

DIETARY MANIPULATION, ETHNICITY, AND SERUM PSA LEVELS

JAMES A. EASTHAM, ELYN RIEDEL, LIANNE LATKANY, MARTIN FLEISHER, ARTHUR SCHATZKIN, ELAINE LANZA, MOSHE SHIKE, AND THE POLYP PREVENTION TRIAL STUDY GROUP

ABSTRACT

Objectives. To examine whether a diet low in fat and high in fiber, fruits, and vegetables and ethnicity had any influence on serum prostate-specific antigen (PSA) levels, because serum PSA is a marker for the presence of prostate cancer. The incidence of prostate cancer increases with age, varies by ethnicity, and is greater among men with a first-degree relative who has had the disease. Large international variations in the rates of prostate cancer incidence and mortality, as well as the incidence changes in migrants and their offspring, also suggest that exogenous factors, including diet, have a strong influence on the development of this disease.

Methods. We used data and blood samples from the Polyp Prevention Trial, a multicenter randomized trial designed to evaluate the impact of a diet low in fat and high in fiber, fruits, and vegetables on the recurrence of colorectal adenomas. Recruitment was from 1991 through 1994. Participants were followed up from their baseline recruitment date for 4 years. From this group, we identified 1100 white men and 97 black men who were 35 years of age or older, did not have prostate cancer, and had serum samples available for study.

Results. At baseline, no difference was present in the fat intake for the black and white men (mean \pm SE, 90 ± 3.6 g/day and 84 ± 1.0 g/day, respectively; $P = 0.15$). The baseline serum PSA levels did not vary by ethnicity. For black men, the mean serum PSA level was 2.2 ± 0.36 ng/mL compared with 2.0 ± 0.07 ng/mL for white men ($P = 0.64$). Although all men assigned to the intervention group markedly reduced their fat intake by approximately 15% and increased their fruit and vegetable intake by approximately 2.25 servings per day, no difference was noted in the kinetics of the serum PSA levels by dietary intervention or race.

Conclusions. Although ethnic differences in the incidence of prostate cancer are well defined, we found no difference in the baseline fat intake among black and white men that might have contributed to this difference. Serum PSA, a marker often used in early detection programs for prostate cancer, was not associated with manipulation of the amount of fat in the diet, regardless of ethnicity. UROLOGY 62: 677-682, 2003. © 2003 Elsevier Inc.

The observation that the prostate cancer incidence can vary dramatically in ethnically similar populations living in different geographic locations, and that the incidence changes in immigrants, strongly suggests that exogenous fac-

tors can greatly influence the risk of developing this cancer.¹⁻³ Diet, especially fat intake, is one such exposure that varies geographically and that can change dramatically in immigrants.⁴ In a case-control study of diet and prostate cancer in China, Lee *et al.*⁵ explored the relationship between dietary factors and prostate cancer risk. Men diagnosed with prostate cancer were more likely than controls to consume food with a high fat content from animal sources and had a greater percentage of energy from fat.⁵ Similarly, Whittemore *et al.*⁶ conducted a population-based case-control study of prostate cancer among black, white, and Asian-American men in the United States and Canada. A statistically significant association of prostate cancer risk and total fat intake was found for all ethnic

A listing of the other members of the Polyp Prevention Trial Study Group is given in the Appendix.

From the Memorial Sloan-Kettering Cancer Center, New York, New York; and Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland

Reprint requests: James A. Eastham, M.D., Department of Urology, Memorial Sloan-Kettering Cancer Center, 353 East 68th Street, Room 527, New York, NY 10021

Submitted: March 18, 2003, accepted (with revisions): May 22, 2003

groups combined. These data support a causal role in prostate cancer for fat intake.

