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Randomized Trial with Fruits and Vegetables in Prevention of Cancer

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Along with tobacco use, diet has the greatest impact on the development of human cancer. Within the broad category 'diet', the consumption of fruits and vegetables apparently plays a dominant role. Considerable efforts have been made to prove the preventive effect of different kinds of fruits and vegetables but randomized chemoprevention trials have failed to prove this presumed effectiveness of their single ingredients. The conclusive demonstration of a cancer-protective effect of a high consumption of fruits and vegetables is considered to be impractical. However, current historical changes in Europe offer a unique opportunity to conduct such a randomized trial in specific European countries. This study describes the nutritional situation and the conditions of the health system in the Baltic countries as appropriate geographic areas and demonstrates some basic design issues of the trial for three variants of outcome assumptions. A realistic assumption would be that a trial needs about 30 000 participants, an intervention period of 10 years and a subsequent follow-up time of 20 years. Annual costs could range between $5 and $10 million. A high intake of fruits and vegetables should be proven scientifically as a valid tool for cancer prevention. For a comparably short period the Baltic countries offer a time-window for a randomized trial. It is unlikely that the costs of such a trial would considerably exceed the costs of the available chemoprevention trials.

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The past 25 years of research have provided a large body of additional knowledge on diet, nutrition and cancer. The present situation, however, must be considered as disappointing: an overall evaluation of available information from the World Cancer Research Fund (1997) indicated a high consumption of fruits and vegetables to be protective of a number of cancer sites (oral, oesophageal, stomach, laryngeal, lung) as a firmly established fact. For other sites (intestine, breast, prostate, etc.), other food groups (meat), or food ingredients, the evidence has been less consistent (probable, possible, or insufficient) (1). Recently, several large prospective cohort studies have failed to demonstrate the presumed protective effect of fruit, vegetable and dietary fibre consumption on cancer risk (2–4). On the other hand, it is known from studies of migrants that migrants tend to adopt the cancer pattern of their host country within 10 to 20 years for colorectal cancers and within a few generations for cancers of the breast, stomach and prostate (5). The recommended 5 servings of fresh fruits and vegetables a day remains valid because a modest reduction in cancer risk is likely (6, 7).

However, it was just the ingredients that from the outset stimulated the hopes of scientists of being able to derive from the epidemiological findings some suggestions for a pharmaceutical pathway towards cancer prevention using a drug based on a vitamin or other ingredient, or some simple combination. Several large-scale randomized intervention studies tested the hypothesis of a cancer protective ability of β-carotene and other substances that have repeatedly shown decreased relative risk in epidemiological studies. In summary, the results were alarming. Two of the four most prestigious trials showed even more lung cancers, more cardiovascular deaths and a higher overall mortality (8) (Table 1).

A pooled analysis of the unweighted results of the Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study

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Table 1

Comparison of relative risks among the four chemoprevention studies involving β-carotene (8)

	Lung cancer		Mortality	
	Relative risk	95% CI	Relative risk	95% CI
ATBC	1.18	1.03–1.36	1.08	1.01–1.16
CARET	1.28	1.04–1.57	1.17	1.03–1.33
PHS	0.93	0.96–1.26	1.02	0.93–1.11
Linxian Study	–	–	0.91	0.84–0.99

Abbreviations: CI = confidence interval; ATBC = Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study; CARET = Beta-Carotene and Retinol Efficacy Trial on Lung Cancer; PHS = Physicians' Health Study; Linxian Study = The Linxian General Population Trial on Oesophageal and Stomach Cancer.

(ATBC), the Beta-Carotene and Retinol Efficacy Trial on Lung Cancer (CARET) and the Physicians' Health Study (PHS) yielded a relative risk of 1.16 (95% CI = 1.05–1.29) for lung cancer incidence and 1.07 with (95% CI = 1.05–1.29) for all-cause mortality (9).

In a commentary in the *Lancet*, it was summarized that '...beta carotene supplements have no value as cancer chemopreventive agents. Indeed, it would now seem difficult to justify any additional investigation of beta carotene for chemoprevention' (10).

