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Plenary Lecture

Nutritional epidemiology of cancer: accomplishments and prospects

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Nutritional epidemiology of cancer has gone through several stages. Initially, the long latency of cancer, the difficulties in undertaking long-term cohort investigations or ascertaining remote diet in case–control studies, and the absence of convenient intermediate biomarkers of disease, such as cholesterol in cardiovascular diseases, discouraged studies on diet and cancer. Subsequently, however, epidemiological successes in the chemical, viral and occupational aetiology of cancer, and the increasing insight into the sources of variation of diet and dietary information, prompted investigators to undertake both case–control and cohort studies. The results have been mixed. On the one hand, vegetables and fruits have been shown to be inversely associated with several forms of cancer. On the other hand, the information concerning specific macro- or micronutrients in relation to particular forms of cancer has been very limited and mostly inconclusive. There are several reasons for the complexity of investigations of the nutritional epidemiology of cancer and these reasons are briefly considered. An overview of our current understanding of the nutritional causes of cancer is also presented. It is noted that, notwithstanding the substantial gaps in our scientific knowledge, preventive nutritional approaches can be envisaged and they are likely to be moderately successful.

Cancer: Nutrition: Cancer epidemiology: Nutritional epidemiology

The complexities of the nutritional epidemiology of cancer

Epidemiology has had some striking successes in the field of cancer causation, including the identification of several occupational carcinogens (International Agency for Research on Cancer, 1987; Colditz *et al.* 1996), the demonstration of tobacco smoking as the most important human carcinogen, the quantification of the carcinogenic potential of ionising radiation, and the discovery of the role of hepatitis viruses B and C in the aetiology of hepatocellular carcinoma (International Agency for Research on Cancer, 1994). These successes have generated an optimism that nutritional causes of cancer could also be identified with the same clarity. The earlier successes of epidemiology, however, have been possible because one or more methodologically favourable conditions were met:

extreme exposures had taken place in unusual and frequently unfortunate natural experiments, such as heavy irradiation following nuclear explosions or intense radiotherapy, or occupational exposure to very high levels of compounds that turned out to be human carcinogens;

groups of unexposed persons could be easily identified, in order to provide a referent category, such as never smokers in the study of tobacco carcinogenesis and non-carriers of hepatitis B or C viruses in the study of liver carcinogenesis;

exposure could be reliably assessed through laboratory measurements, such as ascertainment of hepatitis B surface antigen status, or through recording of fairly stable and easily remembered exposure metrics, e.g. no. of cigarettes per d.

Nutritional exposures have none of these favourable attributes; there are neither very extreme exposures nor completely unexposed individuals, and recollection of diet is hindered by the complex and multidimensional nature of this exposure. Considerable progress in identifying and

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measuring the determinants of dietary variability, as assessed through different dietary instruments, did not overcome the problem, although it allowed the delineation of the problem (Willett, 1998). An additional problem concerning diet in relation to cancer, in contrast to diet in relation to CHD, is the absence in the cancer field of important intermediate biomarkers that exist in the cardiovascular field, such as blood cholesterol, its fractions and homocysteine. There are several other reasons that may help explain why the nutritional epidemiology of cancer is such a complex and demanding field, and many of them are briefly discussed in the following paragraphs.

Instruments for ascertainment of past diet are far from optimal. Random misclassification of dietary factors may, therefore, be extensive, leading to substantial underestimation of genuine causal effects. On the other hand, random misclassification may be so extensive as to substantially reduce the power of a study, to the extent that an apparently positive result could reflect as much a statistical artefact (alpha error) as a biologically genuine association. Furthermore, as there are many nutritional factors with common dietary origins, mutual confounding among them is extensive and complex, and random misclassification of nutritional factors may substantially reduce the ability to control their confounding influences.

To further complicate the situation in the nutritional epidemiology of cancer, when a particular cancer has several independently-operating nutritional causes, the relative risk associated with any particular nutritional cause decreases with the prevalence or the abundance of the other nutritional causes. On the contrary, when two factors are jointly necessary for the causation of a particular cancer, for example an unknown initiator and a particular food item or nutrient as promoter, the relative risk associated with the nutritional factor increases with the prevalence or the abundance of the unknown initiator (Rothman, 1976).