Ethnic differences in the incidence of prostate cancer have been well described.^{1,2} The age-adjusted rate ratio for prostate cancer has been estimated to be 1.73 (95% confidence interval 1.23 to 2.45) for black men compared with white men.⁷ For each year between 1973 and 1994, epidemiologic data derived from the population-based Surveillance, Epidemiology and End Results registry demonstrated that black men had a greater age-adjusted incidence of prostate cancer than did white men.⁸ The reason for this remains unclear. This finding is unlikely to be the result of differential detection of prostate cancer. Several reports have demonstrated a greater incidence of prostate cancer in black men in equal-access healthcare systems.^{7,9,10} Other proposed explanations include genetic factors,^{7,11,12} hormonal factors,^{13,14} and dietary fat intake.^{15,16}

Prostate-specific antigen (PSA) is a serum protease produced by both benign and malignant prostate epithelium. The measurement of serum PSA levels has been used for early diagnosis, staging, and monitoring treatment effects in men with prostate cancer. Ethnic differences in serum PSA levels in men with and without prostate cancer have been described.¹⁷⁻¹⁹ Among men who underwent transrectal ultrasound-guided prostate biopsies to evaluate an elevated serum PSA level and/or abnormal digital rectal examination findings, black men, with and without prostate cancer, had significantly greater mean serum PSA levels and PSA densities than similarly aged white men.¹⁷ Although serum PSA is an important tool in diagnosing and monitoring prostate cancer, little is known regarding how diet may impact serum PSA levels.

Because racial differences exist in prostate cancer, and because of the hypothesis that these differences may be related to racial differences in the quantity of calories obtained from fat, this study attempted to address two important issues. First, do racial differences in fat intake exist between black men and white men? Second, does manipulation of dietary fat, fiber, and fruit and vegetable intake, change serum PSA levels differently in black men compared with white men?

MATERIAL AND METHODS

We used the information and serum samples collected as part of the Polyp Prevention Trial (PPT). Details of the study design, eligibility criteria, randomization procedures, dietary intervention, and end point assessment have been previously reported.²⁰⁻²³ In brief, the PPT was a multicenter randomized trial designed to evaluate the impact of a diet low in fat and high in fiber, fruits, and vegetables on the recurrence of colorectal adenomas. Participants were men and women 35 years of age or older, with one or more adenomas. Recruitment was from 1991 through 1994. Participants were followed up from

their baseline recruitment date for 4 years. Recent examination of the data from the PPT suggested that, overall, no impact on serum PSA levels resulted in the men treated with a reduced fat diet.²³ The impact of ethnicity on these results, however, was not addressed. In the current study, we specifically examined whether racial differences influenced the ability of reduced dietary fat to impact serum PSA levels. For the purposes of the present study, we considered all men ($n = 1351$) who had been enrolled in this trial. Men with a diagnosis of prostate cancer at baseline ($n = 36$), men with ethnicity other than white or black ($n = 33$), and men in whom serum samples were not available ($n = 85$) were excluded from our study. The study population, therefore, consisted of 1197 men: 611 men (559 white and 52 black men) randomly assigned to adopt a diet low in fat and high in fiber, fruits, and vegetables (intervention group) and 586 men (541 white and 45 black men) randomly assigned to follow their usual diet (control group).

Before randomization, and at subsequent annual visits at years 1, 2, 3, and 4, each subject answered a questionnaire^{24,25} assessing a variety of demographic, clinical, and behavioral characteristics and provided a venous blood specimen after an overnight fast. Data and blood samples for each participant were labeled with a new record number by the central data center to ensure the anonymity of the results. The institutional review boards of the Memorial Sloan-Kettering Cancer Center and the National Cancer Institute approved the protocol. For each sample, serum was separated from clot, separated into aliquots, and frozen at -70°C in a central repository within 4 hours of the blood draw. Samples were not thawed from the time of the initial freezing until the serum PSA determinations were made. Coded specimen inventory listings were organized by subject, so that all specimens from a particular subject could be identified and assayed at the same time, thus minimizing the possibility of between-assay variability. The serum PSA concentration was measured by a heterogenous sandwich magnetic separation assay using the Bayer Immuno 1 PSA assay (Bayer Diagnostics) under the supervision of a single clinical chemist (M.F.). Samples with PSA values between 4 and 10 ng/mL were also analyzed for free PSA by a two-site immunoradiometric assay using monoclonal antibodies directed against distinct antigen sites on the free PSA molecule (Hybritech, San Diego, Calif).