Thus, we are faced with the situation that chemoprevention trials based on vitamins and minerals as the most specific attempt to demonstrate the causal role of chemical substances in diet have not proved to be effective so far (11). The results that are available have not been sufficiently appreciated: today, a high consumption of fruits and vegetables is a component of every public health recommendation on cancer prevention. This is considered, however, as a kind of preliminary message, as long as we are unable to provide the actual tool, i.e. a standardized drug that more or less performs the same function, but more easily and possibly more cheaply.

'What next?' is the question asked in many commentary papers and all the answers are different. The costs of the hitherto existing chemopreventive intervention studies have been huge. Should we select the next round of agents, but perhaps more carefully, and spend the next hundreds of millions of dollars?

In their 1981 paper, Peto et al. (12) underlined: 'Preventive measures, especially those that may be relevant over a long period to many millions of people, deserve peculiarly rigorous evaluation. Apart from reducing the amount consumed (or harmfulness) of tobacco, there are few lines of research or governmental action that offer any medium-term hope of achieving substantial reductions in total cancer incidence rates'. They wrote this to propagate randomized trials on a potential preventive effect of β-carotene. Now, after the failure of this pathway, we see the recommendation of regular consumption of fruits and vegetables in exactly the situation Peto et al. described, when they had β-carotene in mind.

Thus, the present paper proposes a randomized trial on the protective role of regular consumption (5 portions a day or more) of fruits and vegetables. The aim of the project is to study (a) the causal and (b) the quantitative relationship between regular consumption of fruit and vegetable, and the risk of cancer. We point out that, owing to the historical changes initiated about 10 years ago, an area of Europe for a relatively short time period offers the unique opportunity of an appropriate environment for such a project.

STUDY DESIGN OF A RANDOMIZED TRIAL WITH FRUITS AND VEGETABLES

Overview

The intervention of the randomized trial will be the free-of-charge distribution of fruits and vegetables over a period of several years. The outcome of interest is the incidence of invasive cancer. The study population will be the inhabitants of villages of the Baltic countries (Estonia, Latvia and Lithuania) selected by cluster randomization.

The planning and execution of the intervention can be divided into three phases, which will be called I) preparation study, II) feasibility study and III) main study. The preparation study will address the design regarding (a) the exposure, (b) outcome measurement, (c) sample size and duration, (d) organization, (e) cost and (f) other design issues which will not assume actual field application. The feasibility study is intended to test the research proposal based on the preparation part and to assess the feasibility of the trial.

Study area: Baltic countries

In the following sections, we confine the description of the study area mostly to Estonia. Latvia and Lithuania show comparable structures.

Territorial and political description. The Baltic countries are situated on the eastern coast of the Baltic Sea with common borders with the Russian Federation to the east (Estonia, Latvia) and southwest (Lithuania). The countries were Socialist Republics and part of the former Soviet Union from 1940 until 1991. Since then, they are independent Democratic Republics. Since 1999, all three countries have been given the official status of candidates for membership in the European Union. The rapid political changes have been accompanied by changes in the social and economic structure, which leads us to suspect that the time-frame for being an appropriate window for the study proposed here is limited (see below).

Population. In 1999, the population in Estonia was 1.4 million, in Latvia 2.4 million and in Lithuania 3.7 million. In all three countries about 69% lived in the urban areas,

which was about the average compared to other countries in Europe and Russia. The population consisted of different ethnic groups comprising ethnic Estonians, Latvians and Lithuanians (65%, 56%, and 81%, respectively), ethnic Russians (30%, 32% and 8%) and others.

