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Achievements and future of nutritional cancer epidemiology

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We consider some of the earlier work and some recent results on diet and cancer (since the 2007 WCRF/AICR report on Diet and Cancer), discuss challenges facing nutritional cancer epidemiology, and consider the field from the perspective of the need to apply what we know in cancer control. We highlight 2 current difficulties; first, we are uncertain on the stage of carcinogenesis on which many nutritional factors act, second, we often do not know what dose of a nutritional factor is needed to achieve its expected protective effect in humans. Part of the difficulty is the measurement error associated with food frequency questionnaires. Calibration studies (as in the European Prospective Investigation on diet and Cancer) have helped to reduce this, and pooled studies have helped to clarify associations. However, there is too little work on new biomarkers of nutrition; with the new techniques available (especially proteomics, and metabolomics) it should be possible to identify more and better biomarkers that could be used in repeated blood or urine samples and give very good information on diet. In cancer control we need to determine how to reduce the prevalence of obesity and increase physical activity in populations, not whether they are causal factors. This could be achieved by community-based interventions linked to some of the new cohort studies being initiated. We conclude we have reached the stage in nutritional cancer epidemiology where we need to concentrate more on applying the lessons we have learnt, than in seeking new aetiological associations.

In the 2007 report of the World Cancer Research Fund/ American Institute of Cancer Research, 9 major recommendations were made aimed at cancer prevention, largely based upon extensive overviews of findings from nutritional epidemiology research.[1] A subsequent report from the same organizations provided recommendations on policy.[2] These 2 reports represent major achievements of nutritional epidemiology, a field which has already identified several causal associations relevant to cancer control. It is not the intent of this mini-review to attempt a replication of this extensive body of work. Rather, we wish to consider some of the earlier work and some recent results (since release of the 2007 WCRF report) with which either one or other of us was involved, to discuss challenges facing nutritional cancer epidemiology, and consider the field from the perspective of the need to apply what we know in cancer control.

Historical Background

By the early 1980s, there was a good deal of evidence that diet might be important in cancer causation by analogy with animal studies and from some epidemiology studies.[3] However, the prevailing opinion among the leaders of cancer epidemiology was that human dietary studies were extremely difficult, as people varied so much in their ability to recall what they eat, that you could not rely on the data you collected. In effect we were being told that the data would be dogged by bias and misclassification, aspects that have not gone away with time. Indeed, the 2 major concerns in analytical nutritional epidemiology are still unaccounted confounding and substantial dietary measurement error.

Increasingly, the prevailing view has become that bias makes case-control studies of diet and cancer uninterpretable, so that they should not be considered in determining causality,[4,5] though not all fully share that view.[6] Recall bias is most commonly mentioned (cases being more likely to recall possible causal factors than controls) but response bias should not be neglected (if individuals with healthy lifestyles are more likely to participate as controls and they have higher intakes of potentially protective factors than those who are less health conscious, spurious associations for these dietary factors could occur). However, cohort studies tend to be more affected by misclassification,[7] which may explain their tendency to be more often negative than case-control studies, in which more detailed data can usually be collected. A comparison of the first report of the World Cancer Research Fund/American Institute of Cancer Research[8] with the second[1] reveals that more reliance was placed in the first report upon case-control studies, but they were more likely to be discounted in the second, a viewpoint that also prevailed in an IARC working group evaluation of Fruits and Vegetables.[9]

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Nearly all early studies of diet and cancer were of the case-control type, in the case of our studies in Toronto based upon an extensive interviewer-administered dietary questionnaire supported by "food models" that provided quantification of intake, and then run through a specially developed dietary data bank to provide estimates of intake of macro- and micro-nutrients.[10] These led to some controversies, especially over energy adjustment, which might be a suppressing difference in metabolism between cases and controls, with cases consuming more energy-dense foods than controls, though this could be related to a consequence of the cancer itself, rather than being a cause of it. However, energy adjustment won the day, though recently in at least 3 cohorts, an effect of energy intake has been found for breast cancer,[11–13] in one, restricted to pre-menopausal women.[13] However, for most studies, we could not find an effect of energy intake, thus adjustment did not really make a difference. Sometimes, however, an effect of energy intake is not seen even in situations where there should be one, *e.g.*, energy intake and risk of obesity,[14] confirming the probability of substantial measurement error in food frequency questionnaires.