Baseline variables were compared by ethnicity, using a non-parametric statistical test (Wilcoxon-Mann-Whitney rank sum test). The primary endpoint was the slope of the serum PSA level (the change in PSA over time) on the basis of ethnicity and dietary intervention. The slope was calculated for each patient using linear regression analysis for the five time points: baseline and annually through year 4. In the 41 men diagnosed with prostate cancer during the study, only the serum PSA values that preceded the diagnosis of prostate cancer were used in calculating the slope of the serum PSA level. The distributions of the slopes were also compared using a nonparametric statistical test. All reported P values are two-sided.

RESULTS

The initial randomization for all participants in the PPT has been previously reported.²⁰ In general, many variables, including age, race, smoking status, alcohol intake, and use of aspirin, calcium, and vitamin supplements, were similar for the intervention and control groups. The baseline clinical and nutritional characteristics for our study population are summarized in Table I. No difference

TABLE I. Baseline characteristics

Characteristic	White Men	Black Men
Total (n)	1100	97
Age (yr)		
Mean	62 ± 0.3	60 ± 0.9
Median	63	61
Range	35–84	38–89
Serum PSA (ng/mL)		
Mean	2.0 ± 0.07	2.2 ± 0.36
Median	1.3	1.1
Range	0.04–18.4	0.04–24.0
Fat intake (g/day)		
Mean	84 ± 1.0	90 ± 3.6
Median	79	84
Range	21–246	28–239

KEY: PSA = prostate-specific antigen.

Data presented as the mean ± standard error, unless otherwise noted.

was found in patient age, baseline serum PSA level, or baseline dietary fat intake according to ethnicity. Specifically, the black men in our study population had a similar baseline fat intake (90 ± 3.6 g/day) compared with the white men (84 ± 1.0 g/day; $P = 0.15$). For black men, the mean serum PSA level was 2.2 ± 0.36 ng/mL compared with 2.0 ± 0.07 ng/mL for white men ($P = 0.64$).

The changes in dietary fat intake are summarized in Figure 1. Regardless of ethnicity, the intervention group reduced daily fat intake more than the control group. This change in dietary fat intake and other dietary changes, however, had a minimal impact on the serum PSA levels (Table II). In white participants, the PSA slope was not different between the control and intervention arms ($P = 0.90$). Although the median and mean PSA slope in black participants was lower in the intervention arm than in the control arm, this, too, was not significantly different ($P = 0.78$). Even in men with an elevated serum PSA level at baseline (PSA greater than 4 ng/mL), a diet low in fat and high in fiber, fruits, and vegetables had no impact on the PSA slope (data not shown). During the study, prostate cancer was diagnosed in 38 white men (3.5%) and 3 black men (3.1%). This did not vary according to baseline dietary fat intake or randomization group.

COMMENT

The potential role of dietary fat in the genesis of prostate cancer is controversial. Several epidemiologic studies have supported a role for dietary fat in the pathogenesis of prostate cancer.^{4–6,16,24} Total fat intake, especially the amount of energy from saturated fats, has been associated with an increased risk of developing prostate cancer.^{5,6} In addition, men consuming a low-fat, high-fiber diet

have a lower risk of prostate cancer than men consuming a Western diet.⁵ These observations are supported by laboratory studies. When the androgen-sensitive LNCaP human prostate cancer cell line is grown in immunodeficient mice, energy restriction significantly reduced tumor growth.²⁵ Others have reported similar findings.²⁶ These data support a role for dietary fat in the genesis of prostate cancer and suggest that dietary fat reduction may impact carcinogenesis and cancer progression. Other studies, however, have shown no relationship between fat intake and the risk of developing prostate cancer.^{27,28} In the Netherlands Cohort Study, the intake of energy, fat, and separate fatty acids were measured by means of a self-administered questionnaire in 58,279 men aged 55 to 69 years.²⁷ No associations were found between prostate cancer and intake of energy, total fat, or total saturated fatty acids. Although reducing fat intake is important for overall health, whether such a change in diet will influence the development or progression of prostate cancer remains unclear.

