Comorbidity and Mortality Results From a Randomized Prostate Cancer Screening Trial

E. David Crawford, Robert Grubb III, Amanda Black, Gerald L. Andriole Jr, Ming-Hui Chen, Grant Izmirlian, Christine D. Berg, and Anthony V. D'Amico

See accompanying editorial on page 345 and article on page 464

ABSTRACT

Purpose

Estimates of prostate cancer–specific mortality (PCSM) were similar for men randomly assigned to intervention compared with usual care on the Prostate, Lung, Colorectal and Ovarian PC screening study. However, results analyzed by comorbidity strata remain unknown.

Patients and Methods

Between 1993 and 2001, of 76,693 men who were randomly assigned to usual care or intervention at 10 US centers, 73,378 (96%) completed a questionnaire that inquired about comorbidity and prostate-specific antigen (PSA) testing before random assignment. Fine and Gray's multivariable analysis was performed to assess whether the randomized screening arm was associated with the risk of PCSM in men with no or minimal versus at least one significant comorbidity, adjusting for age and prerandomization PSA testing.

Results

After 10 years of follow-up, 9,565 deaths occurred, 164 from PC. A significant decrease in the risk of PCSM (22 v 38 deaths; adjusted hazard ratio [AHR], 0.56; 95% CI, 0.33 to 0.95; $P = .03$) was observed in men with no or minimal comorbidity randomly assigned to intervention versus usual care, and the additional number needed to treat to prevent one PC death at 10 years was five. Among men with at least one significant comorbidity, those randomly assigned to intervention versus usual care did not have a decreased risk of PCSM (62 v 42 deaths; AHR, 1.43; 95% CI, 0.96 to 2.11; $P = .08$).

Conclusion

Selective use of PSA screening for men in good health appears to reduce the risk of PCSM with minimal overtreatment.

J Clin Oncol 29:355-361. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Prostate cancer (PC) in the United States is usually diagnosed through serial prostate-specific antigen (PSA) testing¹ and is treated by using radical prostatectomy (RP) or radiation therapy (RT) with or without hormonal therapy (HT). Although these treatments are often curative, the additional number of men who need to be treated (NNT) by using PSA testing compared with usual care to eliminate one death from PC at 9 years has been estimated from early follow-up of the European randomized PC screening study² at 48. Why is this number so large?

About one third of men treated for screen-detected PC will recur.³ However, many recurrences will not progress to death from PC.⁴ The

reason for this is twofold. First, most men are diagnosed with PC later in life during the sixth decade, and most PSA recurrences have long (> 9 months) PSA doubling times in which the median time to prostate cancer–specific mortality (PCSM) following PSA failure is in excess of 15 years, which may exceed the patient's life expectancy.⁵ Second, at the time of recurrence, which can be several years following initial therapy,⁶ the patient may have prior or acquired competing risks of mortality which lead to death before the PC has the opportunity to progress. Both of these factors increase the additional NNT to eliminate one PC death with PSA screening compared with usual care in the general population. However, the additional NNT may be less for men in good health, as suggested by the NNT of 12 in the Göteborg randomized population-based PC

From the University of Colorado Health Sciences Center, Denver, CO; Washington University School of Medicine, St. Louis, MO; National Cancer Institute, Rockville, MD; University of Connecticut, Storrs, CT; Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA.

Submitted May 21, 2010; accepted September 9, 2010; published online ahead of print at www.jco.org on November 1, 2010.

Supported by the National Cancer Institute and Grants No. N01-CN-25514, University of Colorado; N01-CN-25522, Georgetown University; N01-CN-25515, Pacific Health Research Institute; N01-CN-25512, Henry Ford Health System; N01-CN-25513, University of Minnesota; N01-CN-25516, Washington University; N01-CN-25511, University of Pittsburgh Medical Center; N01-CN-25524, University of Utah; N01-CN-25518, Marshfield Clinic Research Foundation; N01-CN-75022, University of Alabama at Birmingham; N01-CN-25476, Westat; and N01-CN-25404, University of California at Los Angeles Immunogenetics Center.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Anthony V. D'Amico, MD, PhD, Department of Radiation Oncology, Brigham and Women's Hospital, 75 Francis St, L-2 Level, Boston, MA 02115; e-mail: adamico@partners.org.