Dietary Aspects of the Aetiology of Cancer

The dietary data banks enabling us to make estimates of consumption of macro- and micronutrients does not necessarily mean that associations derived from analyses of these estimates are causal. Although the fiasco associated with beta-carotene[15,16] has tended to be explained by metabolic overload when pharmacological doses were given, resulting in enhancement of carcinogenesis compared to the protective effect of physiological doses derived from plant foods,[17] this ignores the fact that some studies could not find a protective effect of beta-carotene from food when the food themselves were considered as the subject of interest.[18] Contrasting results from dietary intervention trials and observational epidemiology have since been replicated *e.g.*, for fibre[19] and folate,[20] though the endpoint in the trials, adenomatous polyps, may simply have been at the wrong stage of carcinogenesis, *i.e.*, dietary factors may affect progression from polyps to cancer, a transition not studied in trials that used adenomatous polyps as the endpoint. The other possibility is that the trials were assessing the addition of a micro-nutrient to a group of subjects already consuming an adequate quantity of the micro-nutrient, while the observational studies were able to assess the effect of consumption of lower levels of the micronutrient and identify a protective effect of adequate consumption.[21] However, the possibility that dietary supplements can be hazardous, whereas levels normally consumed in adequate diets may be protective, has again been raised in a trial of folic acid supplements which increased the risk of prostate cancer, whereas baseline dietary folate was inversely associated with the risk of prostate cancer.[22]

These possibilities highlight 2 current difficulties, first, we are uncertain on the stage of carcinogenesis on which many nutritional factors act, and second, we often do not know what dose of a nutritional factor is needed to achieve its expected protective effect in humans.

In the case of beta-carotene the evidence from the trials of lung cancer prevention suggests that the penultimate stage of carcinogenesis was affected. However, although it is clear that the dose of beta carotene used in the trials was too high, we remain uncertain as to whether the lower doses found in carrots and other plant foods are protective. For colorectal cancer, we know from migrant studies that changes of incidence on migration can be detected within 10 years, suggesting a late stage effect, perhaps too late for the nonadenoma to adenoma transformation, but not too late for the adenoma to cancer transformation (at least for those cancers that develop from adenomatous polyps). However, for breast cancer, changes in incidence occur on migration only fully after 2 generations, suggesting that if dietary factors are important, they are relevant in early life, so breast cancer is probably a poor subject for intervention trials of incidence, we need to pay more attention to long term observational studies, or find biomarkers that reflect nutritional changes in early life.

Many of us have made repeated and so far largely unanswered calls for the identification of biomarkers of nutritional intake (analogous to the critical importance of cholesterol and its variants in cardiovascular disease epidemiology). The problems are:

- in interventional studies we are still using precancerous lesions as endpoints (answering the question only whether precancerous lesions can be prevented rather than cancer); we need more studies with cancer as the endpoint;
- there is too little work on new biomarkers of nutrition; with the new techniques available (especially proteomics and metabolomics) it should be possible to identify more and better biomarkers that could be used in repeated blood or urine samples and would give very good information on diet.[23]
- the field of gene-diet interaction is evolving very slowly and for many relevant pathways we do not really have good information about interactions that could affect disease risk.

Methodological Issues

Critical issues are minimizing the measurement error associated with food frequency questionnaires (FFQ), or even replacing them. For example, Bingham *et al.* found good correlation between biomarkers and diet assessed by food diaries but not with FFQ-derived data,[24] while in a study of gastric cancer, dietary vitamin C intake was not inversely related to cancer risk, while plasma levels were.[25] Nutritional biomarkers in blood samples reflect the metabolic situation related to this nutrient (including bioavailability and, at least, first-pass metabolism, including genetic characteristics) and provide an objective measurement. However, depending on the nutrient of interest, blood-based markers often reflect the short-term

situation. Usually, in cohort studies blood samples were collected only once, *i.e.*, at recruitment, and this may not be sufficient to describe long-term exposure by means of biomarker measurements. Thus, repeated sampling of biospecimens both for better characterization of nutrient supply at baseline as well as for monitoring of changes in diet over time, is a major challenge for future cohort studies. This is also true for urinary samples which are the preferred medium for some minerals, dietary substances with very short half-life time, and others, including metabolomic measurements; although difficult to achieve, 24-hr urine samples that were collected repeatedly would be very valuable for diet-cancer research.

So far, the progress on identification and validation of new biomarkers of nutrition by means of modern methods like proteomics or metabolomics (which are still under technological development) is progressing more slowly than expected, though some success is already visible (Jenab et al. 2009; Fave et al. 2009; Holmes et al., 2008).[26–28] However, it still represents a very promising field where high-throughput techniques will allow investigations in the frame of large epidemiological settings at acceptable costs.