Black men have the highest incidence of prostate cancer in the world, and dietary factors have been implicated as a potential cause. This theory derives from studies that have found an association between a high-fat diet and the development of prostate cancer. Taken together, these data suggest that dietary fat may play a role in the observed ethnic differences in prostate cancer. The findings of recent studies, however, do not support this. Whittemore *et al.*⁶ used a common protocol and questionnaire to interview 1655 black, white, Chinese-American, and Japanese-American case patients with prostate cancer and 1645 population-based control subjects matched to the case patients by age, ethnicity, and region of residence. A statistically significant association between prostate cancer risk and total fat intake was found for all ethnic groups, but the differences in dietary fat intake did not explain the interethnic differences that were observed in the actual incidence of prostate cancer. Our results support these findings. We found no difference in baseline fat intake in black and white men. Although dietary fat is likely important in the genesis of prostate cancer, no convincing data are available to suggest it contributes significantly to interethnic differences.

Our study has several potential limitations. The information on ethnicity, fat intake, and serum PSA levels was obtained from data collected for the PPT Study Group. The purpose of this original study was not to examine differences in fat intake, or serum PSA levels, between whites and blacks. In addition, the number of black men in our population was small, such that we may not have had the power to detect small differences. This was un-

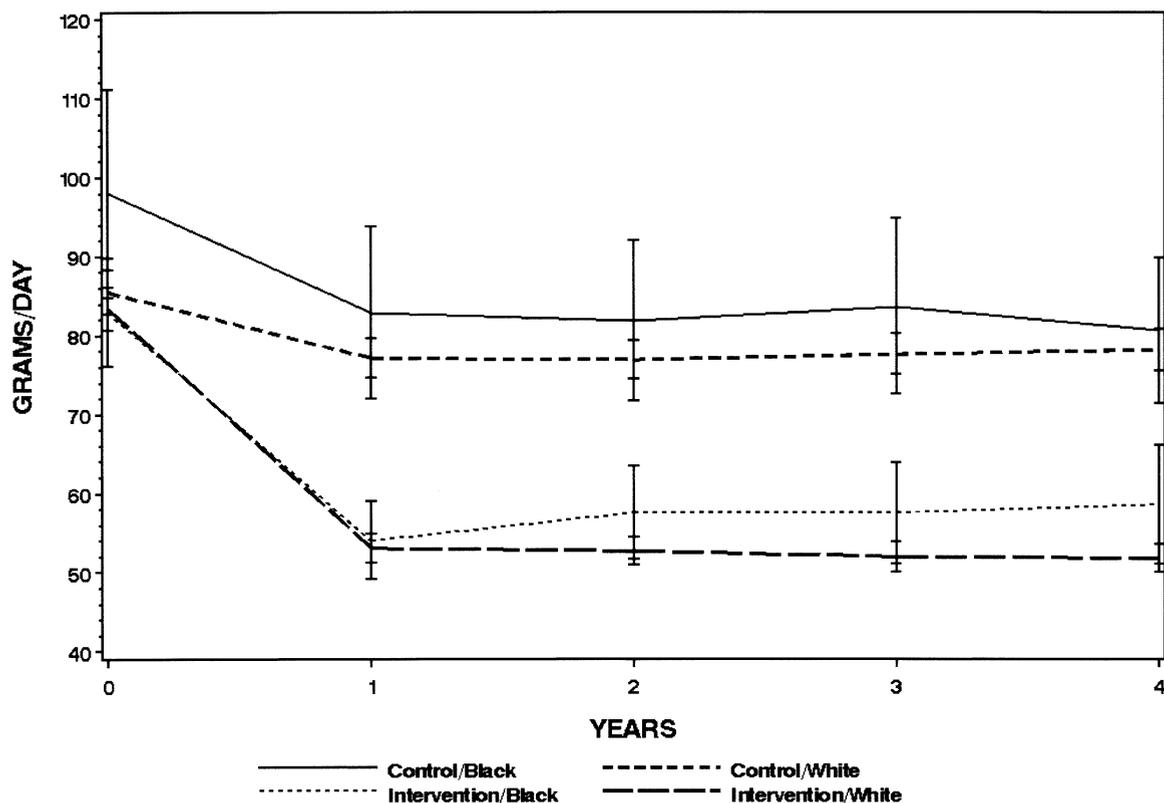


FIGURE 1. Mean fat intake at each year with 95% confidence intervals.

