other reports and what other reports have said about your risk of getting cancer or your risk of getting other chronic diseases. We have 9 centres in the UK, the USA and Europe doing the reviews for us. To give you an indication of the scale of the task, for most cancer sites the number of references have more than trebled and we're looking at 900 references for breast cancer when in 1997 there were just over 300.

So our mission is to publish the most authoritative global report on food nutrition and cancer. But more than that we want to be able to enable governments and officials, scientists, professionals and all people worldwide to be able to use the report and its recommendations effectively and also to develop and promote a new assessment of the nature of evidence that is needed in order to ascertain the causes of cancer and diseases.

In conclusion then, food nutrition and physical activity is important for cancer risk. The issues are complex to study and single studies never give the full picture. The best guide to practice is through a review of all of the evidence. And the current WCRF report is the best evidence that's obtainable at present and the 2007 report will be the best evidence available in the future.