© 2010 by American Society of Clinical Oncology

0732-183X/11/2904-355/\$20.00

DOI: 10.1200/JCO.2010.30.5979

Table 1. Distribution of the Clinical Characteristics of 73,378 Men at Baseline Stratified by the Extent of Comorbidity

Clinical Characteristic	No or Minimal Comorbidity (n = 26,175)		At Least One Significant Comorbidity (n = 47,203)		P
	No.	%	No.	%	
Age at random assignment, years					< .001
55-59	9,847	37.6	13,615	28.8	
60-64	8,334	31.8	14,671	31.1	
65-69	5,360	20.5	11,766	24.9	
70+	2,634	10.1	7,151	15.2	
Median	61		63		< .001
IQR	57-66		59-67		
Randomized arm					
Usual care	12,909	49.3	23,184	49.1	.60
Intervention	13,266	50.7	24,019	50.9	
PSA testing prior to random assignment					< .001
No	12,989	49.6	20,467	43.4	
Yes	11,373	43.5	22,130	46.9	
Unknown	1,813	6.9	4,606	9.8	

NOTE. Percentages may not sum to 100 due to rounding.
Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen.

screening trial⁷ in which the men were younger (median age, 56 years) than in the US¹ and European² studies and likely were healthier.

Given that estimates of PCSM were not analyzed by comorbidity strata in the European PC screening study,² it is possible that the additional NNT in men with no or minimal comorbidity may be < 48. Moreover, it is possible that while the Prostate, Lung, Colorectal and Ovarian (PLCO) PC screening study¹ did not show a reduction in the risk of PCSM with both serial PSA testing and

digital rectal examination (DRE) compared with usual care overall, such a reduction may be observed in men with no or minimal comorbidity. Conversely, diagnosing PC earlier in men with more significant comorbidity may not decrease the risk of PCSM because of competing risks. Therefore, the purpose of this study was to evaluate whether an association existed between the extent of pre-existing comorbidity and the risk of PCSM in men undergoing intervention compared with usual care in the randomized PLCO PC screening trial.

Table 2. Distribution of Treatment Received in the 6,245 Men Diagnosed With Prostate Cancer Stratified by the Comorbidity Subgroup, Randomized Screening Arm, and Prostate Cancer Aggressiveness

Treatment	No or Minimal Comorbidity (n = 2,271)								At Least One Significant Comorbidity (n = 3,974)							
	Usual Care (n = 1,077)				Intervention (n = 1,194)				Usual Care (n = 1,778)				Intervention (n = 2,196)			
	Less Advanced PC* (n = 670; 62%)		Advanced PC† (n = 407; 38%)		Less Advanced PC* (n = 816; 68%)		Advanced PC† (n = 378; 32%)		Less Advanced PC* (n = 1,091; 61%)		Advanced PC† (n = 687; 39%)		Less Advanced PC* (n = 1,464; 67%)		Advanced PC† (n = 732; 33%)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
RP	300	45	181	44	424	52	172	46	413	38	215	31	603	41	267	36
RT	157	23	54	13	174	21	50	13	260	24	113	16	360	25	129	18
RT + HT	96	14	112	28	98	12	99	26	178	16	227	33	206	14	198	27
HT	26	4	43	11	21	3	40	11	70	6	95	14	68	5	93	13
Other	5	1	4	1	2	0.3	2	0.5	10	1	6	1	9	1	9	1
Noncurative	85	13	12	3	93	11	15	4	149	14	30	4	212	14	33	5
Unknown	1	0.2	1	0.3	4	0.5	0	0	11	1	1	0.2	6	0.4	3	0.4

NOTE. Percentages may not sum to 100 due to rounding. All *P* values calculated using the Mantel-Haenszel χ^2 metric.¹² Bonferroni adjustment¹⁶ for a significant *P* value was $< .05 \div 7$ or .007. For no or minimal comorbidity: *P* = .002 for comparing distribution of prostate cancer (PC) aggressiveness across randomized screening arms; *P* = .07 for comparing distribution of treatment across randomized screening arms for less advanced PC; and *P* = .87 for comparing distribution of PC aggressiveness across randomized screening arms for advanced PC. For at least one significant comorbidity: *P* < .001 for comparing distribution of PC aggressiveness across randomized screening arms; *P* = .11 for comparing distribution of treatment across randomized screening arms for less advanced PC; and *P* = .19 for comparing distribution of treatment across randomized screening arms for advanced PC.