Energy intake may be an important cause, an equally important confounder or an indicator of bias, particularly in case–control studies. Control of energy intake is thus necessary whenever particular foods or nutrients are evaluated. When controlling for energy intake, however, it is impossible to distinguish between the effect of the nutritional factor the intake of which is increased and the effect(s) of the nutritional factor(s) the intake of which is decreased. Note that a change is necessary to assess causation, but with energy kept constant, a change in a particular food or nutrient requires a reciprocal change in other foods or nutrients (Willett & Stampfer, 1986; Wacholder *et al.* 1994).

Finally, inter-individual variability of certain food items or nutrients may be too small in comparison with the corresponding intra-individual variability, thus considerably reducing the power of analytical epidemiological studies. Indeed, in many populations diet may be too uniform, and aetiologically-important food items may be too common or too rare, to allow statistical substantiation of risk differentials with standard analytical epidemiological studies. In other instances, the exposure *v.* response curve describing cancer risk in relation to a particular nutritional variable may be sigmoid, implying the existence of thresholds below or above which no association could be documented between the two variables. Furthermore, food patterns, for instance the Mediterranean diet, may have effects considerably different from those of the constituent foods or nutrients because of complex interactions.

Epidemiological evidence on the nutritional aetiology of cancer

Several patterns have emerged from the many epidemiological studies that have been undertaken during the last 30 years on the relationship between diet and cancer, and these patterns have been summarised in Tables 1–4. The associations are distinguished into convincing, probable and possible, and can be either positive (increasing intake of the dietary factor increases cancer risk) or inverse (increasing intake of the dietary factor reduces cancer risk; Willett & Trichopoulos, 1996; World Cancer Research Fund and American Institute for Cancer Prevention, 1997).

Table 1 refers to the cancer risk implications in relation to the intake of major food groups. Vegetables and, to a slightly lesser extent, fruits are inversely associated with risk for several forms of cancer. There is also evidence that intake of red meat increases the risk for some forms of cancer, particularly cancer of the large bowel.

The collective evidence for macronutrients, as summarised in Table 2, is considerably weaker for obvious reasons. In the absence of long-term randomised intervention studies, the evidence concerning macronutrients is derived from the evidence concerning food groups, with additional uncertainties introduced by variability in food composition tables and analytical methods, as well as by uncontrollable confounding due to the possible operation of unidentifiable or immeasurable factors that tend to coexist with some of the macronutrients.

Table 3 summarises the risk implications for major forms of cancer by intake of selected micronutrients. Although the study of micronutrients shares the same constraints as that of macronutrients, Table 3 appears more informative than Table 2 for three reasons, two of which are purely artificial. First, of the many micronutrients, only those for which some evidence exists are included in the table. Second, several carotenoids are included in the single column dedicated to these compounds. Thus, the evidence for lung cancer mostly refers to β-carotene, whereas the evidence for prostate cancer refers almost exclusively to lycopene. The third reason, which is more substantive, is that the physiological and pathophysiological effects of certain micronutrients have been extensively studied, so that the criterion of biological plausibility can be more successfully relied on for micronutrients rather than for macronutrients. For instance, several carotenoids, vitamins C and E, and Se have been intensively studied on account of their experimentally-documented antioxidant potential.

Table 4 refers to non-nutrients and nutritional correlates such as height, obesity and physical activity. Entries in the same column do not imply identical compounds or processes. For instance, alcohol causes liver cancer through cirrhosis, cancer of the oesophagus and larynx mostly through interaction with tobacco smoking, and cancer of the breast possibly by increasing levels of oestrogens. Moreover, coffee and maté are mixtures that have both

similarities and differences. Last, the effect of obesity may refer to stages of carcinogenesis that are not necessarily identical in the various forms of cancer. At the extreme, obesity among premenopausal women reduces risk of breast cancer, whereas it considerably increases this risk among post-menopausal women.

