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ORIGINAL PAPER

Serum selenium and pancreatic cancer: a prospective study in the Prostate, Lung, Colorectal and Ovarian Cancer Trial cohort

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Abstract

Purpose Pancreatic cancer(PCa) is one of the most lethal cancers with few known consistent nutrition-related risk factors. Epidemiologic associations between the trace element selenium and PCa are inconsistent. This study examined the association of pre-diagnostic serum selenium with incident PCa.

Methods We conducted a nested case–control study within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Study (PLCO) cohort of men and women 55–70 years old at baseline (1993–2001). In total, 303 PCa cases developed during the 17-year follow-up period (1993–2009). We selected two controls ($n=606$) for each case who were alive at the time the case was diagnosed who were matched on age, sex, race, and date of blood draw. We used conditional logistic regression analysis to calculate the odds ratio (OR) and 95% confidence intervals (CI) adjusting for smoking status and diabetes mellitus.

Results Mean serum selenium concentrations were slightly lower in cases (mean, 95% CI: 139.0 ng/ml, 135.6–138.9) compared to controls (142.5 ng/ml, 140.4–142.4, $p=0.08$). Overall, serum selenium was not associated with PCa risk (continuous OR: 0.66; 0.32–1.37). There was no significant interaction by sex, smoking, diabetes, or follow-up time ($p>0.05$).

Conclusion Our results do not support the hypothesis that serum selenium is associated with PCa risk.

Keywords Selenium · Pancreatic cancer · Cancer prevention · Case–control study · Humans

Introduction

Pancreatic cancer (PCa) is highly lethal and contributes to cancer mortality globally [1]. Most PCa presents at an advanced stage and treatments have minimal impact on survival [2]. Identifying potentially modifiable risk factors for PCa is important for decreasing its burden.

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Epidemiological evidence, experimental, and animal studies suggest that the trace element selenium protects against carcinogenesis [3, 4]. Selenium, an important antioxidant critical to the formation of antioxidant protein glutathione peroxidase, maintains cellular reducing environment [5]. Selenium supplementation enhances DNA damage repair response by reducing the frequency of DNA adducts and chromosome breaks, consequently reducing detrimental mutations that contribute to carcinogenesis. Additionally, selenium may boost p53 activity leading either to DNA repair or apoptosis [6]. Selenoproteins and selenium metabolites also reduce pancreatic carcinogenesis in animal models [7].

The Nutrition Prevention of Cancer trial (NPCT), the first randomized trial in western population designed to investigate effect of selenium on cancer risk, reported significantly lower total cancer incidence and mortality in patients assigned to selenium supplementation [8]. Additional epidemiologic evidence demonstrating inverse association between selenium, vitamin E and β-carotene, and gastrointestinal cancer comes from large randomized trials

conducted in Linxian, China [9]. A systematic review of nine randomized trials also suggests that selenium reduces the risk of all gastrointestinal cancers significantly by 41% [10].

Association for selenium status/intake and PCa risk is conflicting. Though dietary, serum, and toenail selenium have shown inverse associations with PCa risk [11–14], some of these studies included small number of PCa cases ($n = 22$ to 118) and had limited power [11, 12]. Two meta-analyses of six epidemiologic studies have reported protective associations between selenium intake and PCa risk with stronger associations observed for case–control studies [15]. Dietary selenium may not accurately assess an individual's selenium status [13, 14]. Our main objective was to examine whether pre-diagnostic serum selenium is prospectively associated with PCa risk. We hypothesized that higher serum selenium concentrations would be inversely associated with incident PCa. To the best of our knowledge, this is the largest prospective study to date to evaluate the association between serum selenium and PCa risk.

Methods

Study design and setting

We conducted a nested case–control study within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Study (PLCO) [16]. PLCO was a large randomized multi-center trial conducted at ten centers in the United States (US). Approximately 155,000 participants aged between 55 and 74 years were followed up for ≥ 13 years from day of randomization to ascertain incident cancer cases of prostate, lung, colorectal, and ovary. Written informed consent was obtained from all participants and the study was approved by Institutional Review Boards of all ten participating centers and the US National Cancer Institute [16].