Abbreviations: PC, prostate cancer; RP, radical prostatectomy; RT, radiation therapy; HT, hormonal therapy.

*Less advanced includes men with American Joint Commission on Cancer (AJCC)¹⁰ category T1 or T2 and Gleason score 6 or lower prostate cancer.

†Advanced includes men with Gleason score 7 to 10, AJCC¹⁰ category T3 or T4 node positive or metastatic prostate cancer.

PATIENTS AND METHODS

Patient Population and Randomized Screening Arms

From 1993 through 2001, 76,693 men between the ages of 55 and 74 years were enrolled at 10 study centers across the United States and were randomly assigned to intervention versus usual care. Intervention consisted of being offered annual PSA testing for 6 years and annual DRE for 4 years with prostate biopsy recommended for a PSA > 4 ng/mL and/or an abnormal DRE. Despite these guidelines, the usual care arm was estimated to have a 52% contamination rate due to PSA screening by year 6.¹

Comorbidity Assessment and Assignment

Of 76,693 men who were randomly assigned to usual care versus intervention, 73,378 (96%) were available for mortality analysis by 10 years, and they completed a baseline questionnaire that inquired in detail about comorbidities and prior PSA testing. Two comorbidity strata were defined: (1) no or minimal comorbidity, and (2) having at least one significant comorbidity. A significant comorbidity was defined as one that could increase the risk of dying from one of the two leading causes of death in the United States for men between the ages of 55 and 74 years (ie, cardiovascular disease or cancer) published in the most recent publication of the National Vital Statistics Report by the US National Center for Health Statistics.⁸ For cardiovascular disease, the specific comorbidities included known coronary heart disease and/or myocardial infarction and risk factors⁹ such as hypertension, diabetes, stroke, and obesity defined as a body mass index > 30 kg/m². For cancer, specific medical conditions that increase the risk of developing a non-PC were included, and these were ulcerative colitis, Crohn's disease, familial polyposis syndrome/Gardner's syndrome, diverticulitis, diverticulosis, gallbladder stones/inflammation, colorectal polyps, bronchitis, emphysema, cirrhosis of the liver, and hepatitis. Minimal comorbidities were defined as those that would be unlikely to increase the risk of dying from one of the leading causes of death⁸ for men between the ages of 55 and 74 years and included arthritis and osteoporosis.

Follow-Up and Determination of the Cause of Death

Follow-up started on the day of random assignment and concluded on the date the patient was last observed or the date of death through August 31, 2009, whichever came first. All diagnosed cancers and all deaths occurring during the trial were ascertained, primarily by means of a mailed annual questionnaire that asked about the type of cancer and the date of diagnosis in the previous year. Death certificates were obtained to confirm death and to provisionally determine the underlying cause. Since the true underlying cause may not always be evident or accurately recorded on the death certificate, the trial used a special end point adjudication process to assign the cause of death in a uniform and unbiased manner. All deaths from causes that were potentially related to PC were reviewed, including any cause of death in which the patient had PC or a possible metastasis from PC and all deaths of unknown or uncertain cause. Reviewers of these deaths were unaware of study-group assignments for deceased patients.

For men diagnosed with PC, clinical stage was determined by using the fifth edition of the American Joint Committee on Cancer (AJCC) Staging Manual.¹⁰ Gleason scoring¹¹ was used to grade the cancers. Advanced PC in this analysis was defined as either Gleason score 7 to 10 or AJCC category¹⁰ T3 or T4 node-positive or metastatic PC.

Statistical Methods

Description of the study cohort at random assignment and at the time of PC diagnosis stratified by comorbidity category. A Mantel-Haenszel χ^2 metric¹² was used to compare the distribution of men by randomized screening arm, by age in years at random assignment, and by the presence of prerandomization PSA testing across the two comorbidity strata. A Wilcoxon two-sample test¹³ was used to compare the distribution of the median age in years at random assignment among men in the two comorbidity cohorts.