Some readers may be surprised by the absence of a table referring to additives and contaminants that are frequently reported as carcinogens in the lay press. There are several reasons for this absence. First, the intake of additives and contaminants cannot be documented in most epidemiological research. Second, additives and contaminants are extensively scrutinised in laboratory assays and whenever evidence incriminates them as carcinogens, they are removed from the diet. Third, the alleged breast carcinogenicity of organochlorine compounds, which can be measured in the blood or adipose tissue, has not been documented in large and sophisticated epidemiological investigations, nor has there been direct epidemiological support for a role of nitrosamines in human carcinogenesis. At this stage, the only additive which is likely to play a major role in human carcinogenesis is salt. Among dietary contaminants, only aflatoxin has been conclusively linked to hepatocellular carcinoma and may be causing a non-negligible fraction of liver cancer in developing countries. The suspicion that chlorination by-products in drinking water may be involved in urinary bladder carcinogenesis has not been documented, but is currently under investigation.

Table 1. Risk implications for major forms of cancer by consumption of major food groups

Cancer site	Cereals	Pulses	Vegetables	Fruits	Meat (red)	Fish	Dairies	Eggs	Sugars
Mouth and pharynx			↓↓↓	↓↓↓					
Naso-pharynx									
Oesophagus			↓↓↓	↓↓↓					
Stomach			↓↓↓	↓↓↓					
Large bowel			↓↓	↓	↑↑			↑	↑
Liver			↓						
Gall bladder									
Pancreas			↓	↓	↑				
Larynx			↓↓	↓↓					
Lung			↓↓↓	↓↓					
Breast			↓↓	↓↓					
Endometrium			↓	↓					
Cervix uteri			↓	↓					
Ovary			↓	↓					
Prostate			↓		↑		↑		
Urinary bladder			↓↓	↓↓					
Kidney			↓		↑				

↓↓↓, Convincing inverse association; ↓↓, probable inverse association; ↓ possible inverse association; ↑↑↑, convincing positive association; ↑↑, probable positive association; ↑, possible positive association.

Table 2. Risk implications for major forms of cancer by consumption of macronutrients

				Lipids		
Cancer site	Protein	Starch	Fibre	Saturated	Monounsaturated	Polyunsaturated
Mouth and pharynx						
Naso-pharynx						
Oesophagus						
Stomach		↑				
Large bowel	↑		↓	↑		
Liver						
Gall bladder						
Pancreas	↑	↑	↓			
Larynx						
Lung				↑		
Breast					↓	
Endometrium			↓	↑		
Cervix uteri						
Ovary						
Prostate				↑		
Urinary bladder						
Kidney						

↓↓↓, Convincing inverse association; ↓↓, probable inverse association; ↓, possible inverse association; ↑↑↑, convincing positive association; ↑↑, probable positive association; ↑, possible positive association.

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Table 3. Risk implications for major forms of cancer by consumption of selected micronutrients

Cancer site	Vitamin A and carotenoids	Folate	Vitamin C	Vitamin D	Vitamin E	Ca	Se
Mouth and pharynx			↓				
Naso-pharynx							
Oesophagus	↓		↓				
Stomach	↓		↓↓				
Large bowel	↓	↓		↓	↓	↓	
Liver							
Gall bladder							
Pancreas			↓				
Larynx							
Lung	↓ (β-carotene)		↓		↓		↓
Breast	↓						
Endometrium							
Cervix uteri	↓		↓		↓		
Ovary							
Prostate	↓↓ (lycopene)				↓		↓
Urinary bladder							
Kidney							

↓↓↓, Convincing inverse association; ↓↓, probable inverse association; ↓, possible inverse association; ↑↑↑, convincing positive association; ↑↑, probable positive association; ↑, possible positive association.

Table 4. Risk implications for major forms of cancer by exposure to selected non-nutrients and nutrition-related indicators

Cancer site	Alcohol	Salt	Coffee	Hot drinks	Height	Obesity	Physical activity
Mouth and pharynx	↑↑↑		↑ (maté)				
Naso-pharynx		↑↑					
Oesophagus	↑↑↑		↑↑ (maté)	↑↑			
Stomach	↑	↑↑↑					
Large bowel	↑				↑	↑	↓↓↓
Liver	↑↑↑						
Gall bladder						↑↑	
Pancreas						↑	
Larynx	↑↑↑						
Lung							
Breast	↑↑				↑↑↑	↓↓, ↑↑↑	↓
Endometrium						↑↑↑	
Cervix uteri							
Ovary							
Prostate					↑	↑	↓
Urinary bladder			↑				
Kidney						↑↑	

↓↓↓, Convincing inverse association; ↓↓, probable inverse association; ↓, possible inverse association; ↑↑↑, convincing positive association; ↑↑, probable positive association; ↑, possible positive association.