TABLE II. PSA slope for black and white men in control and intervention groups*

PSA Slope	Control	Intervention
White men (n)	521	528
Median (range)	0.03 (-3.0 to 9.7)	0.03 (-9.2 to 7.3)
Mean (95% CI)	0.12 (0.06 to 0.19)	0.13 (0.06 to 0.19)
Black men	43	48
Median (range)	0.09 (-0.3 to 19 [†])	0.06 (-0.5 to 2.2)
Mean (95% CI)	0.68 (-0.2 to 1.5)	0.23 (0.1 to 0.4)

KEY: PSA = prostate-specific antigen; CI = confidence interval.

* Only participants with ≥ 3 serum specimens included in slope of serum PSA level analysis.

[†] Nineteen is an extreme observation; next highest value is 1.4.

likely to have had a substantial effect on our conclusions, because small ethnic differences in baseline dietary fat intake are unlikely to contribute significantly to the known large ethnic difference in the incidence of prostate cancer. Also, the dietary intervention was of relatively short duration. Perhaps longer intervention is needed to produce an effect. Similarly, the dietary intervention may need to occur earlier in life, as the median age of our study population was about 60 years. Finally, greater fat reduction (or perhaps an increase in the quantity of fruits and vegetables) than what was achieved in the PPT may be necessary to see an effect on serum PSA levels.

Little information is available regarding the impact of dietary manipulation on serum PSA levels. Animal studies using an LNCaP xenograft model for prostate cancer demonstrated that only when dietary fat was reduced to 2.3% of total calories did serum PSA levels decline.²⁶ This is far below most recommendations for dietary fat intake. In our study population, we found no association between serum PSA level and a diet low in fat and high in fiber, fruits, and vegetables. This finding suggests that dietary manipulation may not result in significant changes in serum PSA levels. This does not imply that these dietary changes are not important. Rather, serum PSA levels may not completely reflect the benefit of this treatment strategy.

CONCLUSIONS

Serum PSA levels are used in apparently normal men for prostate cancer screening, as well as in men with a diagnosis of prostate cancer to determine the response to therapy. It is important to determine which factors, including dietary manipulation, alter serum PSA levels and whether these factors must be considered when interpreting a serum PSA result. Because of the racial differences that exist in prostate cancer, and the hypothesis that these differences are in some way related to racial differences in quantities of fat intake, we believed the data from the PPT could address two important issues. First, in this study population, were there racial differences in fat intake? Second, would manipulation of dietary fat change serum PSA levels differently in black men than in white men? Our results suggest that serum PSA levels are not associated with manipulation of the amount of fat, fiber, fruits, and vegetables in the diet, regardless of ethnicity.