Case ascertainment and control selection

Cases in this study were defined as confirmed incident cases of primary PCa (ICD-O-3 code C25.0-C25.9) [17]. Endocrine pancreatic tumors thought to have different etiology from exocrine tumors were excluded. Controls were alive and free of PCa when case was diagnosed and were matched to cases by age (± 5 year), sex, race, and date of blood draw in 2-month blocks (case–control ratio: 1:2). Vital status of cases and controls were recorded from annual mail-in survey, cancer registries, and National Death Index.

Serum selenium

Non-fasting blood samples, collected at baseline from intervention arm participants were processed within 2 h, either on site or at a designated laboratory and stored at − 70 °C [18]. Selenium was measured by an automated electro-thermal atomic absorption spectrophotometer using graphite tubes on an instrument with detection limit of 20 ng selenium/ml (Perkin-Elmer model 3030; Perkin-Elmer Corporation, Norwalk, Connecticut). All specimens were similarly handled with laboratory blinded to case–control status. The selenium was run consecutively across multiple batches. Matched case and control samples were analyzed consecutively as triplets within batches and we included a 10% blinded replicate quality control (QC) . Using nested components of variance analysis, with logarithmically transformed QC measurements across all batches, the estimated overall coefficient of variation for serum selenium assay was 5.5% for intra-batch and 7.4% for between-batch reliability.

Diet, vitamin/mineral supplements, and baseline characteristics

At screening, participants completed a self-administered baseline questionnaire that included medical history, family history of cancer, tobacco use, selected drug use, height, weight, physical activity, and other exposures. Dietary intake was assessed using a self-administered food frequency questionnaire, which used a grid to determine frequency of 137 food items consumed over past 12 months, 77 of which inquired about usual portion size [19]. Fourteen types of supplemental vitamin and mineral were assessed by asking number of pills, and whether supplement was taken currently or 2 years or 5 years ago. Supplemental selenium use and dose was derived from multivitamin use.

Statistical analysis

The distribution of selected characteristics of cases and controls were compared using Wilcoxon rank-sum tests for continuous variables and Chi-square (χ^2) tests for categorical variables. Dietary nutrients and foods highly correlated with energy were energy-adjusted using residual method [20]. Quintile cut-points were based on distribution of controls with the lowest quintile as the reference group, and a score variable of median value of each quintile was used for trend tests. Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Multivariable models were developed by individually adding potential confounders (Table 1) to model. Covariates were included if they were associated with both disease and risk factor and changed the risk estimates ≥ 10%. Smoking status and history of diabetes were included in our final model. Linear trends were tested with use of a p value based on a continuous score variable of the median values within each quintile of controls. Continuous ORs were determined

Table 1 Selected baseline characteristics of pancreatic adenocarcinoma cases and control participants (median and inter-decile range or number and proportion)

Characteristics	Cases ($n=303$)	Controls ($n=606$)	p value[a]
Age, years	64.6 (64.03–65.2)	64.5 (64.1–64.9)	0.84
Sex, male, *n* (%)	187 (61.7%)	374 (61.7%)	1.00
Serum selenium, nmol/L			
Overall	139.0 (135.6–138.9)	142.5 (140.4–142.4)	0.08
Smokers	137.1 (129.8–144.4)	132.8 (126.9–138.7)	0.37
Diabetes mellitus	142.7 (134.5–150.9)	146.4 (138.1–154.6)	0.39
Race, *n* (%)			
White	271 (89.4)	542 (89.4)	1.00
Black	12 (3.9)	24 (3.9)	
Hispanic	4 (1.3)	8 (1.3)	
Asian	15 (4.9)	30 (4.9)	
Cigarette smoking history, *n* (%)			
Never	121(39.9)	301 (49.7)	< 0.0001
Current	54 (17.8)	42 (6.9)	
Former	128 (42.2)	263 (43.4)	
Height, cm			
Male	177 (176–178)	171.9 (171.1–172.7)	0.14
Female	162.6 (161.3–163.9)	162.3 (161.4–163.2)	0.7
Body Mass Index, kg/m^2	26.6 (22.4–32.6)	26.6 (22–32.6)	0.61
WHO cut-points, *n* (%)			
< 25.0	105 (34.7)	215 (35.5)	0.68
≥ 25.0 and < 30	129 (42.6)	268 (44.2)	
≥ 30	69 (22.8)	123 (20.3)	
Medical history, *n* (%)			
Diabetes mellitus	39 (12.8)	49 (8.1)	0.02
Gallbladder disease	42 (13.9)	70 (11.6)	0.33
Family history of pancreatic cancer, *n* (%)	10 (3.3)	17 (2.8)	0.14
Education, *n* (%)			
School education	92 (30.4)	190 (31.4)	0.37
Post-high school, vocational training	39 (12.9)	58 (9.6)	
Some college	57 (18.8)	133 (21.9)	
College and post graduate education	115 (37.6)	225 (37.1)	
Dietary intake[b], per day			
Alcohol, g	13.6 (9.6–17.9)	11.3 (9.1–13.5)	0.47
Red meat, g	31.1 (26.5–35.6)	29.7 (26.5–32.9)	0.96
Vigorous physical activity, hours per week[c], *n* (%)			
None or < 1 h	101 (36.3)	166 (29.1)	0.9
1 to 3 h	73 (26.3)	163 (28.6)	
> 3 h	104 (37.4)	242 (42.4)	