Men who were diagnosed with PC and the treatment they received were enumerated and stratified by randomized screening arm and by comorbidity strata. A Mantel-Haenszel χ^2 metric¹² was used to compare the distribution of men and the treatment they received stratified by the presence or absence of advanced PC and comorbidity strata across randomized screening arms.

PC incidence and death stratified by randomized screening arm and comorbidity category. The cumulative incidence¹⁴ method was used to estimate and characterize PC incidence and PCSM stratified by the randomized screening arm for each comorbidity subgroup. Comparisons of these estimates were performed by using a k-sample *P* value.¹⁵ For the purpose of illustration, unadjusted cumulative incidence estimates of PC incidence and PCSM stratified by screening arm are displayed for men with no or minimal and at least one significant comorbidity. A two-sided *P* < .05 was considered statistically significant with a Bonferroni correction made for multiple comparisons lowering the level for significance to .05 divided by the number of comparisons.¹⁶

Calculation of additional NNT to prevent one PC death by 10 years. We first calculated the numerical difference in the cumulative incidence estimates of PCSM at 10 years between usual care and intervention arms. To prevent one PC death during a 10-year period, the number of additional men who would need to be screened would be one divided by difference in the 10-year estimates of PCSM.

Next, we computed the numerical difference in the cumulative incidence estimates of PC diagnoses at 10 years in men randomly assigned to intervention compared with usual care. To prevent one PC death during a 10-year

Fig 1. (A) Unadjusted cumulative incidence estimates¹⁴ of prostate cancer incidence in men with no or minimal comorbidity randomly assigned to usual care or intervention. k-sample *P* = .04. (B) Unadjusted cumulative incidence estimates¹⁴ of prostate cancer incidence in men with at least one significant comorbidity randomly assigned to usual care or intervention. k-sample *P* < .001.

period, the additional NNT¹⁷ would equal the numerical difference in the cumulative incidence estimates of PC incidence at 10 years in men randomly assigned to intervention compared with the usual care arm multiplied by the additional number of men who would need to be screened.

Competing risks regression and assessment for interaction between comorbidity and randomized screening arm. The primary end point of this study was the risk of PCSM. A multivariable Fine and Gray's competing risks regression analysis¹⁸ was used to evaluate whether randomized screening arm was significantly associated with the risk of PCSM within each comorbidity subgroup, adjusting for age at random assignment and the use of prerandomization PSA testing. Men who reported undergoing PSA testing before random assignment or if this was unknown were placed into separate categories. The baseline category for this three-level categorical covariate was no prerandomization PSA testing. Age in years at random assignment was treated as a continuous covariate.

To assess whether a significant interaction¹⁸ existed between comorbidity and randomized screening arm, arm $\times$ comorbidity was evaluated in the multivariable model. Unadjusted hazard ratios and adjusted hazard ratios (AHRs) for PCSM with associated 95% CIs and *P* values were calculated for each covariate from the Fine and Gray regression model. Schoenfeld residuals were computed for each covariate, and residuals were plotted against time in years. A nonzero slope of Schoenfeld residuals against time is an indication of a violation of the proportional hazard assumption, which we did not observe. Therefore, no evidence was found against proportional hazards assumption. R version 2.6.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all calculations pertaining to Gray's *k*-sample *P* value and Fine and Gray regression. SAS version 9.2 (SAS Institute, Cary, NC) was used for all remaining analyses.

RESULTS

Description of the Study Cohort at Randomization and PC Diagnosis Stratified by the Two Comorbidity Cohorts

Men with no or minimal comorbidity represented 35.7% (26,175 of 73,378) of the study cohort and were significantly younger (median age, 61 v 63 years; *P* < .001; Table 1) when compared with men with at

least one significant comorbidity. The distribution of the randomized screening arm across the two comorbidity cohorts was not significantly different (*P* = .60).