The future of the nutritional epidemiology of cancer

We are uncertain about the prospects of the nutritional epidemiology of cancer. In theory, randomised trials of micronutrients or non-nutrients should be able to provide strong evidence about the carcinogenicity, anti-carcinogenicity or lack of demonstrable effect of particular compounds. However, power limitations may hinder the demonstration of existing effects for one or more of the reasons previously indicated. On the other hand, statistical documentation of a particular association is rarely convincing without replication, and randomised prevention studies are rarely done and even more rarely replicated, since these studies, in contrast to therapeutic trials, are expensive and complicated undertakings. For example, many scientists may consider as credible the evidence derived from randomised studies that Se and vitamin E could prevent prostate cancer (Clark *et al.* 1998; Heinonen *et al.* 1998), but very few scientists are eager to argue for the implementation of these findings in clinical practice.

In the absence of randomised prevention trials, it is difficult to foresee major methodological breakthroughs in observational epidemiological studies of diet and cancer. Identification of intermediate biomarkers is clearly an objective, but there are no promising leads; even colo-rectal adenomas have not been a satisfactory intermediate biomarker for colo-rectal cancer. Some methodological approaches have been advocated, e.g. multiple measurements of dietary intakes with independent sources of error,

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in an effort to better estimate the variables thought to be of critical importance. Thus, if two independent methods of dietary ascertainment (e.g. food-frequency questionnaire and blood levels) generate correlation coefficients with the true, but unmeasured, dietary intake in the order of 0·2–0·3, their joint utilisation could increase the correlation coefficient to more than 0·5 (Marshall *et al.* 1980). Other investigators have argued for the creation of hybrid ecological–analytical designs, in order to exploit the advantages of both approaches, i.e. higher genuine variability of exposure and better control of confounding respectively. Other suggested approaches can be found in specialised textbooks (Willett, 1998).

Prevention of diet-related cancers

According to studies in migrants and ecological investigations, up to 30 % of cancer mortality in developed countries could be attributed to diet. Notwithstanding our limited knowledge on the mechanisms of diet-related carcinogenesis, we can clearly outline the prudent diet that reduces cancer risk in human subjects. This diet should be high in vegetables, fruits, pulses and cereals, low in red meat and salt, and low in saturated fat of animal origin. Added lipids should be of plant origin and, among them, olive oil has a long safety record. Alcohol, which is known to protect against cardiovascular diseases, but also contributes to the causation of cancer at several sites, including the breast, should be consumed in moderation, particularly by women. Excess body weight should be avoided, preferably by increasing physical activity, which in itself can reduce the risk for colo-rectal cancer and perhaps other forms of cancer as well. Regular physical activity during childhood and adolescence may also slow down excessive growth, as reflected in attained height, and have beneficial consequences on several cancer types.

As indicated, it has been estimated that about 30 % of mortality from cancers of all types can be explained by diet, and a similar proportion has been attributed to tobacco smoking. Yet, there is a substantial difference in the way the two estimates are derived. The proportion attributable to tobacco smoking is derived directly from analytical epidemiological studies, while that attributable to diet is derived from ecological evidence and migrant studies and it is, therefore, indirect. Moreover, attribution to tobacco smoking is by definition unidimensional, whereas diet is complex and multidimensional. This factor makes it difficult to directly calculate or estimate the proportion of cancer mortality in a particular setting that could be prevented through adoption by a certain proportion of the population of a prudent diet, however these conditions are defined. Several approaches have been used, but the simplest relies on the calculation of a linear score that summarises the information about the dietary aetiology of a particular cancer. Thus, the score is calculated by adding the consumption of foods or food groups that increase risk, and subtracting the consumption of foods or food groups that decrease risk for the specific cancer. Simple algebraic addition of frequency of consumption or multiple logistic regression-derived coefficients can be used. Individuals can then be distributed by linear score values, with increasing values indicating increased risk, and can be further distinguished into, for example, quintiles (Trichopoulos *et al.* 1985). Suppose that the high-risk quintile for, for example, colo-rectal cancer has a score of about 5. The quintile next to the high-risk quintile has a score of about 4 etc. Thus, between individuals consuming low quantities of vegetables and fruits and high quantities of red meat etc., and those who consume high quantities of vegetables and fruits and low quantities of red meat etc. the relative risk is about 5. If we know, or can predict, the extent of adoption of a prudent diet, e.g. that one-third of individuals in each category, except the first category, will move to the adjacent lower risk category, we can calculate the expected risk reduction by applying a simple formula suggested by Wahrendorf (1987). Using this approach, Trichopoulou *et al.* (2000) have found that widespread adoption of the Mediterranean diet could reduce the overall mortality from colo-rectal cancer in northern Europe and North America by about 25 %. The approach is crude and cannot accommodate latencies and interactive effects. Nevertheless, it allows realistic predictions that are compatible with the ecological patterns around the world.