[a]p values for categorical variables based on chi-square or Fisher's exact test and p values for continuous variables based on Wilcoxon rank-sum test

[b]Dietary intake adjusted for energy using the residual method

[c]Vigorous activity variables based on n = 278 cases and n = 571 controls

by standardizing to per-unit quintile change. Effect modification by sex, BMI, diabetes, smoking, and follow-up time were also evaluated in stratified analysis and tested with a multiplicative interaction term added to the model. Analyses were done employing SAS® V9.2 (Cary, NC).

Results

There were 303 incident PCa cases that developed between baseline (1993 to 2001) and 2009 (follow-up to 16 years, median 7 years). Most participants were non-Hispanic

Whites (89%) and cases and controls were mostly males (61%). There was no significant difference ($p = 0.08$) in mean selenium levels between cases (mean 139.0 ng/ml, 95% CI 135.6–138.9 ng/ml) and controls (mean: 142.5 ng/ml, 95% CI 140.4–142.4 ng/ml). Significantly more cases than controls reported being diabetic ($p = 0.02$) and current smoker ($P < 0.0001$). Other baseline characteristics were similar between cases and controls (Table 1). Table 2 shows higher serum selenium concentrations to be related to more college education, being overweight (BMI 25 to 30 kg/m^2) and diabetes. In contrast, being a current smoker

Table 2 Selected characteristics of control subjects (means or proportions) by quintile of serum selenium concentration

