Prevention of Cancer with Selenium

Danish Pilot Study

Status Report - February 2000

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Table of contents:

1 Protocol for the Danish Pilot Study

The study Prevention of Cancer with Selenium aims at testing the hypothesis that enhancing selenium intake with nutritional supplements will reduce cancer incidence rates. The Danish Pilot Study aimed at testing in a Danish population the willingness of the population to participate, the logistics of the study, and the resources needed to conduct the study.

A random sample of about 2,900 inhabitants in the county of Funen aged 60-74 years were invited to participate in the pilot study. Approximately 22% of the invited agreed to participate. The participants were invited by mail and recruitment followed the planned procedures for the study Prevention of Cancer with Selenium.

Letters of invitation were sent out from the Selenium Centre located at Odense University Hospital. Potential participants then called the Selenium Centre by phone to make an appointment for a baseline interview. Further they were asked whether they used selenium supplements (more than 50 μg of selenium per day) and/or whether they had had a previous cancer diagnosis.

First visit

At the baseline interview at the Selenium Centre the participants received further information regarding the study. They were interviewed according to the core questionnaire (Appendix A) and had a blood specimen drawn (Appendix B). Test tablets for the following four weeks and a food frequency questionnaire were handed out as well as an envelope for toe nail clippings. An appointment for the second visit at the Centre four weeks later was made.

After the first visit to the Selenium Centre the potential participants were informed about the results of the analyses of the blood samples. If the liver enzymes were marginally elevated we proposed analysing a second blood sample.

The day before the second visit eligible participants were randomized to receive placebo, or 100, 200, or 300 μg of selenium per day, and the tablets were labelled and packed.

Second visit

At the second visit, the interviewers received the blisters from the test period to assess compliance together with toe nail clippings, informed and written consent, and the filled-in food frequency questionnaire, which was checked for errors. The prelabelled tablets were handed out and arrangements were made for semiannual follow-up.

The interviewers and the data manager entered the data into the study database.

2 Study organisation

Søren Cold, M.D. Ph.D., is principal investigator for the Danish Pilot Study and the daily leader of the Selenium Centre. He is responsible for planning of practical procedures, employment, and education of the staff and for appointments with contractors.

Carsten Rose, M.D., is head of the National Steering Committee and responsible for relevant applications (The Danish Drug Administration, The Scientific Ethical Committee, The Data Surveillance Authority), for the budget, and for the clinical aspects of the study.

A Steering Committee has been established which is scientifically responsible for the Danish Pilot Study and for the Danish cohort.

The National Steering Committee includes the following experts:

Carsten Rose, Dept. of Oncology, Odense University Hospital: Oncology and clinical trials.
Anne Tjønneland, The Danish Cancer Society: Epidemiology, cohort studies, diet and cancer.
Kim Overvad, Department of Epidemiology and Social Medicine, Aarhus University: Selenium, epidemiology, cohort studies, diet and cancer.

The National Steering Committee further includes representation of organisations directly affected:

Oncology: Niels Holm, Dept. of Oncology, Odense University Hospital.

General practice: Jakob Kragstrup, professor, M.D., Ph.D., Institute of Medicine, Odense University.

Food administration: Lars Ovesen, director, The Danish Veterinary and Food Administration.

Medication: Sven Moesgaard, director, Pharma Nord.

Søren Cold is member of and secretary for the National Steering Committee.

During the recruitment period, the staff at the Selenium Centre included:

The principal investigator working part-time (1/4), who is the leader of the daily work at the Centre.

Two full-time interviewers, who take care of all interviews and most of the data management.

One part-time data manager (1/2), who looks after the budget and makes the appointments for the interviews.

One part-time secretary (1/4), who takes care of all the correspondence.

One part-time laboratory technician (1/4), who draws the blood specimens and handles the blood for analyses and storing. The laboratory technician is employed at the Dept. of Oncology, which influences the amount of analyses possible in the pilot study.

One part-time pharmacist (1/10), who handles the randomization and the tablets.

One part-time computer adviser, who installs and develops the relevant computer software.

During the follow-up period the staff includes:

Two part-time interviewers (1/2 x 2),who take care of all contacts to the participants and data entry.

One part-time secretary (1/10), who takes care of all the correspondence.