There are many large cohort studies with stored banks of biospecimens in place or planned. Many feel it is these biobanks that will yield most advances in the future. However, if sufficient attention in developing these new cohort studies is paid to the dietary instrument used, the data eventually derived from them could be of equal or even greater value in the future, though care may need to be taken to ensure that the dietary data are updated periodically, especially as follow-up continues on the cohort, as dietary changes could affect the associations with cancer relating to late-stage carcinogenic effects. When the originally administered diet questionnaire was readministered in the Heidelberg component of the European prospective investigation on diet and cancer, after a mean follow-up of 69 months, there was a shift toward a more healthy diet compared to the baseline but consistently for food groups, 60–70% of the participants in both genders were reclassified to the same or an adjacent quintile of intake.[29] These fairly high correlation coefficients indicate good agreement between baseline and repeat measurements in an adult population aged 35–65 years at enrolment after a 5-year interval, so that repeated measurements may not have to be done too often. However, a careful consideration of the assessment period and the future use of updated dietary information are necessary since diet–disease relationships may be attenuated (rather than strengthened) when the critical time period for disease development is not studied.

A relatively recent feature of modern epidemiology has been to combine the findings from reported studies by meta-analytic techniques. A further refinement is to collect the data from the individual studies and perform a pooled analysis. An early example was that of Howe with a combined analysis of 12 case-control studies of diet and breast cancer,[30] and then 13 of diet and colorectal cancer.[31] More recently this approach has been applied to cohort studies. One concern with pooled analyses is that they may combine datasets of different quality (dietary questionnaires with limited and more extensive enquiries on food items), yet there is little or no control for this. For example, 2 components of the Nurses Health Study, the initial initiated in 1980 and followed to 1986 with 61 food items in the baseline questionnaire, and the later following an updated questionnaire administered in 1986 with 131 items are included in the Pooling Project, being regarded as 2 separate cohorts.[32] Indeed, the number of food items on the questionnaires used in the studies contributing to the Pooling Project range from 45 in the New York State Cohort to 276 in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study.[32] Thus although in this largest such endeavor individual study reports are cited and tested for heterogeneity of effect, there may be major differences in the findings around the null value, with the largest datasets tending to swamp the smaller.

One of the major issues therefore is the extent one can, in conducting a cohort study, impose on the participants to provide sufficient detail on their diet. In our case control studies in Canada in the 1980s, we were able to encourage respondents to sit through a one and a half hour long interview, with questions on over 200 food items,[10] with no apparent effect on the response rates. When we began to evaluate possible questionnaires for use in a cohort study, we eventually concluded we could achieve good concordance using a self-administered questionnaire with just 69 food items.[33] We recognized that reducing the numbers of food items would increase misclassification, but there seemed no other option; although we had piloted using interviewers for the dietary enquiry in the cohort, in the end, we could not justify the requirement for resources, as we moved from case control studies of 100s, to cohort studies of 1,000s. So a limited self-administered questionnaire was used, a similar experience to EPIC and other groups. Endeavors have been made in EPIC to calibrate the data obtained from the self-administered questionnaires by using a validated 24-hr recall on a random sample of each contributing group. This process serves to help to control for the use of different questionnaires in the various centers and the heterogeneous nature of diet across different geographical regions, enabling the diet/disease association to be evaluated by exploiting the variability of intake over the entire study.[34] However, this process does not entirely solve the problem of misclassification. In the future, more precise methods have to be applied in cohort studies that will allow a valid characterization of individual diets over longer time periods. Such methods include diet records or 24-hr diet recalls which can take care of day-to-day and seasonal variation if repeatedly applied; in combination with new technical possibilities (web-based option, mobile phone use); repeated 24-hr diet recalls are among the most promising options.

The conundrum of fruits and vegetables

When one of us reviewed the evidence on prevention of cancer for the Ontario Government in the early 1990s, one of

the most important set of potential protective factors identified were fruits and vegetables.[35] The evidence at the time seemed conclusive, later confirmed by the first WCRF/AICR review, in which a strong recommendation was made on the protective effect of plant foods.[8] In our early case control study of colorectal cancer we found an inverse association for cruciferous vegetables in females for colon cancer, but not for males, but we did not evaluate potential associations for all vegetables or for vegetables combined with fruits.[36] In a case-control study of diet and lung cancer we found a protective effect of vegetables, but not of fruits.[18] The effect of fruits and vegetables upon lung cancer was later evaluated in the EPIC study, where a protective effect of fruits was found, but not of vegetables.[37] A similar association with fruits (and a weaker one with vegetables) was found in the pooling project.[38] However, when these studies were considered by an IARC working group, it was concluded that residual confounding by smoking could not be excluded, in spite of the care taken in all these analyses to adequately adjust for smoking.[9] Such a conclusion in effect means that it may not be possible ever to fully adjust for the effect of a strong confounder, either because the baseline data collected may not have been adequate, or we can not take note of changes in smoking after baseline (often true for diet also, as indicated above) or that our analytic methods are inadequate to adjust for confounding. We find such conclusions depressing, all recognize that no single study, or even combination of studies, can be conclusive, but we have to be prepared to draw conclusions on what we have, and sometimes act upon them, as ignoring even poor evidence, is to proclaim that we have no evidence at all. Nevertheless this philosophy persisted in the second report of the WCRF/AICR, though fortunately, the authors did not refrain from making recommendations for action, even on fruits and vegetables![1] Perhaps we need to recall that it has been agreed, by those specializing in occupationally induced cancer, that confounding by smoking does not prevent conclusions of the causality of associations of other carcinogens and cancer.[39] Is there not a risk that we may ignore causal associations in diet and cancer because they are weak, and strongly affected by misclassification, while over-emphasizing the possibility of confounding by a variable that we are able to measure with better precision than diet?