REFERENCES

1. Greenlee RT, Murray T, Bolden S, *et al*: Cancer statistics, 2000. *CA Cancer J Clin* 50: 7–33, 2000.
2. Morton RA Jr: Racial differences in adenocarcinoma of the prostate in North America. *Urology* 44: 637–645, 1994.
3. Kolonel LN: Racial and geographic variations in prostate cancer and the effect of migration, in Fortner JG, Sharp PA (Eds): *Accomplishments in Cancer Research*, 1996. Philadelphia, Lippincott-Raven, 1997, pp 221–230.
4. Kolonel LN, Nomura A, and Cooney RV: Dietary fat and prostate cancer: current status. *J Natl Cancer Inst* 91: 414–428, 1999.
5. Lee MM, Wang RT, Hsing AW, *et al*: Case-control study of diet and prostate cancer in China. *Cancer Causes Control* 9: 545–552, 1998.
6. Whittemore AS, Kolonel LN, Wu A, *et al*: Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the United States and Canada. *J Natl Cancer Inst* 87: 652–661, 1995.
7. Platz EA, Rimm EB, Willet WC, *et al*: Racial variation in prostate cancer incidence and hormonal system markers among male health professionals. *J Natl Cancer Inst* 92: 2009–2017, 2000.
8. Stephenson RA: Prostate cancer trends in the era of prostate-specific antigen: an update of incidence, mortality, and clinical factors from the SEER database. *Urol Clin North Am* 29: 173–181, 2002.
9. Robbins AS, Whittemore AS, and Van Den Eeden SK: Race, prostate cancer survival, and membership in a large health maintenance organization. *J Natl Cancer Inst* 90: 986–990, 1998.
10. Powell IJ, Schwartz K, and Hussain M: Removal of the financial barrier to health care: does it impact on prostate cancer at presentation and survival? A comparative study between black and white men in a Veterans Affairs system. *Urology* 46: 825–830, 1995.
11. Smith JR, Freije D, Caupter JD, *et al*: Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. *Science* 274: 1371–1374, 1996.
12. Irvine RA, Yu MC, Ross RK, *et al*: The CAG and GGC microsatellites of the androgen receptor gene are in linkage disequilibrium in men with prostate cancer. *Cancer Res* 55: 1937–1940, 1995.
13. Carter HB, Pearson JD, Metter EJ, *et al*: Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. *Prostate* 27: 25–31, 1995.
14. Kubricht WS, Williams BJ, Whatley T, *et al*: Serum testosterone levels in African-American and white men undergoing prostate biopsy. *Urology* 54: 1035–1038, 1999.
15. Rose DP, Boyar AP, and Wyder EL: International comparisons of mortality rates for cancer of the breast, ovary, prostate, and colon, and per capita food consumption. *Cancer* 58: 2363–2371, 1986.
16. Giovannucci E, Rimm ED, Colditzm GA, *et al*: A prospective study of dietary fat and risk of prostate cancer. *J Natl Cancer Inst* 85: 571–579, 1993.
17. Eastham JA, May RA, Whatley T, *et al*: Clinical characteristics and biopsy specimen features in African-American and white men without prostate cancer. *J Natl Cancer Inst* 90: 756–760, 1998.
18. Bozeman C, Williams BJ, Whatley T, *et al*: Clinical and biopsy specimen features in black and white men with clinically localized prostate cancer. *South Med J* 93: 400–402, 2000.
19. Powell IJ, Heilbrun LK, Sakr WD, *et al*: The predictive value of race as a clinical prognostic factor among patients with clinically localized prostate cancer: a multivariate analysis of positive surgical margins. *Urology* 49: 726–731, 1997.
20. Schatzkin A, Lanza E, Freedman LS, *et al*: The Polyp Prevention Trial. I Rationale, design, recruitment and baseline participant characteristics. *Cancer Epidemiol Biomarkers Prev* 5: 375–383, 1996.
21. Lanza E, Schatzkin A, Ballard-Barbash R, *et al*: The Polyp Prevention Trial. II. Dietary intervention and baseline participant dietary characteristics. *Cancer Epidemiol Biomarkers Prev* 5: 385–392, 1996.
22. Schatzkin A, Lanza E, Corle D, *et al*: Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. *N Engl J Med* 342: 1149–1155, 2000.
23. Shike M, Latkany L, Riedel E, *et al*: Lack of effect of a low fat, high fruits, vegetables, and fiber diet on serum prostate specific antigen (PSA) of men without prostate cancer: results from a randomized trial. *J Clin Oncol* 20: 3592–3598, 2002.
24. Herbert JR, Hurley TG, Olendzki BC, *et al*: Nutritional and socioeconomic factors in relation to prostate cancer mortality: a cross-national study. *J Natl Cancer Inst* 90: 1637–1647, 1998.
25. Wang Y, Corr CG, Thale HT, *et al*: Decreased growth of established human prostate LNCaP tumors in nude mice fed a low-fat diet. *J Natl Cancer Inst* 87: 1456–1462, 1995.
26. von Holtz RL, Fink CS, and Awad AB: beta-Sitosterol activates the sphingomyelin cycle and induces apoptosis in LNCaP human prostate cancer cells. *Nutr Cancer* 32: 8–12, 1998.
27. Schuurman AG, van den Brandt PA, Dorant E, *et al*: Association of energy and fat intake with prostate carcinoma risk. *Cancer* 86: 1019–1027, 1999.
28. Moyad MA: Dietary fat reduction to reduce prostate cancer risk: controlled enthusiasm, learning a lesson from breast or other cancers, and the big picture. *Urology* 59: 51–62, 2002.