One part-time laboratory technician (1/4),who draws the blood specimens and handles the blood for analyses and storing. The laboratory technician is employed at the Dept. of Oncology, which influences the amount of analyses possible in the pilot study.

One part-time pharmacist (1/10), who handles the tablets.

3 The first fifteen months of the Danish Pilot Study

The relevant permissions for the Danish Pilot Study were received by November 1, 1998 and the staff was employed early November. The database regarding the relevant population was received and on November 13th the first 300 letters of invitation were posted. On November 20th the first participants came for the first interview.

By September 1st , a total of 2,897 individuals have been invited to participate in the study. Six-hundred- and thirty have accepted to participate, 5.9% of the invited subjects have accepted after a reminder. The cumulative positive response thus equals 22%. The figures regarding invitation and participation are shown in Table 1.

The participation declines with increasing age. Thus, 43.5% were recruited in the age group 60-64 years, while only 23.2% in the age group 70-74 years (Table 2). Reasons for negative response are listed in Table 3. Questionnaire data from 493 participants are listed in Table 4.

The time spent conducting a first time interview is 30-40 minutes and 20-25 minutes for the second. In the spare time between the interviews, the interviewers enter data into the computer, prepare the interviews including printing of questionnaires etc., and plan letters of invitation and check the results of the analyses of the blood samples. In the pilot study the slow recruitment of participants and the limited staff limits optimal use of resources when e.g. an interview is concluded.

Adverse events

For the time being, 13 participants have withdrawn from the study due to possible side-effects, two during run in and 11 after randomization. The characteristics of these participants are were:

During run in:

2 gastrointestinal side-effects

After randomization:

4 hair loss/problems; 2 central nerve system (dizziness); 2 bad odour/perspiration; 1 itching; 1 gastrointestinal; 1 swollen legs.

Only one participant was hospitalized with known arthritis and stomach problems. The stomach problems disappeared after discontinuation of the study medication.
All other possible adverse events disappeared after discontinuation of the study medication.

First semi-annual follow-up (visit 0.5)

Summing up

Our aim of reaching 500 active participants has almost been reached by 463 randomized participants still active in the study. From the invitations for the first semi-annual follow-up the impression is that the compliance is excellent. Thus, only the participants who experienced side-effects (please see above) or were too ill (not related to trial participation) have dropped out. Regarding obtaining an equal number of active participants in the three 5-year age groups, one has to take into account the declining participation in the older age groups.

4 Economy and resources

The budget and the time resources allocated seem to meet the scheduled work load. From the original budget, the costs for computers, operations and staff regarding manager, interviewers, secretary and data manager have balanced, while the costs for programme development, laboratory technician, and pharmacist were somewhat larger than expected and could only be covered from the overhead of the other budget items (Appendix C).

Regarding extension of the study pilot in time the cost for each month equals about 50,000 D.Kr. For the time being the costs are covered until the end of June 2000.

5 Experiences from the Danish Pilot Study

A reminder letter was sent out to all potential participants who did not respond to the first letter of invitation. The response to the first letter was approximately 20% and the response increased to approximately 25% after the reminder letter. A reminder letter will thus increase participation,

but if the source population is large enough, it will be more efficient to invite new potential participants.

The PI, Søren Cold, did spent about 50% effort in developing procedures and questionnaires, hiring staff, and supervising the daily work. After establishing the study, approximately 10% effort seems required to further develop, report, and supervise daily routines.

Costs for the laboratory technician and pharmacist should be incorporated into the budget for the full scale study.

It is probably possible to optimize and perhaps automate some of the daily routines with regard to interview and data management, when the study runs in large scale. Minor overbooking may also be an option with further interviewers.

Due to the original protocol some limits for liver and kidney function were introduced. These limits seemed to exclude approximately 10% of the potential participants. There are no substantial arguments for this exclusion and for the future only potential participants reporting serious chronic liver or kidney diseases will be excluded.