Table 2 illustrates that among men diagnosed with PC who were randomly assigned to intervention compared with usual care, there were more men with less advanced PC in both the no or minimal comorbidity cohort (62% v 68%; *P* = .002) and at least one significant comorbidity cohort (61% v 67%; *P* < .001). While no significant differences existed in the distribution of PC treatments among men randomly assigned to intervention compared with usual care, men with at least one significant comorbidity compared with those with no or minimal comorbidity were less likely to receive curative treatment (RP, RT, and RT and HT) and more likely to be treated with noncurative or HT (*P* < .001).

Estimates of PC Incidence Stratified by Randomized Screening Arm for Men in the Two Comorbidity Subgroups

Men with no or minimal as well as those with more extensive comorbidity had estimates of PC incidence that were higher than those randomly assigned to intervention compared with the usual care arm (*P* = .04 and *P* < .001, respectively) as shown in Figures 1A and 1B, respectively. Ten-year estimates of PC incidence were 9.12% (95% CI, 8.64% to 9.63%) and 8.46% (95% CI, 7.99% to 8.96%) for men with no or minimal comorbidity randomly assigned to intervention and usual care arms, respectively. These respective estimates were 9.28% (95% CI, 8.91% to 9.66%) and 7.79% (95% CI, 7.44% to 8.14%) for men with at least one significant comorbid illness.

Risk of PCSM and Assessment for Interaction Between Comorbidity and Randomized Screening Arm

After 10 years of follow-up (interquartile range, 9.9 to 10), 9,565 deaths have occurred, 164 from PC. A significant interaction was

Table 3. Hazard Ratio for Prostate Cancer-Specific Mortality for Patient and Clinical Characteristics at Random Assignment From the Univariable and Multivariable Fine and Gray's Competing Risks Interaction Model¹⁸ for the 73,378 Men in the Study Cohort

Covariate	No. of Men	No. of Events	Univariable Analysis			Multivariable Analysis		
			Hazard Ratio	95% CI	<i>P</i>	Adjusted Hazard Ratio	95% CI	<i>P</i>
No or minimal comorbidity								
Usual care arm	12,909	38	1.000 Ref		—	1.000 Ref		—
Intervention arm	13,266	22	0.56	0.33 to 0.95	.03	0.56	0.33 to 0.95	.03
At least one significant comorbidity								
Usual care arm	23,184	42	1.000 Ref		—	1.000 Ref		—
Intervention arm	24,019	62	1.43	0.96 to 2.11	.08	1.43	0.96 to 2.11	.08
Usual care arm								
No or minimal comorbidity	12,909	38	1.000 Ref		—	1.000 Ref		—
At least one significant comorbidity	23,184	42	0.61	0.40 to 0.95	.03	0.55	0.35 to 0.86	.009
Intervention arm								
No or minimal comorbidity	13,266	22	1.000 Ref		—	1.000 Ref		—
At least one significant comorbidity	24,019	62	1.56	0.96 to 2.53	.07	1.39	0.85 to 2.28	.19
Interaction term between screening arm and comorbidity	73,378	164	2.532	1.315 to 4.875	.005	2.526	1.312 to 4.863	.006
Age, years	73,378	164	1.10	1.07 to 1.13	< .001	1.11	1.08 to 1.14	< .001
PSA testing prior to random assignment								
No	33,456	91	1.000 Ref		—	1.000 Ref		—
Yes	33,503	56	0.61	0.44 to 0.85	.004	0.55	0.39 to 0.76	< .001
Unknown	6,419	17	0.97	0.58 to 1.63	.91	0.91	0.54 to 1.54	.73

Abbreviation: PSA, prostate-specific antigen; Ref, reference value.

noted between comorbidity extent and randomized screening arm (AHR, 2.53; 95% CI, 1.31 to 4.86; $P = .006$) as depicted in Table 3. Specifically, a significant decrease in the risk of PCSM (22 v 38 deaths; AHR, 0.56; 95% CI, 0.33 to 0.95; $P = .03$) was observed in men with no or minimal comorbidity randomly assigned to intervention versus usual care, and the additional numbers needed to screen and treat to prevent one PC death were 723 and 5, respectively, at 10 years. However, among men with at least one significant comorbidity, those randomly assigned to intervention versus usual care did not have a decreased risk of PCSM (62 v 42 deaths; AHR, 1.43; 95% CI, 0.96 to 2.11; $P = .08$). Prerandomization PSA testing (AHR, 0.55; 95% CI, 0.39 to 0.76; $P = .001$) was associated with a decreased risk of PCSM, whereas increasing age at randomization was associated with an increased risk (AHR, 1.11; 95% CI, 1.08 to 1.14; $P < .001$) of PCSM.