APPENDIX

The other members of the Polyp Prevention Trial Study Group were as follows: National Cancer Institute—L. Freedman, R. Ballard-Barbash, C. Clifford, J. Tangera, and D. Corle; State University of New York at Buffalo—P. Lance, D. Hayes,

N. J. Petrelli, M. Beddone, K. Kroldart, S. Rauth, and L. Wodarski; Edward Hines, Jr. Hospital, Veterans Affairs Medical Center—F. Iber, P. Murphy, E. C. Bote, L. Brandt-Whittington, N. Haroon, N. Kazi, M. Moorse, S. B. Orloff, W. J. Ottosen, M. Patel, R. L. Rothschild, M. Ryan, J. M. Sullivan, and A. Verma; Kaiser Foundation Research Institute—B. Caan, J. V. Selby, G. Friedman, M. Lawson, G. Taff, D. Snow, M. Belfay, M. Schoenberger, K. Sampel, T. Giboney, and M. Randel; Memorial Sloan-Kettering Cancer Center—A. Schaeffer, R. Morse, D. D'Amato, S. Winawer, L. Cohen, A. Bloch, and J. Mayer; University of Pittsburgh—J. Weissfeld, R. E. Schoen, R. R. Schade, L. Kuller, B. Gahagan, A. Caggiola, T. Coyne, C. Lucas, S. Pappert, G. Landis, L. Dyjak, R. Robinson, L. Search, and D. Hanson; University of Utah—R. Burt, M. Slattery, N. Viscofsky, J. Benson, J. Neilson, R. O'Donnel, M. Briley, K. McDivitt, K. Heinrich, and W. Samowitz; Wake Forest University Baptist Medical Center—M. R. Cooper, E. Paskett, S. Quandt, C. DeGraffinreid, K. Bradham, L. Kent, M. Self, D. Boyles, D. West, L. Martin, N. Taylor, E. Dickenson, P. Kuhn, J. Harmon,

I. Richardson, H. Lee, and E. Marceau; Walter Reed Army Medical Center—J. W. Kikendall, D. J. Mateski, R. K. H. Wong, C. Cheney, E. Rueda-Pedraza, V. Jones-Miskovsky, A. Greaser, E. Stoute, S. Hancock, S. Chandler, M. Burman, E. Crutchfield, C. Slivka, and L. Johnson; University of Arizona—J. Marshall; Data and Nutrition Coordinating Center (Westat)—J. Cahill, M. Hasson, C. Daston, B. Brewer, C. Sharbaugh, B. O'Brien, N. Odaka, K. Umbel, J. Pinsky, H. Price, and P. Clark; Central Pathologists—K. Lewin (University of California, Los Angeles), and H. Appleman (University of Michigan); Laboratories—P. S. Bachorisk, K. Lovejoy (Johns Hopkins University) and A. Sowell (Centers for Disease Control and Prevention); and Data and Safety Monitoring Committee—E. R. Greenberg (Norris Cotton Cancer Center and Dartmouth Medical School), E. Feldman (Augusta, Georgia), C. Garza (Cornell University), R. Summers (University of Iowa), S. Wieand (University of Minnesota), and D. DeMets (University of Wisconsin).