Table 1

Participation in the Danish Pilot Study

Number of people invited		2897
No response		2050
Negative total response		217
Positive response		630
- first letter of invitation	593	
- after one reminder	37	

Withdrawn participants by 01.01.2000	
Non-participating for various reasons	4
Dropped out before first visit	5
Too high Selenium intake at first visit	9
Forgot to take tablets	6
Previous cancer	0
Increased creatinine	4
Increased SPGT	44
Increased creatinine (spouse)	2
Increased SPGT (spouse)	8
Regretted enrolment	38
Side-effects (placebo tablets)	2
Side-effects (project tablets)	11
Side-effects (spouse)	1
Illness	25
Illness (spouse)	7
Death	1
Total	167

Table 2

Participation in the Danish Pilot Study according to age

Age	Invited	Accepted to participate	% of participants
60-64	1061	274	43.5
65-69	978	210	33.3
70-74	836	146	23.2
75+	22		
Total	2897		

Table 3

Reasons for initial negative response

- do not speak Danish	8
- cancer	24
- transportation	17
- diseases/deaths	64
- consumes Selenium	40
- unknown	64
Total	217

Table 4:

Data from 493 patients where all data have been computerized:

Education	
7 years or less	271
8-10 years	184
More than 10 years	38
Unknown	0
Further education	
No vocational education	140
Short further education (shorter than 3 years)	81
Medium length education (3-4 years)	226
Long education (more than 4 years	46
Information not given	0
Employment	
Employed (part-time work included)	63
Unemployed	3
Retired	170
Retired due to illness	38
Retired due to age	205
Homebound mother or father	10
Others: _____	4
Information not given	0
Marital status	
Married	397
Unmarried	16
Separated	4
Divorced	25
Widow/widower	51
Information not given	0

Are you living alone?	
Yes	72
No	421
Information not given	0

Smoking habits

Did you use to smoke?	
Yes	334
No	159
Information not given	0
Do you smoke daily presently?	
Yes	148
No	345
Information not given	0

Average/day:	
- cigarettes	13 (based on 114 participants)
- cheroots	5 (based on 10 participants)
- cigars	2 (based on 1 participant)
- pipe	9 (based on 31 participants)

Alcohol habits:

How <u>often</u> do you usually drink alcohol (beers, wine, fortified wine, or spirits)?

		Average drinks/week
Do not drink beer, wine, fortified wine or spirits	12	0
Less than once a month	33	0.03
1-3 times a month	85	1.18
Once a week	136	4.85
2-4 times a week	59	7.71
5-6 times a week	16	11.13
Every day	152	14.68

Vitamin / medicine

Do you consume vitamin tablets and/or other kinds of dietary supplements?

		Average
Yes	333	2.05
No	160	

Medication prescribed by GP:

Yes	178	2.63
No	315	

Screening tests

Did you ever participate in a screening test?

Mammography	221
Intestine	87
Cervix uteri (smear)	82
Others	11

Level of physical ability

How is your physical ability?

Normal, no complaints	419
Normal activity, light signs of disease or symptoms	49
Normal activity, but with difficulty	15
Resourceful, decreased activity, unable to work	6
Ambulatory, need some help, but in general resourceful	3
Outside area	(1)

Appendix A: Questionnaire

Education and employment

Education

1 How many years did you go to school?

- 7 years or less (primary school) ❑
- 8-10 years (high school) ❑
- More than 10 years (A-levels) ❑
- Information not given ❑

2 Which further education have you done?

- No vocational education ❑
- Short further education (shorter than 3 years) ❑
- Medium length education (3-4 years) ❑
- Long education (more than 4 years) ❑
- Information not given ❑

Employment

3 Are you presently:

- Employed (part-time work included) ❑
- Unemployed ❑
- Retired due to illness ❑
- Retired due to age ❑
- Homebound mother or father ❑
- Others: _____ ❑
- Information not given ❑

The next questions deal with marital status:

4 What is your marital status?

- Married ❑
- Unmarried ❑
- Separated ❑
- Divorced ❑
- Widow/widower ❑
- Information not given ❑

5 Are you living alone?

Yes ❑

No ❑

Information not given ❑

Smoking habits:

6 Did you ever smoke cigarettes, cheroots, cigars or pipe regularly, i.e. at least one cigarette, one cheroot, one cigar or one pipe stop daily during one year?