Nutrition. The traditional food as exemplified by Estonia has been characterized as rich in fat and cholesterol, overuse of salt and sugar, deficiency of certain vitamins, minerals and fibre, adequate protein, with over-consumption of calories and refined food (13). There is clearly a higher consumption of fruits and vegetables among the urban population compared to the rural population as well as among non-Estonians compared to Estonians, as non-Estonians live mostly in the urban areas. Another characteristic of the Estonian nutrition is the seasonal change during winter and spring, leading to a traditional problem of hypovitaminosis of C, A, carotenoids and B complex. An effort has therefore been made to carry out increased media promotion as well as preventive vitamin supply programmes. Until the middle of 1990s, the main reason for insufficient vitamin supply was the shortage of vegetables, fruits, juices and some other animal products (whole milk, lean meat, some cereals, etc.). Currently, lack of money to buy fruits and vegetables and inadequate health education seem to be the most important determinants of this shortage. It can also be assumed that vitamin levels depend strongly on social-economic status. The production of fruits is not yet sufficient to cover the needs of the winter period.

In 1996, WHO facilitated the Baltic Project to support each country to carry out initial surveys of national food intake, nutritional status and information about healthy lifestyle (14). Survey data were also to be used as baseline information against which future dietary consumption could be compared. In this project considerable differences in consumption of vegetables and roots (excluding potatoes) were observed among countries. While 78% of Lithuanians consumed vegetables daily, this was the case in 60% of Latvians and in only 48% of the Estonian respondents. In all three countries women were more likely to consume vegetables daily. Fruit intake was particularly low in men, with median intakes equal to zero in all countries. Latvian women consumed less fruit than Estonian and Lithuanian women.

The Estonian Health Interview Survey 1996–1997 showed that 15.4% of men preferred food with a higher fat content, and this preference was more widespread in rural men (18.2%) than in urban (14.2%) men (15). A survey among schoolchildren (mainly aged 10–15 years) revealed that in 1997–1998 only 59.5% of the children in Tallinn and 45.6% in the rural Võru County consumed fruits/juices daily; the frequency of daily consumption of vegetables in these areas was 32.8% and 25.1%, respectively (16). Behavioural change in choices of food is a slow process reflecting the conservative nature of eating habits. This indicates potential problems of compliance but also the small probability of contamination and dilution even during a prolonged follow-up.

Cancer. Cancer in the Baltic countries is the second leading cause of death after cardiovascular diseases (CVDs). Table 2 shows some of the most frequent cancer sites of males and females during the 5-year period from 1992 to 1997 (17).

The data on cancer incidence in Estonia also show some trends towards an increased risk of stomach cancer in areas with a high proportion of non-Estonians as well as an increased risk of colorectal cancer among the urban population, and an obvious rise in incidence over time in the majority of areas (17).

The intervention

The proposed intervention consists of providing healthy food to a target population, which will be selected by randomizing clusters of rural areas of the three Baltic countries (Estonia, Latvia and Lithuania) into intervention and control groups. The occurrence of cancer during the follow-up is the outcome of the intervention.

We will be faced with the following problems, which have to be further investigated in the preparation study:

Sources of food. Our preferred source of fruits and vegetables is the European Union, as it is known that the members of the Union have had an agricultural overproduction for many years. Alternatively, the food can be purchased from the market, carefully including the local market.

Logistics. The transportation of fresh fruits and vegetables from different European countries to the study area and also possible storage will likely be one of the major logistical problems of the intervention. The distribution of the food to the study population will be organized through local health centres (also responsible for taking biological samples) as well as schools.

Avoidance of contamination. There is the probable effect of selling or giving the free food to the controls by the intervention group if the exposure contrast is substantial. And there is the likelihood of a disappearance of the exposure contrast when the standard of living improves. These effects will be precluded by electing a rural population as the base and by applying cluster randomization to villages that are sufficiently isolated from one another. Monitoring of consumption will be organized through blood samples.

Up until now there is not much evidence of a change in the traditional diet in the remote Baltic countryside. This is a possibility that any long-term population study will have to face, whether clinical or preventive. However, there are no good alternatives.