Estimates of PCSM Stratified by Randomized Screening Arm for Men in the Two Comorbidity Subgroups

For men with no or minimal comorbidity, estimates of PCSM were lower ($P = .03$) in those randomly assigned to the intervention compared with the usual care arm as shown in Figure 2A. However, as shown in Figure 2B, a significant reduction in estimates of PCSM was not observed ($P = .07$) in men with at least one significant comorbidity. Ten-year estimates of PCSM were 0.17% (95% CI, 0.11% to 0.25%) and 0.31% (95% CI, 0.22% to 0.42%) for men with no or minimal comorbidity randomly assigned to intervention or usual care arm, respectively. These respective estimates were 0.27% (95% CI, 0.21% to 0.34%) and 0.19% (95% CI, 0.14% to 0.25%) for men with at least one significant comorbidity.

Being randomly assigned to intervention compared with usual care was associated with a reduction in all-cause mortality (AHR, 0.93; 95% CI, 0.86 to 1.02) in men with no or minimal comorbidity, but because of the small proportion ($< 5\%$) that PCSM represented in all deaths, this reduction was not significant ($P = .11$). Specifically, 10-year estimates of non-PCSM were 8.2% (95% CI, 7.8% to 8.5%) and 16.1% (95% CI, 15.7% to 16.4%) in men with no or minimal comorbidity compared with significant comorbidity, respectively.

DISCUSSION

This study observed a significant interaction between the randomized screening arm and the extent of comorbidity at random assignment on the primary end point: the risk of PCSM. Specifically, intervention with annual PSA screening compared with usual care in men with no or minimal comorbidity was associated with the more frequent diagnosis of less advanced PC and a significant reduction in the risk of PCSM requiring the treatment of five additional men to eliminate one PC death at 10 years. However, a reduction in the risk of PCSM was not observed in men who had at least one significant comorbidity, despite the more frequent diagnosis of less advanced PC in these men on the intervention arm compared with those on the usual care arm.

The clinical implication of these findings is that annual PSA testing by using a PSA cut point of 4 ng/mL and/or an abnormal DRE to recommend prostate biopsy leads to the more frequent diagnosis of less advanced PC, and in healthy men with no or minimal competing risks, following curative treatment for PC, a significant reduction in the risk of PCSM may be achieved. Conversely, in men with more

Fig 2. (A) Unadjusted cumulative incidence estimates¹⁴ of prostate cancer-specific mortality in men with no or minimal comorbidity randomly assigned to usual care or intervention. k-sample $P = .03$. (B) Unadjusted cumulative incidence estimates¹⁴ of prostate cancer-specific mortality in men with at least one significant comorbidity randomly assigned to usual care or intervention. k-sample $P = .07$. Bonferroni adjustment¹⁶ for a significant P value was $< .05 \div 2$ or .025.

significant comorbidity, a reduction in the risk of PCSM was not observed. Why might this be? First, given the competing risks due to the significant comorbidity, the patient may die of another cause before any possible benefit of PSA testing, early PC detection, and curative treatment have the opportunity to manifest. This is supported by the two-fold increase in the 10-year estimates of non-PCSM in men with significant comorbidity compared with no or minimal comorbidity. Second, similar to a prior report,¹⁹ in this study, men with significant comorbidity compared with no or minimal comorbidity were significantly less likely to undergo curative therapy and more likely to be treated with primary HT or other noncurative therapy. Yet, less advanced and potentially curable PC was diagnosed significantly more often in men randomly assigned to the intervention arm (67%) compared with the usual care arm (61%). Therefore, it is possible that if the comorbidity present at random assignment was subsequently addressed, then the increased use of noncurative therapies in men with

less advanced PC could lead to PC progression and subsequent PCSM, further reducing the likelihood of seeing any benefit to PSA testing in these men. Finally, men with more extensive comorbidity are more likely to experience treatment interruptions during RT, leading to increased PC recurrence rates,²⁰ and the 30-day treatment-related mortality rates are higher in men with significant comorbidity compared with no or minimal comorbidity following RP²¹ and RT.²²