In practice, since the IARC conclusions were drawn, evidence has continued to accrue that fruits and vegetables may be protective for lung cancer,[40] upper aero-digestive tract and head and neck cancer[41,42] and possibly for stomach cancer and oesophageal adenocarcinoma,[43] as well as colorectal cancer, especially for distal colon cancer,[44] but not for renal cell cancer.[45]

Foods and dietary patterns

Our early passion for analyses of estimated macro- and micronutrient consumption is being expanded by analyses of specific food consumption and of dietary patterns, important if we use the data to make recommendations to the public. On the basis of the currently used data from food frequency questionnaires, we may be able to distinguish dietary patterns or specific intake of certain foods with more precision than we can measure the intake of macronutrients.

An example is the recent emphasis on positive associations of colorectal cancer with red and processed meat consumption,[1] largely based upon relatively recent cohort studies, *e.g.*, that in EPIC,[46] though there were indications of this in our early case-control study for individual red meat items.[36] Indeed, the adverse effects of red meat may not be restricted to colorectal cancer, recent studies have found that red meat increases the risk of stomach cancer[47] while among subjects with the rapid NAT2 acetylation genotype, higher levels of heterocyclic amines, found in well-done meat, are a risk factor for bladder cancer.[48]

It has been long recognized that many cancers tend to be at higher rates with Western dietary patterns, as recently reconfirmed in a multi-site case-control study in Uruguay,[49] it has also been found that adherence to a Mediterranean diet is associated with less obesity, and thus probably of cancers induced by obesity, especially colorectal and breast cancer in postmenopausal women.[50] Further, a dietary pattern characterized by low consumption of bread and fruit juices, and high consumption of processed meat, fish, butter, other animal fats and margarine, explaining >42% of total variation in fatty acid intake, was found to be associated with a 2-fold risk of breast cancer (hazard ratio 2.00; 95% CI 1.30, 3.09), comparing extreme tertiles of the pattern score.[51] The findings from this study suggest that our early case control study that reported an effect of dietary, and especially saturated fat, in increasing the risk of breast cancer, was correct,[52] a conclusion buttressed by a metaanalysis,[53] and by findings from the EPIC study.[54]

There has been much interest in whether dietary fiber is important in reducing the risk of colorectal, and perhaps other cancers, though it was recognized that it may not be fiber that was protective, but the foods within which fibers are found. Two reports from the EPIC study provide evidence on the potential protective effect of dietary fiber. In one, it was fiber from cereals but not other sources that appeared to be protective for gastric cancer,[55] in the other, after calibration with detailed dietary data, the adjusted relative risk for colorectal cancer for the highest versus lowest quintile of fiber from food intake was 0.58 (0.41–0.85).[56] No food source of fiber was significantly more protective than others.

A relatively limited area of enquiry has been the effects of diet on prognosis of cancer. For breast cancer, obesity appears to result in an impaired outcome[57] as does a high prediagnosis fat intake.[58] It is possible that many nutritional factors acting at the later stages of carcinogenesis affect not only the risk of developing cancer, but also its subsequent progression.

Needed current actions for cancer control

For cancer control, the recommendations of the WCRF/AICR[2] represent the state of the art. Several of them are also

relevant to the control of cardiovascular disease and that on breast feeding for general health, as well as cancer. However, it is likely that they do not represent all that could be done nutritionally to facilitate the control of cancer and other non-communicable diseases, so that more research is needed.

In such research, we need to understand the reasons for some of the anomalies that persist, especially within and between countries. We need to pay more attention to the trend in nutritionally associated cancers in developing countries, for example the trends in colorectal cancer incidence as an index of success or failure of a population-based nutritional intervention. We can use the knowledge we have on nutritional causes of cancer in western countries to make policy recommendations in low and middle income countries, though the ways to implement these should be a major focus of local research. We do not know how to apply the knowledge we have on nutrition and cancer in most populations, so that a major part of our research agenda needs to turn to intervention studies in populations to obtain this knowledge, while continuing to refine our studies so that we can make more specific and directed recommendations.