Quality control (measurements of intake). Using experiences from the European Prospective Study on Nutrition,

Table 2

Total number of new cases (No.) per year and age-standardized incidence (ASIR, world standard population) rates per 100 000 of all cancers and some selected sites in 1993–1997 (17)

Males			Females		
Site	No.	ASIR	Site	No.	ASIR
Estonia					
All cancers	2738	315.2	All cancers	2842	208.7
Lung	642	73.0	Breast	505	41.5
Stomach	279	31.9	Stomach	225	14.8
Prostate	319	35.8	Colon	203	13.0
Colon	143	16.1	Corpus uteri	183	13.8
Rectum	121	13.8	Cervix uteri	172	15.1
Kidney	128	14.9	Ovary, etc.	159	12.4
			Lung	133	8.7
			Rectum	115	7.3
Latvia					
All cancers	3868	261.1	All cancers	4158	181.7
Lung	944	62.8	Breast	814	39.9
Stomach	429	28.8	Stomach	345	13.2
Prostate	290	19.2	Colon	260	9.8
Colon	188	12.5	Corpus uteri	387	17.5
Rectum	174	11.6	Cervix uteri	183	9.7
Kidney	168	11.5	Ovary, etc.	282	13.5
Bladder	194	13.0	Lung	168	6.2
			Rectum	195	7.4
Lithuania					
All cancers	5949	282.8	All cancers	5900	191.7
Lung	1375	65.8	Breast	1052	37.7
Stomach	629	29.7	Stomach	439	12.6
Prostate	577	26.1	Colon	300	8.9
Colon	250	11.8	Corpus uteri	394	13.2
Rectum	283	13.2	Cervix uteri	386	14.6
Kidney	210	10.2	Ovary, etc.	386	13.3
			Lung	221	6.3
			Rectum	261	7.6

Cancer and Health (EPIC) (18), we can conclude that serum and plasma are preferred materials in which we can measure target substances such as β-carotene, α-carotene, lutein and lycopene as biomarkers of a diet high in vegetables and fruits (19) in order to control the level of compliance of food intake.

Assumptions on outcome and sample size calculation

Our hypothesis is that a high intake of vegetables and fruits is associated with a reduced risk of cancers at many sites, so that we can consider diet and food consisting mainly of fresh vegetables and fruits as healthy. It has been estimated (based on data from Western and Northern Europe) that there would be a 23% reduction in overall cancer incidence when the average vegetable and fruit consumption increases from 250 to 400 g/day. However, the change is not expected immediately but after about one or two decades (20) (cited in (1)). Diets high in vegetables and fruits (more than 400 g/day) could prevent at least 20% of incidence of all cancers (1). WHO also recommends an intake of more than 400 g of vegetables and fruits per day to prevent micronutrient deficiency and to contribute to the prevention of non-communicable diseases (14).

The ultimate selection of the food items and the daily amount per capita is an objective of the preparation study and will depend not only on the potential health effect but also upon the cost.

Prevention effect and outcome. The estimation of the size of the intervention group is based on a two-sided test with a 5% significance level and a power of 90% to detect a reduction in cancer incidence according to the following sets of assumptions on effect by years of follow-up:

A (realistic): 5% reduction in cancer incidence every 5 years.
B (moderate): 5% reduction in cancer incidence every 3 years.
C (optimistic): 5% reduction in cancer incidence every 2 years.

Selection of the study population. Given that the delivery of food will run by the family as a unit, there will be subjects of different ages. We have assumed a three-generation

family with average ages of 10, 30 and 60 years, and that in a family there are on average 2:2:1 members of each generation, the ultimate number of individuals will be of the order of magnitude of 30 000.

The choice of clusters, such as families as a unit of randomisation, usually results in a reduced statistical efficiency depending on the sizes of clusters randomized, the degree of intra-cluster correlation and/or between-cluster variance, which increases the population size by the so-called inflation factor or design effect (21, 22).

Planning of sample size, power and the length of the study. Our calculations are based on the Poisson approximation (Formula 1a and 1b), which can be used to compare probabilities below the lower limit of 0.05 or above the upper limit of 0.95 (23), provided that nP_{ref}, nP_{int} are large enough (≥ 10).

$$N = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (P_{ref} + P_{int})}{(P_{ref} - P_{int})^2} \quad [1a]$$

$$Z_{1-\beta} = \frac{\sqrt{N}(P_{ref} - P_{int})}{\sqrt{P_{ref} + P_{int}}} - Z_{1-\alpha/2} \quad [1b]$$

where

N = Size of one group (reference or intervention).