Conclusion

Nutritional epidemiology of cancer has made considerable advances over the last three decades, and the results of the relevant studies permit an outline of the prudent diet in terms of food groups. Advances at the level of nutrients have been less evident, and relied largely on interventional, rather than observational, epidemiology. Unless intermediate biomarkers for particular cancers can be established, it is difficult to see in the near future advances comparable to those of the past. Preventive randomised trials provide a theoretical answer, but these trials are very difficult to undertake and even more difficult to replicate in order to reach generally acceptable conclusions.

References

Clark LC, Dalkin B, Krongrad A, Combs GF Jr, Turnbull BW, Slate EH, Witherington R, Herlong JH, Janosko E, Carpenter D, Borosso C, Falk S & Rounder J (1998) Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *British Journal of Urology* **81**, 730–734.

Colditz G, DeJong W, Hunter D, Trichopoulos D & Willett W (editors) (1996) Harvard Report on Cancer Prevention Volume 1: Causes of Human Cancer. *Cancer Causes and Control* **7**, Suppl. 1, pp. 1–59.

Heinonen OP, Albanes D, Virtamo J, Taylor PR, Huttunen JK, Hartman AM, Haapakoski J, Malila N, Rautalahti M, Ripatti S, Maenpaa H, Teerenhovi L, Koss L, Virolainen M & Edwards BK (1998) Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *Journal of the National Cancer Institute* **90**, 440–446.

International Agency for Research on Cancer (1987) *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42*, Suppl. 7. Lyon, France: IARC.

https://doi.org/10.1079/PNS2002145 Published online by Cambridge University Press

International Agency for Research on Cancer (1994) *Hepatitis viruses*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 59, Lyon, France: IARC.

Marshall J, Priore R, Haughey B, Rzepka T & Graham S (1980) Spouse-subject interviews and the reliability of diet studies. *American Journal of Epidemiology* **112**, 675–683.

Rothman KJ (1976) Causes. *American Journal of Epidemiology* **104**, 587–592.

Trichopoulos D, Ouranos G, Day N, Tzonou A, Manousos O, Papadimitriou Ch & Trichopoulou A (1985) Diet and cancer of the stomach: a case-control study in Greece. *International Journal of Cancer* **36**, 291–297.

Trichopoulou A, Lagiou P, Kuper H & Trichopoulos D (2000) Cancer and Mediterranean dietary traditions. *Cancer Epidemiology Biomarkers and Prevention* **9**, 869–873.

Wacholder S, Schatzkin A, Freedman LS, Kipnis V, Hartman A & Brown CC (1994) Can energy adjustment separate the effects of energy from those of specific macronutrients? *American Journal of Epidemiology* **140**, 848–855.

Wahrendorf J (1987) An estimate of the proportion of colo-rectal and stomach cancers which might be prevented by certain changes in dietary habits. *International Journal of Cancer* **40**, 625–628.

Willett W (1998) *Nutritional Epidemiology*, 2nd ed. New York: Oxford University Press.

Willett W & Stampfer MJ (1986) Total energy intake: implications for epidemiologic analyses. *American Journal of Epidemiology* **124**, 17–27.

Willett WC & Trichopoulos D (1996) Nutrition and cancer: a summary of the evidence. *Cancer Causes and Control* **7**, 178–180.

World Cancer Research Fund and American Institute for Cancer Prevention (1997) *Food, Nutrition and the Prevention of Cancer: A Global Perspective*. Washington, DC: World Cancer Research Fund and American Institute for Cancer Prevention.