Characteristics	Serum selenium, nmol/L[a] (quintiles)				
	Q1	Q2	Q3	Q4	Q5
	≤ 125	> 125 to ≤ 137.6	> 137.6 to <146.6	> 146.6 to ≤ 160	> 160
Serum selenium, nmol/L	111	127	142	155	172
Age, years	64.8	64.7	65.3	63.8	64.2
Sex, male, *n* (%)	71 (57.7)	74 (61.7)	73 (60.3)	86 (70.5)	70 (58.3)
Race, *n* (%)					
White	106 (86.2)	106 (88.3)	110 (90.9)	109 (89.3)	111 (92.5)
Black	8 (6.5)	6 (5.0)	6 (5.0)	2 (1.6)	2 (1.7)
Hispanic	2 (1.6)	2 (1.7)	2 (1.7)	1 (0.8)	1 (0.8)
Asian	7 (5.7)	6 (5.0)	3 (2.5)	8 (6.6)	6 (5.0)
Cigarette smoking history, *n* (%)					
Never	58 (47.2)	66 (55.0)	61 (50.4)	58 (47.5)	58 (48.3)
Current	13 (10.6)	8 (6.7)	11 (9.1)	9 (7.4)	1 (0.8)
Former	52 (42.3)	46 (38.3)	49 (40.5)	55 (45.1)	61 (50.8)
Height, cm					
Male	178.5	177.1	178.6	177.0	178.3
Female	162.4	162.9	162.1	161.1	162.6
Body Mass Index, kg/m^2					
WHO cut-points, *n* (%)					
< 25.0	46 (37.4)	43 (35.8)	43 (35.5)	45 (36.9)	38 (31.7)
≥ 25.0 and < 30	50 (40.7)	54 (45.0)	57 (47.1)	48 (39.3)	59 (49.2)
≥ 30	27 (22.0)	23 (19.2)	21 (17.4)	29 (23.8)	23 (19.2)
Medical history, *n* (%)					
Diabetes mellitus (yes)	8 (6.6)	12 (10.1)	5 (4.1)	10 (8.3)	14 (11.7)
Gallbladder disease (yes)	16 (13.1)	17 (14.3)	12 (9.9)	10 (8.3)	15 (12.5)
Family history of pancreatic cancer, *n* (%)	4 (3.3)	1 (0.8)	2 (1.7)	3 (2.5)	7 (5.8)
Education, *n* (%)					
School education	37 (30.1)	40 (33.3)	36 (29.8)	44 (30.1)	33 (27.5)
Post-high school, vocational training	11(8.9)	12 (10.0)	1 1(9.1)	10 (8.2)	14 (11.8)
Some college	33 (26.8)	16 (13.3)	35 (28.9)	24 (19.7)	25 (21.0)
College and post graduate education	42 (34.2)	52 (43.3)	39 (32.2)	44 (36.1)	48 (40.0)
Dietary intake,[b]per day					
Alcohol, g	10.1	11	11.6	15.5	8.2
Red meat, g	35.5	34.8	35	38.1	37.1
Vigorous physical activity, hours per week[c], n (%)					
None or < 1 h	21 (17.1)	27 (22.5)	25 (20.7)	19 (15.6)	15 (12.5)
1 to 3 h	53 (43.1)	45 (37.5)	48 (39.7)	54 (44.3)	57 (47.5)
>3 h	49 (39.8)	48 (40.0)	48 (39.7)	49 (40.2)	48 (40.0)

[a]Serum quintiles based on distribution of all controls (n = 606)

[b]Dietary intake adjusted for energy using the residual method

[c]Vigorous activity variable based on 571 controls

and greater alcohol use was associated with lower selenium concentrations.

Overall, there was no significant association between serum selenium and PCa risk (adjusted OR 0.74, 95% CI 0.46–1.20; $p_{trend} = 0.34$). A threshold analysis done comparing Q2-5 to Q1 also did not show a significant association between serum selenium and PCa risk (adjusted OR 0.84, 95% CI 0.57–1.23; $p = 0.40$). Inverse associations were apparent among participants with higher BMI (> 25 kg/m^2, high vs. low quintile, OR 0.53, 95% CI 0.27–1.03, $p_{trend} = 0.16$), but no such association was observed among participants with BMI ≤ 25 kg/m^2 and the interaction did not reach statistical significance ($p_{interaction} = 0.5$). There was no significant interaction of selenium and PCa association by sex, smoking, diabetes, or follow-up time (p value > 0.05). Association among cases diagnosed during first 5 years of follow-up (OR 0.79, 95% CI 0.28–2.23; $p_{trend} = 0.55$) was similar to those diagnosed 5 years or more after baseline (OR 0.74, 95% CI 0.43–1.27, $p_{trend} = 0.46$) (Table 3).