The future of nutritional epidemiology

Several new cohort studies are being initiated, both in Europe and North America. Almost invariably dietary enquiries are included, and all collect biospecimens, some plan to update the dietary data periodically. However, more studies are needed focusing on early life; children and young adults are vulnerable groups, and this could also be the time when nutritional factors are most important.

Many potential cancer prevention activities have to be applied by individuals, but require the availability of community facilities to put them into full effect, and in some countries, very major changes may be needed. For example, in the German population 60% are overweight and 20% are obese; while the processed meat intake in men is on average 80 g day^{-1}, the highest in EPIC-Europe.[59] In the short term, therefore, it may be necessary to set realistic, population-specific goals.

This raises the question as to whether interventions in line with those recommended by WCRF/AICR[2] can be more efficiently promoted in some communities than others, and could lead to the identification of changes that will make peoples living and working environments more conducive to health (and cancer prevention).

Cohort studies are usually based upon special groups (*e.g.*, those recruited already into a screening programme). However, there are a number of reasons why recruitment for new cohort studies should be community based. The outcome could be more relevant to future interventions if the cohort were to be more representative of the population where interventions will be applied than may have happened in the past. Recruiting in a community could be linked to an intervention at a community level—with a planned programme of approaches to health promotion that could be a reason for individuals agreeing to participate in the cohort. However, it would not be necessary for the same means to the end to be promoted in all communities, different interventions could be applied, with the decision on which to promote being based on cluster randomization, either at the individual community level, or at sub-community levels, these levels being subdivided on the basis of readily determined geographical boundaries. If large enough in size, such settings also allow for stratification for genetic and metabolic characteristics with sufficient statistical power.

Two potential interventions are:

1. Promotion of weight reduction (healthy weight maintenance) and physical
2. Promotion of increased consumption of plant foods, especially fruits and vegetables and whole grain products, in expense of foods of animal origin (except forfish).

These examples illustrate 2 different roles for such intervention studies. There is general agreement on the causal role of obesity and physical inactivity in the etiology of several chronic diseases, and the knowledge we need is how to reduce the prevalence of obesity and increase physical activity in populations, not whether they are causal factors. This will require both actions at the individual as well as community level. Similar actions will be required in promoting increased fruit and vegetable consumption—except that the focus of the community intervention will require collaboration between government and the food industry in increasing accessibility, and both interventions may require taxation of unhealthy foods.

For the cohort objectives to be achieved, it is going to be necessary to monitor the extent the participants change relevant exposures from the baseline information documented. To collect such data will help to determine the relative success of interventions. Decisions will be needed on the nature of the interventions, but they could range from advice in the form of pamphlets, through individual counseling, to financial incentives to permit individuals to subscribe to health clubs, or to purchase specific foods.

Conclusions

The main theme of this review is that we have reached the stage in nutritional cancer epidemiology where we need to concentrate more on applying the lessons we have learnt, than in seeking new etiological associations. However, we believe that these actions are complementary, and can reenforce each other. By achieving change at the population level, we can determine the validity of our hypotheses with much greater confidence than our largely observational-based discipline has so far permitted. This, to us, is the future.