P_{ref} = Probability (incidence rate) of the reference group.

P_{int} = Probability (incidence rate) of the intervention group.

$Z_{1-\alpha/2} = 1.96$ (two-sided) or 1.64 (one-sided) with $\alpha = 0.05$.

$Z_{1-\beta} = 1.28$ with $1-\beta = 0.90$ or 0.84 with $1-\beta = 0.80$.

On the basis of crude sample size calculations, it appears that the effects in a young cohort and with a short follow-up result in unrealistically large sample sizes. Instead, exposure at 30 years of age and with a 20-years' follow-up will result in a sample size of substantially less than 10 000 subjects under the moderate assumption on effect. It is unlikely that any effect will be seen among those at 60 years at the start of the trial. However, if there is an effect, a relatively small number of individuals, (about 2 000–5 000) will be sufficient. Hence, it is likely that a sample size of about 70 000 persons or less than 10 000 families will ultimately, i.e., with a long follow-up, provide a definitive answer on the preventability of cancer by consumption of fruits and vegetables.

In order to plan for realistic sample sizes, we developed an alternative way to calculate the person years of our prospective cohort of a given size for a maximum of 50 years of follow-up. The calculation of the person years and the power is based on a method presented in Breslow & Day (24). We used the Estonian age-specific cancer incidence and age-specific general mortality data from 1988–1992 (25, 26). For determination of power and sample size, formulas 1a and 1b were used, where P_{ref} (probability of total cancer in the reference group) and P_{int} (probability of total cancer in the intervention group) are determined after a stepwise calculation of cumulative incidence rates in the corresponding age group for each additional year of follow-up (Table 3).

There are some restrictions and limitations in our calculations. First, we have only focused on figures of total cancer. Especially in the 10+ age group, these data come from childhood cancers, which are not expected to be influenced by environmental exposures, including diet. Second, person years and cumulative incidence rates are based on incidence and mortality data from 1988–1992, which we have to assume to be constant over the study period. Third, the maximum possible prevention effect of the intervention is assumed to be a 50% reduction in total cancer incidence.

In the 60+ age group, higher incidence rates result in lower sample sizes, but too small samples over many years are strongly influenced by higher mortality rates in higher age groups, so that the contribution to the total person years after each year grows more slowly, which leads to a slower increase in power by longer duration of the follow-up. According to Table 3, having 1 000 people in the younger age group (10+) requires 49 years of follow-up under assumption A to achieve the power of 90%. This is in contrast to 65 years of follow-up in the older age group (60+) under the same conditions. Again, with a total sample size of 20 000, i.e. 8 000 families, the trial would assume a follow-up of 20–30 years.

The final determination of sample size taking into consideration the cluster randomization and also the cost analysis based on it is to be provided in detail in the preparation study.

Cost estimates

Given that food can be obtained from sources with over-production, e.g. the European Union, and we have a defined study population of a maximum of 30 000 persons, the consumption would be about 500 g per day and person, which gives a daily requirement of about 15 000 kg. The

Table 3

Number of follow-up years required to demonstrate an effect by age group (trial starting at 10, 30 or 60 years of age) and assumption (A: realistic, B: moderate, C: optimistic as described before) and some sample sizes (N)

N	10+			30+			60+		
	A	B	C	A	B	C	A	B	C
1 000	49	43	42	41	32	27	65	38	23
2 000	44	38	36	35	28	23	47	26	17
5 000	39	33	30	29	23	19	31	18	13
10 000	35	29	26	26	20	17	22	15	11
20 000	32	27	23	23	18	14	18	12	9
30 000	30	25	21	21	16	13	16	11	8
50 000	28	23	19	19	14	12	14	10	7
100 000	25	20	18	16	13	10	12	8	6

transportation of 20 tons to the field from Germany, for example, would cost about €2 500 per day (Table 4).

