# On the Long and Winding Road to an Evidence-Based Diet

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Observational epidemiological studies almost invariably find a dose-dependent inverse association between frequency of fruit or vegetable intake and risk of epithelial cancers (1). The strength of this association is generally unimpressive, but since a sizeable and unavoidable exposure measurement error tends to bias any association towards the null, it has been assumed that the true effect is underestimated. Although adjustments for factors related to education, socioeconomic status and healthy lifestyle often attenuate the crude estimates, the inverse relationship usually persists after what could be considered adequate control for confounding. The consistency across studies and the plausibility—largely hinged on an undisputable antioxidative action—built a strong case for causality. Therefore, the total absence of any protection in three well-performed large-scale randomized chemoprevention trials with the vitamins believed to be most responsible for the beneficial effects of fruits and vegetables (2–4) came as a shock to the epidemiological community.

While issues regarding doses and timing need some consideration, the discrepancy between observational data and the results from the randomized trials is most likely explained by either of two alternatives: 1) some constituent(s) other than the substances administered in the chemoprevention trials account for the anticarcinogenic action of fruits and vegetables; or 2) the seemingly protective effect in observational studies does not come from these foods, but comes from other factors that might be related to the general lifestyle of frequent consumers or to other components of their diet. The lesson to be learned from this major setback is that even the most evident causal relationship noted in observational studies could potentially be explained by confounding. As far-reaching campaigns are presently being launched in order to promote fruit and vegetable consumption (5)—notwithstanding the chemoprevention failures—and billions of Euros will be spent in the near future on programmes for distributing these foods to children and other targeted categories, it is difficult not to sympathize with the idea of making an appropriate assessment of their effect. And since confounding is the main concern, a randomized controlled trial is the method of choice. Provided that the study is large enough, randomization—properly done—will ensure that all factors causally related to the outcome, regardless of whether they are known or unknown, will be evenly distributed across the treatment arms. Hence, randomization safeguards against any known or unknown confounding.

In this issue of *Acta Oncologica*, Mehr et al. propose a grand randomised, controlled trial in the Baltic countries aimed at providing valid and persuasive confirmation of the wholesome effects of fruit and vegetables (6). According to their appraisal, an almost unique window of opportunity will be open in these countries in the years to come. No doubt, such confirmation is needed. The question is whether the scheme is feasible and whether valid results will be obtained. Or in other words, will the huge investment that is required really be worthwhile?

The authors behind the proposal are well aware of the complexity of such a trial, and some of the issues are touched upon in their thought-provoking article. Commendably, they recommend a multistage approach, with in-depth preparation and feasibility studies preceding the main intervention study. This is a very sensible standpoint. Even with the best of intentions, interference with entrenched habits and social structures can produce unpredictable results—a well-known fact among relief workers involved in aid to developing countries. Therefore, it is important to study the secondary effects of the intervention at the individual, group and community levels before the full-scale study is launched.

The ideal design of any intervention study involves individual randomization. It is, however, evident that this will be impractical in the proposed study. First, it would be exceedingly expensive individually to deliver 1 500–2 000 g of bulky food twice a week to 30 000 subjects scattered over large areas. Second, it would be virtually impossible to

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prevent the study subjects from sharing the food with their families. It is almost inconceivable that healthy study subjects, year after year, would maintain a diet that markedly differs from that of their nearest and dearest. Thus, families need to be left intact in the randomization process. Randomization of families, particularly if done in close-knit, isolated communities, however, may both create social tensions and increase the risk of contamination of the intervention across treatment arms. Mehr et al. believe that cluster randomization of whole villages is the solution. They acknowledge that the sample size needs to be increased considerably because of the lack of independency of observations within clusters. But there are more potential problems inherent in cluster trials. Complete balance of confounding factors may not be attained despite vast numbers of participants (7). For instance, in a randomized two-armed trial of breast-cancer screening, an imbalance in socioeconomic groups was noticed even though 50 000 women in 87 clusters were included (8). Although the method for obtaining informed consent is not elaborated by Mehr et al., it must be emphasized that it may be important. If the post-randomized consent method, analogous to that described by Zelen (9), were to be used, then there would be a possibility of selection bias if a significant proportion refuses. If pre-randomization consent is sought, and one of the treatment arms is undesirable, there is a risk that the overall participation rate will be rather low. And even if non-participation after pre-randomization consent is unrelated to treatment allocation, penetration of the intervention may be incomplete in the active intervention arm. Dietary habits are governed only to a small extent by economic incentives. Personal preferences and deep-rooted tradition may be more important. Therefore, free availability of certain foods does not necessarily result in higher consumption.

The non-blinded nature of the trial, combined with the media attention that invariably accompanies large-scale intervention studies, may give rise to a compensatory intake of vegetables and fruit in the control arm. This will lead to an underestimation of the absolute and relative effects of the intervention. Another possible pitfall in an open study is the possibility of ascertainment bias, i.e. awareness of the treatment allocation affects the subject's vigilance for cancer symptoms, leading to a higher probability of early diagnosis in one of the treatment arms.

Nutritional epidemiology is complicated. Since the total energy intake needs to be kept on a constant level if steady state is to be preserved, the intervention would not simply add fruit and vegetables to the previous diet, but it would replace other foods. The question, then, is what other foods would be removed from the participants' diets. Any beneficial effects of the intervention could potentially be attributed to the removal of unhealthy foods rather than to the addition of fruits and vegetables. Some subjects, on the other hand, might not remove anything from their previous diet but might, instead, increase their total energy intake and become fatter (which could have deleterious health effects). As the already existing fruit and vegetable intake is likely to be the first to be replaced by the intervention food, the investigators cannot only provide supplementary doses. *All* of the desired plant food intake has to be supplied, and if this is implemented in entire villages, what will happen to the local grocery shops? Will the trend towards closure of barely profitable small local units be accelerated in villages randomized to the active intervention? As a consequence, other essential foods might become less accessible to those who receive free fruits and vegetables. The villagers will perhaps need to travel long distances to urban supermarkets. One can only speculate on the impact of such a change on dietary habits. People might have to store up food for longer periods than previously, leading to a switch away from fresh food to more frozen or otherwise processed food.

If free food is supplied, this will entail some economic relief as well, i.e. the participants in the active intervention arm will not have to buy foods corresponding to the energy addition that is provided. For a large family, the annual savings may be substantial. How important will this economic boost be to participating households? For one thing, it may in itself change the dietary pattern. Furthermore, it might potentially lead to better housing, less residential crowding and a decrease in the incidence/prevalence of infectious diseases, among them *Helicobacter pylori* gastritis, which is strongly linked to gastric cancer risk. But it might also lead to an accelerated motorization, with increasing risk of traffic injuries, and greater access to satellite television and computers, all of which might contribute to decreasing physical activity, higher incidence rates of diabetes, cardiovascular diseases and cancer of the breast and colorectum.

Notwithstanding their importance and desirability, valid evidence-based data regarding major dietary changes are difficult to obtain. In this commentary, I have played the devil's advocate and pointed to a number of possible pitfalls that may not be remedied by randomization in open cluster trials. I have also alluded to possible secondary effects on society—effects that might at worst counteract, or at least complicate the interpretation of, the genuine effects of fruit and vegetable supplementation. The ethical issues have only been briefly touched upon, but they need careful consideration. Although the intervention may seem benign, encroachments onto deep-rooted habits should not be taken lightly. However, the general idea of stringent evaluation of preventive measures is indeed praiseworthy, and I am a keen supporter of the proposed attempt. But in order to make the results of the intervention interpretable, we need to know more about the primary and secondary consequences of the

intervention, both on the individual and the population level.

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