Discussion

We did not observe significant association between prediagnostic serum selenium levels and subsequent PCa risk. Our findings are consistent with the cancer prevention study conducted within a Finnish cohort reporting non-significant association of baseline dietary selenium intake with PCa risk [21]. Though an initial meta-analysis of nine randomized trials reported an inverse association of selenium with PCa risk, sub-group analysis after excluding five high-bias studies showed no association (OR 0.67, 95% CI 0.19–2.38) [10]. In contrast to our study, other prospective studies of selenium intake and PCa risk have observed inverse associations. The European Prospective Investigation of Cancer (EPIC)-Norfolk cohort study, which assessed dietary selenium intake using 7-day food diaries (23,658 cohort participants, 49 cases), demonstrated that high selenium intake was associated with reduced PCa risk across a threshold (Q2-4 vs. Q1, Hazard ratio (HR) 0.49, 95% CI 0.26–0.93, $P < 0.05$) [14]. Similar results were reported from the VITAL study for selenium from foods (77,446 cohort participants, 162 cases, medium vs. low intake: HR 0.58, 95% CI 0.35–0.94; high vs. low intake: HR 0.44 95% CI 0.23–0.85; $p_{trend} = 0.01$) but not total selenium which included supplements [13]. While our results are suggestive of a threshold association like these studies, we did not observe a significant threshold association. Finally, a recent French cohort study of 38,812 middle-aged participants showed inverse associations between total dietary selenium (diet and supplements) and gastrointestinal cancers which included 26 PCa cases with stronger inverse associations observed among those with higher alcohol use [22]. It is possible that the inverse associations in these studies might be related to other exposures correlated with higher selenium intake and/or the synergistic effect of several correlated micronutrients. Moreover, selenium in these studies assessed from the participants' dietary intakes might have measurement errors that can lead to inaccurate risk estimates. Correlation between dietary measurements and selenium biomarkers (in whole blood and plasma) have often shown poor to modest results ($r = 0.1$ to 0.4) or no correlation at all [23].

Our results also differ from those of three observational studies that found significant inverse associations between plasma or toenail selenium concentrations and PCa risk. A prospective nested case–control study conducted in Washington County Maryland showed a 3.9-fold elevated risk of PCa comparing lowest to highest tertiles of serum selenium that was independent of smoking, education level, and total carotenoids, ß-carotene, lycopene, or α-tocopherol [11]. The study reported pre-diagnostic serum selenium concentrations to be lower in cases (median 1.29 ± 0.04 µmol/l) than in controls (median 1.42 ± 0.03 µmol/l) [11]. The study was, however, conducted on a small number of cases and controls ($n = 22$ cases; $n = 44$ controls) with limited power [11].

A case–control study conducted on 118 cases and 399 controls [12] reported high concentrations of toenail selenium to be inversely associated with PCa risk (Q4 > 0.68 ug/g compared to Q1 ≤ 0.52 ug/g adjusted OR = 0.06 95% CI 0.02–0.16, p trend $= 2.62 \times 10^{-10}$). An additional Polish case–control study of 100 advanced PCa cases and 100 healthy matched controls showed a threshold association with participants with serum selenium concentration < 67.45 Ug/l, having an elevated PCa risk [24]. Higher selenium concentrations were associated with a non-significant longer survival [24]. These latter studies were also limited by their relatively small number of cases and their retrospective design and potential of reverse causation as selenium concentrations might be lower in cases with prevalent disease. In contrast to these studies, our study is prospective with a larger number of incident cases and up to 16 years of follow-up.

Rodent studies examining the effect of selenium supplementation on PCa risk have reported mixed results. While some studies have demonstrated protection particularly in combination with beta-carotene or retinol [25], others have shown no effect of selenium alone on PCa risk [26]. Effect of selenium supplementation on PCa risk in recently developed animal models has not been reported.

Inverse associations for selenium and gastrointestinal cancer risk has been observed in locales with relatively low soil selenium content and in malnourished populations [9]. It is possible that, in populations with marginal or deficient selenium status, selenium supplementation may be protective for cancer through supporting optimal expression of antioxidant selenoenzymes. At least one of those, the

Table 3 Adjusted odds ratios (OR) and 95% confidence intervals (CI) of baseline serum selenium concentration and pancreatic cancer, among 303 cases and 606 matched control subjects