References

1. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity and the prevention of cancer: a global perspective. Washington DC: AICR, 2007.
2. World Cancer Research Fund/American Institute for Cancer Research. Policy and action for cancer prevention. Food, nutrition, physical activity: a global perspective. Washington DC: AICR, 2009.
3. Committee on Diet Nutrition and Cancer. Diet, nutrition and cancer. Washington, D.C.: National Academy Press, 1982.
4. Michels KB. The role of nutrition in cancer development and prevention. *Int J Cancer* 2005;114:163–5.
5. Michels KB. Diet and cancer: current knowledge, methodologic pitfalls and future directions. *Int J Cancer* 2005;116: 665–6.
6. Kaaks R, Riboli E. Epidemiological studies of nutrition and cancer: let us not throw out the baby with the bath water. *Int J Cancer* 2005;116:662–4.
7. Kipnis V, Freedman LS. Impact of exposure measurement error in nutritional epidemiology. *J Natl Cancer Inst* 2008;100: 1658–9.
8. World Cancer Research Fund/American Institute for Cancer Research, Food, Nutrition and the Prevention of Cancer: a global perspective. Washington DC: AICR, 1997.
9. IARC. Handbooks on cancer prevention, fruits and vegetables, vol.8. Lyon: IARC Press, 2003.
10. Morgan RW, Jain M, Miller AB, Choi NW, Matthews V, Munan L, Burch JD, Feather J, Howe GR, Kelly A. A comparison of dietary methods in epidemiologic studies. *Am J Epidemiol* 1978;107:488–98.
11. Chang SC, Ziegler RG, Dunn B, Stolzenberg-Solomon R, Lacey JV, Jr., Huang W-Y, Schatzkin A, Reding D, Hoover RN, Hartge P, Leitzmann MF. Association of energy intake and energy balance with postmenopausal breast cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev* 2006; 15:334–41.
12. Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE. Energy balance and breast cancer risk: a prospective cohort study. *Breast Cancer Res Treat* 2006;97:97–106.
13. Ferrari P, Carroll RJ, Gustafson P, Riboli E. A Bayesian multilevel model for estimating the diet/disease relationship in a multicenter study with exposures measured with error: the EPIC study. *Stat Med* 2008; 27:6037–54.
14. Rodríguez G, Moreno LA. Is dietary intake able to explain differences in body fatness in children and adolescents? *Nutr Metab Cardiovasc Dis* 2006;16:294–301.
15. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL, Valanis B, Williams JH, Barnhart S, Hammar S. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Eng J Med* 1996;334:1150–5.
16. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group.The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Eng J Med* 1994;330: 1029–35.
17. IARC. Handbooks on cancer prevention, vol 2. Carotenoids. Lyon: International Agency for Research on Cancer, 2008.
18. Jain M, Burch JD, Howe GR, Risch HA, Miller AB. Dietary factors and risk of lung cancer: results from a case-control study. Toronto, 1981–1985. *Int J Cancer* 1990;45: 287–93.
19. Schatzkin A, Lanza E, Corle D, Lance P, Iber F, Caan B, Shike M, Weissfeld J, Burt R, Cooper MR, Kikendall JW, Cahill J, *et al.* Lack of effect of a low-fat, high fiber diet on the recurrence of colorectal adenomas.Polyp prevention trial study group. *N Engl J Med* 2000;342: 1149–55.
20. Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, McKeown-Eyssen G, Summers RW, Rothstein RI, Burke CA, Snover DC, Church TR, *et al.* Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA* 2007; 297:2351–9.
21. Martinez ME, Marshall JR, Giovanucci E. Diet and cancer prevention: the roles of observation and experimentation. *Nat Rev Cancer* 2008;8:694–703.
22. Figueiredo JC, Grau MV, Haile RW, Sandler RS, Summers RS, Bresalier RS, Burke CA, McKeown-Eyssen GE, Baron JA. Folic acid and risk of prostate cancer: results from a randomized clinical trial. *J Natl Cancer Inst* 2009;101:432–5.
23. Bartsch H, Miller AB. Editors' comments, "Epidemiologic studies of nutrition and cancer." *Int J Cancer* 2005;116:661.
24. Bingham S, Luben R, Welch A, Low YL, Khaw KT, Wareham N, Day N. Associations between dietary methods and biomarkers, and between fruits and vegetables and risk of ischaemic heart disease, in the EPIC Norfolk Cohort Study. *Int J Epidemiol* 2008;37:978–87.
25. Jenab M, Riboli E, Ferrari P, Sabate J, Slimani N, Norat T, Friesen M, Tjønneland A, Olsen A, Overvad K, Boutron-Ruault M-C, Clavel-Chapelon F, *et al.* Plasma and dietary vitamin C levels and risk of gastric cancer in the European prospective investigation into cancer and nutrition (EPIC-EURGAST). *Carcinogenesis* 2006;27: 2250–7.
26. Favé G, Beckmann ME, Draper JH, Mathers JC. Measurement of dietary exposure: a challenging problem which may be overcome thanks to metabolomics? *Genes Nutr* 2009;4:135–41.
27. Jenab M, Slimani N, Bictash M, Ferrari P, Bingham SA. Biomarkers in nutritional epidemiology: applications, needs and new horizons. *Hum Genet* 2009;125: 507–25.
28. Holmes E, Loo RL, Stamler J, Bictash M, Yap IK, Chan Q, Ebbels T, De Iorio M, Brown IJ, Veselkov KA, Daviglus ML, Kesteloot H, *et al.* Human metabolic phenotype diversity and its association with diet and blood pressure. *Nature* 2008; 453:396–400.
29. Nagel G, Zoller D, Ruf T, Rohrman S, Linseisen J. Long-term reproducibility of a food-frequency questionnaire and dietary changes in the European prospective investigation into cancer and nutrition (EPIC)-Heidelberg cohort. *Br J Nutr* 2007; 98:194–200.
30. Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan J-M, Katsouyanni K, Lubin F, Marubini E, Modan B, Rohan T, Toniolo P, Shunzhang Y. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *J Natl Cancer Inst* 1990;82:561–9.
31. Howe GR, Benito E, Castelleto R, Cornée J, Estève J, Gallagher RP, Iscovich JM, Deng-ao J, Kaaks R, Kune GA, Kune S, L'Abbé KA, *et al.* Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. *J Natl Cancer Inst* 1992;84:1887–96.
32. Smith-Warner SA, Spiegelman D, Ritz J, Albanes D, Beeson WL, Bernstein L, Berrino F, van den Brandt PA, Buring JE, Cho E, Colditz GA, Folsom AR, *et al.* Methods for pooling results of epidemiologic studies. The pooling project of prospective studies of diet and cancer. *Am J Epidemiol* 2006;163:1053–64.
33. Jain MG, Harrison L, Howe GR, Miller AB. Evaluation of a self-administered dietary questionnaire for use in a cohort study. *Am J Clin Nutr* 1982;36:931–5.
34. Ferrari P, Day NE, Boshuizen HC, Roddam A, Hoffmann K, Thiébaut A, Pera G, Overvad K, Lund E, Trichopoulou A, Tumino R, Gullberg B, *et al.* The evaluation of the diet/disease relation in the EPIC study: considerations for the calibration and the disease models. *Int J Epidemiol* 2008;37:368–78.