Compared to the cost of chemoprevention trials with an annual budget of about €50–100 million or the costs of developing a new chemotherapeutic agent in oncology, these estimates seem to be feasible. Notice that, for example, in 1999, the Gross Domestic Product (GDP) per capita among Baltic countries ranged from $6 262 to $8 355, i.e. about 3–5 times lower than that of the US (31 872) providing a rough indication of the costs of personnel, which are correspondingly lower. Thus, the costs of infrastructure would also be substantially lower than, for example, those in the US and give additional support for the allocation of the study in these countries. Nevertheless, a detailed estimation of the costs of the study is needed and must be an essential part of a pilot study.

DISCUSSION

In the present paper, we propose a randomized intervention trial with healthy food in order to study (a) the causal and (b) the quantitative relationship between regular consumption of fruit and vegetables and the risk of cancer. We argue that the Baltic countries currently offer an ideal frame to investigate this issue: to some extent malnutrition from fruits and vegetables together with a developed healthcare system. However, the economic and social transition towards the modern western European lifestyle limits the time-frame of this unique opportunity to the next 10–15 years. We show that the costs of such a trial may be high but are no higher than those of the above-mentioned chemoprevention trials. Given the relevance of the issue, the investment appears justified. For the elaboration of the design, we only use data from Estonia, but the conclusions are also applicable to Latvia and Lithuania.

Many ethical issues need to be addressed when dealing with prevention trials. Nyrén (1998) points out that in the case of chemopreventive trials, a comparably small public health benefit (but often a considerable scientific benefit) should be weighed against a number of possible adverse effects also among those not participating in the study (27). A major characteristic of the population-based primary prevention trials is the absence of the disease under study. Large numbers of healthy people are to be included in the study over a long period of time, where no harm or side effects can be accepted and tolerated. The cost-benefit aspect and possible impact on society, e.g. medicalization of life, of such large-scale trials should be carefully investigated. A placebo control group is ethically acceptable only in short-term clinical trials but not in preventive trials lasting for several years. It is unethical to expect people to take placebos for many years unless they are aware of the consequences and are fully informed about the possibility of changing to the treatment group, which would face the investigators with methodological problems. Therefore, it would sometimes be useful to skip the control condition and to use incidence and mortality statistics from the source population as reference (27). While such considerations may be pertinent for chemopreventive trials, a healthy food trial should be mainly free of such drawbacks.

In the case of the proposed trial with fruits and vegetables, a careful cost-benefit analysis should be carried out in the preparation study. No harmful or adverse effects of consuming fruits and vegetables in the defined amount can be expected. In addition to cancer, CVDs have to be registered and monitored. In case of a significant protective effect regarding CVD after some years, the intervention should consequently be extended to the whole study population. Nevertheless, the effect on cancer incidence would remain detectable for a sufficient period of time. The ethics regulations in the Baltic countries will also be strictly followed. The major ethical objections are that the trial is unnecessary because the result is known before the start of the trial, the intervention is not valid because it is not specific enough, the cost exceeds benefit, and it is unethical to give free food to some and not to all.

The issues of cost and specificity of exposure have already been dealt with in this paper. There is no experimental (i.e. based on a randomized preventive trial) evidence so far. The evidence is indirect, laboratory-based and otherwise (and not generalizable to a public health policy) non-experimental (and subject to potential biases) epidemiology-based. 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, as it is not certain who—those exposed or controls—would benefit, it is better to provide benefit for somebody than for nobody, since obviously it is impossible to provide benefit for

Table 4

Cost model of the intervention according to different prices, based on daily need of 500 g of fruits and vegetables per person as well as a daily transport cost of about €2 500. Personal and storage costs have not been taken into consideration

Cost per kg	€1.00	€0.50	€0.10	Free of charge
Daily cost for 30 000 study population	€15 000	€7 500	€1 500	€0
Total daily cost including €2 500 for transport	€17 500	€10 000	€4 000	€2 500
Total annual cost during intervention	€6 387 500	€3 650 000	€1 460 000	€912 500

everybody. Promoting identical health habits such as those among the exposed is not justified as long as the evidence is not there, and as long as the trial is still incomplete.

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