	Serum selenium units[a] (quintiles)					*p* trend	OR- cont
	1	2	3	4	5		
	≤ 125	> 125 and ≤ 137.6	> 137.6 and ≤ 146.6	> 146.6 and ≤ 160	> 160		
Combined characteristics							
Case/controls, *n*	80 /123	53/120	51/121	58/122	59/120		
Crude OR (95% CI)[b]	1.00 (referent)	0.63 (0.41–0.98)	0.59 (0.38–0.93)	0.66 (0.43–1.06)	0.67 (0.42–1.07)	0.18	0.57 (0.28–1.17)
Adjusted OR (95% CI)[c]	1.00 (referent)	0.65 (0.41–1.02)	0.60 (0.38–0.96)	0.67 (0.42–1.07)	0.74 (0.46–1.20)	0.34	0.66 (0.32–1.37)
Men							
Case/controls, *n*	46/71	36/74	30/73	35/86	39/70		
Crude OR (95% CI)[b]	1.00 (referent)	0.70 (0.40–1.23)	0.60 (0.34–1.07)	0.57 (0.32–1.03)	0.78 (0.43–1.40)	0.42	0.74 (0.30–1.82)
Adjusted OR (95% CI)[c]	1.00 (referent)	0.72 (0.40–1.28)	0.59 (0.33–1.07)	0.57 (0.31–1.05)	0.87 (0.47–1.56)	0.64	0.87 (0.34–2.21)
Women							
Case/controls, *n*	34/52	17/46	21/48	23/36	20/50		
Crude OR (95% CI)[b]	1.00 (referent)	0.52 (0.26–1.05)	0.58 (0.28–1.20)	0.84 (0.42–1.69)	0.52 (0.24–1.13)	0.25	0.38 (0.12-1,21)
Adjusted OR (95% CI)[c]	1.00 (referent)	0.54 (0.26–1.20)	0.62 (0.29–1.29)	0.86 (0.41–1.78)	0.56 (0.25–1.24)	0.33	0.41 (0.12–1.38)
P interaction (gender) = 0.64							
BMI ≤ 25							
Case/controls, *n*	25/46	21/43	14/43	18/45	26/38		
Crude OR (95% CI)[b]	1.00 (referent)	1.04 (0.37–2.97)	0.85 (0.32–2.23)	0.78 (0.28–2.23)	1.09 (0.38–3.12)	0.99	1.12 (0.23–5.52)
Adjusted OR (95% CI)[c]	1.00 (referent)	1.04 (0.33–3.24)	0.69 (0.23–2.03)	0.72 (0.23–2.29)	1.10 (0.34–3.60)	0.99	1.16 (0.20–6.77)
BMI > 25							
Case/controls, *n*	55/77	32/77	37/78	40/77	33/82		
Crude OR (95% CI)[b]	1.00 (referent)	0.39 (0.21–0.73)	0.51 (0.26–0.96)	0.62 (0.34–1.15)	0.52 (0.27–0.99)	0.14	0.36 (0.14–0.96)
Adjusted OR (95% CI)[c]	1.00 (referent)	0.40 (0.21–0.76)	0.46 (0.25–0.90)	0.61 (0.33–1.16)	0.53 (0.27–1.03)	0.16	0.37 (0.14–1.01)
P interaction (BMI) = 0.5							

[a]Serum selenium quintiles based on distribution of all controls

[b]Crude OR adjusted for matching variables (age, race, sex, date of blood draw based on 2 month blocks)

[c]Age adjusted for history of diabetes (median trend WHO categories) and smoking (never, former quit > 15 years ago, former quit < 15 years ago, current)

extracellular glutathione peroxidase is known to be suboptimally expressed in individuals with serum selenium concentrations below 70 ng/ml [27]. Subjects in our study had serum selenium levels much greater than that range (96% had plasma selenium above 90 ng/ml). Different associations for PCa risk might be observed in populations with lower selenium status.

Our study has methodological strengths. Our study is a prospective study with cases and controls selected from same source population, therefore not subject to selection bias of either cases or controls and has internal validity. Serum selenium measures were performed on blood samples collected prior to PCa diagnosis reducing the likelihood of reverse causation. Limitations of our study include having only a single measure of serum selenium level. However, a

single measure of selenium in blood may reasonably reflect long-term selenium intake and is relatively accurate in assessing selenium intake in population. Our study did not assess the role of genetic interaction with selenium in the development of PCa. Genetic data might provide insight into biological mechanisms that underlie differing associations observed across studies.

In conclusion, our results do not support the hypothesis that serum selenium level is associated with PCa risk. Selenium and its association with PCa remain an area of further research particularly in populations with more marginal selenium levels than our well-nourished population and those that include a larger number of PCa cases.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants and the study was approved by Institutional Review Boards of all ten participating centers and the US National Cancer Institute..

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