Three points require further discussion. First, the association between a significant reduction in the risk of PCSM in men with no or minimal comorbidity as defined in this study and randomly assigned to intervention compared with the usual care arm is hypothesis generating, given that this was a postrandomization analysis. However, the estimated 52% contamination rate by year 6 in the usual care arm¹ and the 15% nonattendance rate in the intervention arm¹ add support to the association because these issues^{23,24} should reduce the likelihood of observing a significant reduction in the risk of PCSM between the two randomized screening arms. Second, people who participate in screening studies are generally more healthy and more health conscious than nonattendees,²⁵ meaning that the 35.7% estimate of men with no or minimal comorbidity in this study may be an overestimate when applied to the general population. Finally, a perfect screening test would have an additional NNT of 1. Therefore, both overdetection and overtreatment can still exist.

Despite these considerations, given the uncertainty about the possible benefit of PSA testing in the general population and concerns regarding overtreatment, these data serve to raise awareness that the selective use of PSA screening for men in good health appears to reduce the risk of PCSM with minimal overtreatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships

marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** E. David Crawford, GlaxoSmithKline (C), Ferring Pharmaceuticals (C); Gerald L. Andriole Jr, Amgen (C), Caris Life Sciences (C), EMD Serono (C), Ferring Pharmaceuticals (C), The France Foundation (C), Gen-Probe (C), GlaxoSmithKline (C), Johnson & Johnson (C), Myriad Genetics (C), Nema Steba (C), Onconome (C), Ortho Clinical Diagnostics (C) **Stock Ownership:** Gerald L. Andriole Jr, Cambridge Endoscopic Devices, Envisioneering, Viking Medical Technologies **Honoraria:** E. David Crawford, AstraZeneca, Ferring Pharmaceuticals, GlaxoSmithKline; Gerald L. Andriole Jr, GlaxoSmithKline **Research Funding:** Robert Grubb III, GlaxoSmithKline; Gerald L. Andriole Jr, Aeterna Zentaris, Antigenics, Ferring Pharmaceuticals, Veridex **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Anthony V. D'Amico

Administrative support: Robert Grubb III, Amanda Black, Gerald L. Andriole Jr, Christine D. Berg, Anthony V. D'Amico

Provision of study materials or patients: E. David Crawford,

Robert Grubb III, Amanda Black, Gerald L. Andriole Jr, Christine D. Berg

Collection and assembly of data: Amanda Black, Ming-Hui Chen, Grant Izmirlian, Christine D. Berg

Data analysis and interpretation: E. David Crawford, Amanda Black, Ming-Hui Chen, Grant Izmirlian, Anthony V. D'Amico

Manuscript writing: E. David Crawford, Robert Grubb III, Amanda Black, Gerald L. Andriole Jr, Ming-Hui Chen, Grant Izmirlian, Christine D. Berg, Anthony V. D'Amico

Final approval of manuscript: E. David Crawford, Robert Grubb III, Amanda Black, Gerald L. Andriole Jr, Ming-Hui Chen, Grant Izmirlian, Christine D. Berg, Anthony V. D'Amico