Yes ❑

No ❑

Information not given ❑

7 Do you smoke daily now?

Yes ❑

No ❑

Information not given ❑

8 If yes, how much do you smoke on a daily basis?

Cigarettes: _____

Cheroots: _____

Cigars: _____

Pipe: _____

Alcohol habits:

9 How <u>often</u> do you usually drink alcohol (beers, wine, fortified wine, or spirits)?

Do not drink beer, wine, fortified wine or spirits ❑

Less than once a month ❑

1-3 times a month ❑

Once a week ❑

2-4 times a week ❑

5-6 times a week ❑

Every day ❑

10 How many drinks (beer, wine, fortified wine, or spirits) do you usually drink during the week? _____ drinks

11 Do you consume vitamin tablets and/or other kinds of dietary supplements?

Yes ❑

No ❑

If yes, please fill in the questionnaire

"Vitamins, minerals, herbs, and other dietary supplements"

Vitamins, minerals, herbs, and other dietary supplements

12 If you presently consume vitamin tablets and/or other kinds of dietary supplements, we kindly ask you to state the different preparations here.

If you do not consume any kinds of dietary supplements, please tick here ❑

Type of dietary supplement	Dosage	How often?	Reason	Date of first consumption
Example: Iron	325 mg	1 x daily	Anaemia	111992

Medical information

13 We kindly ask you to state all the medication prescribed by your physician you are consuming presently?

If you do not consume any medicine, please tick here ❑

Type of dietary supplement	Dosage	How often?	Reason	Date of first consumption	Physician
Example: **Penicillin**	**250 mg**	**3 x daily**	**Bronchitis**	**1297**	**NO**

14 Did you ever participate in a screening test?

Mammography? Yes ❑ No ❑ Information not given ❑

Date for latest test: _____

Intestine? Yes ❑ No ❑ Information not given ❑

Date for latest test: _____

Cervix uteri (smear)? Yes ❑ No ❑ Information not given ❑

Date for latest test: _____

Others: _____ Yes ❑ No ❑ Information not given ❑

Date for latest test: _____

15 How is your physical ability?

Normal, no complaints ❑

Normal activity, light signs of disease or symptoms ❑

Normal activity, but with difficulty ❑

Resourceful, decreased activity, unable to work ❑

Ambulatory, need some help, but in general resourceful ❑

Appendix B:

Handling of blood specimens

Samples taken from each participant:

1. 2 x 10 ml Sodium Heparin Venoject Tubes (green top).
2. 3 x 5 ml silicone-coated Venoject Tubes (red top).

1 a.:

Each tube is marked with the participant's serial number. The two tubes for plasma are immediately after drawing inverted 8 - 10 minutes to mix anticoagulant with blood. Approximately 20 minutes later, they are centrifuged for 10 minutes at 3000 rotations/minute at 6 - 8° C. From the Heparin tubes 6 ml of plasma and 2 ml of red blood cells are stored. In the pilot study, buffy coat preparations are not done due to lack of resources (cannot be fitted in to the daily working routine of the laboratory technicians working at the department of Oncology).

Six 1 ml Nunc-polypropylene tubes of plasma are stored at - 80° C immediately after these procedures.

1 b.:

The two Sodium Heparin tubes that contain RBC are washed twice with 0,9 % Nace. Two 1 ml Nunc-polypropylene tubes of RBC are stored at - 80° C immediately after the procedure.

2a.:

One of the three silicone-coated Venoject tubes is used for determination of S-alanin-aminotransferase and S-creatinin. The two other tubes are stored at room temperature for an hour to clot. Thereafter, the tubes are centrifuged for 10 minutes at 3000 rotations / minute at 6 - 8 ° C. Four 1 ml Nunc-polypropylene tubes of serum are stored at - 80°C immediately after the procedure.

Appendix C

Budget for the Danish Pilot Study - end of 1999

Income (in Danish Kroner):

The Research Foundation of Funen*)	637,000
The Foundation Office at Odense University Hospital	50,000
The Research Foundation of the County of Funen	65,000
Granted from Cypress Systems $50,000	318,000
The Danish Cancer Society	120,000
In total	**1,190,000**

Expenses:			
- Computers	62,000		
- Computer consultant	130,000		
- Miscellaneous	4,000		198,000
Staff:			
- Study coordinator	140,000		
- Interviewers (2) and data manager	696,000		
- Secretary (3 hrs./week)	45,000		
- Laboratory technician	75,000		
- Pharmacist	22,000		978,000
Operational expenditures			14,000
In total			**1,190,000**

*) Donations received from K.A.Rohde's Foundation, Dagmar Marshall's Foundation, Pharma Nord, Danish Veterinary and Food Administration, The Clinical Experimental Research Foundation at Department of Oncology, Odense University Hospital.