Keyvan Tadjalli Mehr

A Randomized Healthy Food Cancer Prevention Trial - Study Design –

Geboren am 17.06.1964 in Teheran / IRAN
Reifeprüfung in Juni 1982 in Teheran / IRAN
Studium der Fachrichtung Medizin vom SS 1993 bis WS 2000/2001
Physikum am 29.03.1995 an der Universität Heidelberg
Klinisches Studium in Heidelberg
Praktisches Jahr in Heidelberg (St. Josefskrankenhaus)
Staatsexamen am 14.11.2000 an der Universität Heidelberg

Promotionsfach: Krebsepidemiologie
Doktorvater: Herr Priv.-Doz. Dr. Nikolaus Becker

The scientific research on the role of fresh fruits and vegetables in the development of cancer shows, quite consistently, a protective role on the risk of many cancers, and perhaps on cancer in general. This evidence, however, relies only on observational epidemiologic studies and biological studies. Consequently, many substances have been identified to be responsible for the protective effect of fruits and vegetables, foe which biological mechanisms from in vitro and animal studies were also suggested.
Chemoprevention based vitamins and minerals, is the most specific attempt to demonstrate the causal relationship between chemical substances in diet and development of cancer. These trials, however, have not shown to be effective so far.
The missed success of chemopreventive trials my be due to several reasons:

1. The structure of dietary exposures and their relationship to development of cancer is very complex.
2. A long latency exists between the first exposure and diagnosis of the invasive cancer. Preventive efforts should, therefore, start early in the life.
3. A single nutrient may serve as a marker for other protective dietary factors or correlated life styles. Their protective role may develop only in a natural matrix allowing synergistic interactions with other antioxidants and phytichemicals.
4. There might be differences between natural and synthetic nutrients used in chemoprevention.
5. The biological mechanisms of cancer protection and/or promotion of micronutrients in combination with other environmental exposures (tobacco, etc.) and individual status (well-nourished, malnourished, etc.) are not sufficiently understood.
6. Therefore, there is an important question whether it is unethical to run any chemopreventive trials.

There is an urgent need to conduct randomized controlled trials of different diets especially fresh fruits and vegetables in order to bring the final scientific proof for their observed cancer protective role.
We have presented, in this thesis, major design aspects for such a trial:
The population under study should have a poor nutritional status regarding the consumption of fresh fruits and vegetables, be living, however, in a health system with an advanced infrastructure of cancer registration in order to be able to identify all occurrences of clinical cancer cases. The Baltic countries (Estonia, Latvia, Lithuania) were identified to fulfill these

prerequisites, however, for an only short period of time because of the rapid socioeconomic transition to modern western European lifestyle.
For the elaboration of the design, we have used only data from Estonia, but the conclusions are also applicable to Latvia and Lithuania. The exposure will be through the provision of identified, culturally and socially accepted food items mainly consisting of fresh fruits and vegetables. The food items will be distributed free of charge to ensure a high level of compliance, which will be controlled by analysis of biomarkers in blood samples. The duration of the trial will be about ten years and the subjects will be followed up for an additional number of years. The outcome to be measured over the study period is the diagnosed invasive cancer.
The study focuses on three major age groups: children about 10, adults about 30 and elderly about 60. On basis of three assumptions of prevention effect (realistic, moderate and optimistic) and the cumulative incidence rates for cancers of all sites as well as lung, stomach and colorectum, we estimated the population size required for each age group, resulting in high values (person years) especially for children.
Using another method of stepwise calculation of power based on a defined number of subjects per age group and for each additional year of follow-up allows us to simulate any combinations of population sizes of each group in order to achieve a sufficient statistical power within a realistic number of follow-up years. In this method, the age specific general mortality data were also considered.
Towards the realization of such a trial, we propose three phases: a preparation study to finalize the design issues, a feasibility study and finally the main study.
We show that the costs of such a trial may be high but are not higher than those of the above mentioned chemoprevention trials.
Given the relevance of the issue, the investment appears justified. Because there is no experimental (i.e. based on a randomized prevention trial) evidence so far, and the experience with chemopreventive trials shows that there is, in fact, a balance, both preventive and risk-increasing effects of the trial are possible. Therefore, it is neither sure who – those exposed or controls – would benefit, it is better to provide benefit for somebody than for nobody, obviously it is impossible to provide benefit for everybody. Promoting identical health habits as those among the exposed is not justified as long as the evidence is not there, and as long as the trial is not completed.