REFERENCES

- Andriole GL, Crawford ED, Grubb RL 3rd, et al: Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 360:1310-1319, 2009
- Schröder FH, Hugosson J, Roobol MJ, et al: Screening and prostate-cancer mortality in a randomized European Study. *N Engl J Med* 360:1320-1328, 2009
- D'Amico AV, Chen MH, Roehl KA, et al: Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med* 351:125-135, 2004
- Roberts WB, Han M: Clinical significance and treatment of biochemical recurrence after definitive therapy for localized prostate cancer. *Surg Oncol* 18:268-274, 2009
- Freedland SJ, Humphreys EB, Mangold LA, et al: Death in patients with recurrent prostate cancer after radical prostatectomy: Prostate-specific antigen doubling time subgroups and their associated contributions to all-cause mortality. *J Clin Oncol* 25:1765-1771, 2007
- Buyyounouski MK, Hanlon AL, Horwitz EM, et al: Interval to biochemical failure highly prognostic for distant metastasis and prostate cancer-specific mortality after radiotherapy. *Int J Radiat Oncol Biol Phys* 70:59-66, 2008
- Hugosson J, Carlsson S, Aus G, et al: Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol* 11:725-732, 2010
- U.S. National Center for Health Statistics, National Vital Statistics Report (NVSR) Deaths: Final Data for 2006, Vol. 57, No. 14, April 24, 2009
- Framingham Heart Study: General Cardiovascular Disease (10-year risk). www.framinghamheartstudy.org/risk/gencardio.html
- Fleming ID, Cooper JS, Henson DE, et al (eds): *AJCC Cancer Staging Manual* (ed 5). Philadelphia, PA, Lippincott-Raven, 1997
- Gleason DF, Veterans Administration Cooperative Urological Research Group: Histologic grading and staging of prostatic carcinoma, in Tannenbaum M (ed): *Urologic Pathology*. Philadelphia, PA, Lea & Febiger, 1977, pp 171-187
- Agresti A (ed): *An Introduction to Categorical Data Analysis* (ed 2). New York, NY, John Wiley & Sons, 2002, pp 16-52
- Hollander M, Wolfe DA (eds): *Nonparametric Statistical Methods* (ed 2). New York, NY, John Wiley & Sons, 1999, pp 189-269
- Gaynor JJ, Feuer EJ, Tan CC, et al: On the use of cause-specific failure and conditional failure probabilities: Examples from clinical oncology data. *J Am Stat Assoc* 88:400-409, 1993
- Gray RJ: A class of k-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 16:1141-1154, 1988
- Neter J, Wassermann W, Kutner M (eds): *Simultaneous inferences and other topics in regression analyses-1*, in *Applied Linear Regression Models*. Homewood, IL, Richard D. Irwin, 1983, pp 150-153
- Hildebrandt M, Vervölgyi E, Bender R: Calculation of NNTs in RCTs with time-to-event outcomes: A literature review. *BMC Med Res Methodol* 9:21, 2009
- Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 94:496-509, 1999
- Marr PL, Elkin EP, Arredondo SA, et al: Comorbidity and primary treatment for localized prostate cancer: Data from CaPSURE. *J Urol* 175:1326-1331, 2006
- D'Ambrosio DJ, Li T, Horwitz EM, et al: Does treatment duration affect outcome after radiotherapy for prostate cancer? *Int J Radiat Oncol Biol Phys* 72:1402-1407, 2008
- Alibhai SM, Leach M, Tomlinson G, et al: 30-day mortality and major complications after radical prostatectomy: Influence of age and

comorbidity. *J Natl Cancer Inst* 97:1525-1532, 2005

22. Alibhai SM, Leach M, Warde P: Major 30-day complications after radical radiotherapy: A population-based analysis and comparison with surgery. *Cancer* 115:293-302, 2009

23. Cuzick J, Edwards R, Segnan N: Adjusting for non-compliance and contamination in randomized clinical trials. *Stat Med* 16:1017-1029, 1997

24. Bergdahl AG, Aus G, Lilja H, et al: Risk of dying from prostate cancer in men random-

ized to screening: Differences between attendees and nonattendees. *Cancer* 115:5672-5679, 2009

25. Weiss NS, Rossing MA: Healthy screened bias in epidemiologic studies of cancer incidence. *Epidemiology* 7:319-322, 1996

Let *JOP* Online Work for You

- Access all content from the first to the current issue of the *Journal of Oncology Practice (JOP)*
- Consult ASCO Clinical Guideline summaries
- Link to citations from more than 1,300 HighWire-hosted journals
- Receive regular e-mail alerts on topics of interest
- Receive RSS feeds of the most widely read articles from the current issue and the last two issues
- Get the latest cancer policy news
- Access practice resources and tools for enhancing quality of care
- Find a job through the online career center
- Download content to your PDA
- Download figures into preformatted PowerPoint slides

Visit jop.ascpubs.org to see what *JOP* online has to offer.