35. Miller AB (Chairman). Recommendations for the primary prevention of cancer. Report of the Ontario task force on primary prevention of cancer, Ministry of Health. Ontario: Queen's Printer for Ontario, 1995.
36. Miller AB, Howe GR, Jain M, Craib KJP, Harrison L. Food items and food groups as risk factors in a case-control study of diet and colo-rectal cancer. *Int J Cancer* 1983; 32:155–61.
37. Miller AB, Altenburg H-P, Bueno de Mesquita B, Boshuizen HC, Agudo A, Berrino F, Gram IT, Janson L, Linseisen J, Overvad K, Rasmuson T, Vineis P, *et al.* Fruits and vegetables and lung cancer: findings from the European prospective investigation into cancer and nutrition. *Int J Cancer* 2004;108:269–76.
38. Smith-Warner SA, Spiegelman D, Yuan S-S, Albanes D, Beeson WL, van den Brandt PA, Feskanech D, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, Goldbohm RA, *et al.* Fruits, vegetables and lung cancer: a pooled analysis of cohort studies. *Int J Cancer* 2003;107: 1001–11.
39. 't Mannetje A, Kogevinas M, Chang-Claude J, Cordier S, González CA, Hours M, Jöckel KH, Bolm-Audorff U, Lynge E, Porru S, Donato F, Ranft U, *et al.* Smoking as a confounder in case-control studies of occupational bladder cancer in women. *Am J Ind Med* 1999;36:75–82.
40. Linseisen J, Rohrmann S, Miller AB, Bueno de Mesquita B, Buchner FL, Agudo A, Vineis P, Gram IT, Janson L, Krogh V, Overvad K, Rasmuson T, *et al.* Fruits and vegetable consumption and lung cancer risk: updated information from the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer* 2007;121:1103–14.
41. Boeing H, Dietrich T, Hoffmann K, Pischon T, Ferrari P, Lahmann PH, Boutron-Ruault MC, Clavel-Chapelon F, Allen N, Key T, Skeie G, Lund E, *et al.* Intake of fruits and vegetables and risk of cancer of the upper aero-digestive tract: the prospective EPIC-study. *Cancer Causes Control* 2006;17:957–69.
42. Freedman ND, Park Y, Suab AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and head and neck cancer in a large United States prospective cohort study. *Int J Cancer* 2008;122:2330–6.
43. González CA, Pera G, Agudo A, Bueno-de-Mesquita HB, Ceroti M, Boeing H, Schulz M, Del Giudice G, Plebani M, Carneiro F, Berrino F, Sacerdote C, *et al.* Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European prospective investigation into cancer and nutrition (EPIC-EURGAST). *Int J Cancer* 2006;118:2559–66.
44. Koushik A, Hunter DJ, Spiegelman D, Beeson WL, van den Brandt PA, Buring JE, Calle EE, Chu E, Fraser GE, Freudenheim JL, Fuchs CS, Giovannucci E, *et al.* Fruits, vegetables and colon cancer risk in a pooled analysis of 14 cohort studies. *J Natl Cancer Inst* 2007;99: 1471–83.
45. Weikert S, Boeing H, Pischon T, Olsen A, Tjonneland A, Overvad K, Becker N, Linseisen J, Lahmann PH, Arvaniti A, Kassapa C, Trichoupoulou A, et al. Fruits and vegetables and renal cell carcinoma: findings from the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer* 2006;118: 3133–9.
46. Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, Overvad K, Olsen A, Tjønneland A, Clavel F, Boutron-Ruault MC, Kesse E, *et al.* Meat, fish, and colorectal cancer risk: the European prospective investigation into cancer and nutrition. *J Natl Cancer Inst* 2005;97: 906–16.
47. González CA, Jakszyn P, Pera G, Agudo A, Bingham S, Palli D, Ferrari P, Boeing H, del Giudice G, Plebani M, Carneiro F, Nesi G, *et al.* Meat intake and risk of stomach and esophageal adenocarcinoma within the European prospective investigation into cancer and nutrition (EPIC). *J Natl Cancer Inst* 2006;98:345–54.
48. Lumbreras B, Garte S, Overvad K, Tjonneland A, Clavel-Chapelon F, Linseisen JP, Boeing H, Trichopoulou A, Palli D, Peluso M, Krogh V, Tumino R, *et al.* Meat intake and bladder cancer in a prospective study: a role for heterocyclic aromatic amines? *Cancer Causes Control* 2008;19:649–56.
49. De Stefani E, Deneo-Pellegrini H, Boffetta P, Ronco AL, Aune D, Acosta G, Mendilaharsu M, Brennan P, Ferro G. Dietary patterns and risk of cancer: a factor analysis in Uruguay. *Int J Cancer* 2009;124:1391–7.
50. Mendez MA, Popkin BM, Jakszyn P, Berenguer A, Tormo MJ, Sanchéz MJ, Quirós JR, Pera G, Navarro C, Martinez C, Larrañaga N, Dorronsoro M, *et al.* Adherence to a Mediterranean diet is associated with reduced 3-year incidence of obesity. *J Nutr* 2006;136:2934–8.
51. Schulz M, Hoffmann K, Weikert C, Nöthlings U, Schulze MB, Boeing H. Identification of a dietary pattern characterized by high-fat food choices associated with increased risk of breast cancer: the European prospective investigation into cancer and nutrition (EPIC)—Potsdam Study. *Br J Nutr* 2008; 100:942–6.
52. Miller AB, Kelly A, Choi NW, Matthews V, Morgan RW, Munan L, Burch JD, Feather J, Howe GR, Jain M. A study of diet and breast cancer. *Am J Epidemiol* 1978;107:499–509.
53. Boyd NF, Stone J, Vogt KN, Connelly BS, Martin LJ, Minkin S. Dietary fat and breast cancer risk revisited: a meta-analysis of the published literature. *Br J Cancer* 2003;89: 1672–85.
54. Sieri S, Krogh V, Ferrari P, Berrino F, Pala V, Thiébaut AC, Tjønneland A, Olsen A, Overvad K, Jakobsen MU, Clavel-Chapelon F, Chajes V, *et al.* Dietary fat and breast cancer risk in the European prospective investigation into cancer and nutrition. *Am J Clin Nutr* 2008;88:1304–12.
55. Mendez MA, Pera G, Agudo A, Bueno-de-Mesquita HB, Palli D, Boeing H, Carneiro F, Berrino F, Sacerdote C, Tumino R, Panico S, Berglund G, *et al.* Cereal fiber intake may reduce risk of gastric adenocarcinomas: the EPIC-EURGAST study. *Int J Cancer* 2007;121: 1618–23.
56. Bingham SA, Day NE, Luben R, Ferrari P, Slimani N, Norat T, Clavel-Chapelon F, Kesse E, Nieters A, Boeing H, Tjønneland A, Overvad K, *et al.* Dietary fibre in food and protection against colorectal cancer in the European prospective investigation into cancer and nutrition (EPIC): an observational study. *Lancet* 2003;361: 1487–8.
57. Newman SC, Miller AB, Howe GR. A study of the effect of weight and dietary fat on breast cancer survival time. *Am J Epidemiol* 1986;123:767–74.
58. Jain M, Miller AB, To T. Premorbid diet and the prognosis of women with breast cancer. *J Natl Cancer Inst* 1994;86: 1390–7.
59. Linseisen J, Kesse E, Slimani N, Bueno-de-Mesquita HB, Ocké MC, Skeie G, Kumle M, Dorronsoro Iraeta M, Morote Gómez P, Janzon L, Stattin P, Welch AA, *et al.* Meat consumption in the European prospective investigation into cancer and nutrition (EPIC) cohorts—results from the 24-hr dietary recalls. *Pub Health Nutr* 2002;5:1243–58.