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Prediction of Long-Term Other-Cause Mortality in Men with Early-Stage Prostate Cancer: Results from the Prostate Cancer Outcomes Study

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Abstract

Objective—To provide population-based estimates of other-cause mortality by age and comorbidity in men with prostate cancer for use at the point-of-care in shared decision making

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Patients and Methods—We sampled 3,183 men with non-metastatic prostate cancer from the Prostate Cancer Outcomes Study, a U.S. population-based, prospective cohort. Survival analysis accounting for competing risks was used to provide predictions of other-cause and cancer-specific mortality by age, comorbidity, and tumor risk through 14 years of follow-up.

Results and Limitations—Older men had a higher absolute risk of other-cause mortality associated with comorbidity. For men with comorbidity counts of 0, 1, 2, and 3+, cumulative incidence of other-cause mortality at fourteen years was: 9%, 18%, 30%, and 35% for those younger than 60; 26%, 26%, and 48%, and 52% for those aged 60-70: and 49%, 57%, 66%, and 74% for those older than 70. Prostate cancer mortality at fourteen years was 5%, 8%, and 23% for men with low-, intermediate-, and high-risk disease. Competing-risks pictograms for each age/comorbidity/tumor-risk pair provide visual characterization of these risks over time.

Conclusions—Our survival tables may be used at the point-of-care as part of shared decision making. Men >60 with multiple comorbidities have substantial risk of other-cause mortality within 15 years of diagnosis and should consider conservative management for low-risk disease, given its low incidence of cancer-specific mortality. Men with high-risk disease, regardless of age or comorbidity, are at greater risk for cancer mortality and may still be appropriate candidates for aggressive treatment.

Keywords

comorbidity; outcome assessment; prostate; prostatic neoplasms; survival

INTRODUCTION

One of the most difficult decisions that a man diagnosed with early-stage prostate cancer must make is whether to pursue potentially curative but morbid aggressive treatments such as surgery or radiation. When considering therapy, it is important to note that studies have shown that any significant survival benefit associated with aggressive therapy does not become evident until 7-10 years after treatment [1]. To this end, it has been suggested that men with less than a 10-year life expectancy do not gain a survival advantage from aggressive treatment [2]. In fact, these men may be harmed by treatment, since all forms of aggressive treatment are associated with adverse side effects such as erectile dysfunction, urinary incontinence, and bowel dysfunction that can significantly affect quality of life [3-5]. As a result, guidelines uniformly advocate for conservative management of these tumors for men with a life expectancy less than 10 years [6-8].

Despite general agreement on this issue, there is still no widely accepted, reproducible method for determination of life expectancy for prostate cancer patients that incorporates both age and health status. The American Urological Association currently recommends using life tables [6]—which predict longevity based on age but not health status—to estimate life expectancy, but life tables have been shown to overestimate life expectancy by up to 22% [9]. The National Comprehensive Cancer Network recommends adding or subtracting 50% of projected life expectancy if men are in the upper or lower quartile of health for their age, but it offers no method for determining health status [7]. The European Association of Urology suggests incorporating health, dependence, and nutritional status

into treatment decisions for older men but does not settle on a single approach to accomplish this aim [8]. As a result of this ambiguity, older and sicker men are often inappropriately treated for early-stage disease. For example, a recent study of men at two VA Hospitals showed that 54% of those with low-risk disease and Charlson comorbidity scores of 3+ were treated with surgery or radiation despite a 70% probability of other-cause mortality at eight years after diagnosis [10].

In this study, we used longitudinal survival data from a large, U.S. population-based, prospective cohort study of men with early-stage prostate cancer to provide estimates of other-cause mortality based on age and a count of 12 comorbidities at diagnosis. This study builds on our previously published work on this topic [11] by providing survival tables for physicians to use at the point-of-care to counsel men about their likelihood of sufficient longevity to benefit from aggressive primary treatment. We also created pictograms showing the longitudinal cumulative incidences of other-cause and prostate cancer mortality at different levels of age, comorbidity, and tumor risk, to serve as a visual characterization of these competing risks over time.

MATERIALS AND METHODS

Study Participants

The Prostate Cancer Outcomes Study (PCOS) is a population-based, prospective cohort study of U.S. men diagnosed with prostate cancer. Details of the PCOS have been published previously [12]. Subjects were identified using the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program; men residing in an area covered by six SEER tumor registries and diagnosed between October 1, 1994 and October 31, 1995 were eligible. All men aged 39–89 years were included except in King County, where inclusion was limited to men aged 60–89 years. A total of 3,533 (62%) eligible men completed the 6-month survey. The institutional review board of each participating institution approved the study.

For this study, we included all men in PCOS with non-metastatic prostate cancer at diagnosis. We excluded men with nodal or distant metastases, those without information on comorbidities at diagnosis, and those diagnosed incidentally at the time of cystoprostatectomy. Our final analytic sample included 3,183 men.

Data Collection

All patients included in this analysis completed a baseline survey within 6 months of diagnosis that included sociodemographic and clinical information (including presence or absence of specific comorbid conditions) as well as self-reported urinary, sexual, and bowel function and general quality of life.

Medical record data—All participants underwent a review of their medical records at one and five years after diagnosis to obtain demographic and clinical information. Treatment types were defined as aggressive (surgery, external beam radiation therapy, or brachytherapy) or non-aggressive (androgen deprivation therapy (ADT) or watchful

waiting). In addition, information on tumor characteristics, primary treatment, and vital status were collected from the SEER registries.

Comorbidity—PCOS used the Charlson Comorbidity index [13] modified for patient self-report to assess the presence or absence of comorbid conditions. We assessed comorbidity as a count of the following twelve major conditions at the time of diagnosis: Diabetes, bleeding gastrointestinal ulcer, chronic lung disease, congestive heart failure (CHF), stroke, myocardial infarction, angina/chest pain, cirrhosis/liver disease, arthritis, inflammatory bowel disease/colitis/Crohn's disease, hypertension, and depression/anxiety. Subjects answered yes/no to ever having a physician's diagnosis or currently using medication(s) for these conditions on the baseline survey.

Tumor characteristics—Tumors were stratified using the D'Amico criteria, as low- (diagnostic PSA <10, clinical stage ≤T2a, and Gleason score ≤6), intermediate- (PSA 10-20, clinical stage T2b, or Gleason score 7), or high-risk (PSA >20, clinical stage ≥T2c, or Gleason score ≥8) [14,15].

Vital status—Vital status and underlying cause of death were determined through 14 years following diagnosis using data from the National Death Index and the National Center for Health Statistics collected through SEER.

Statistical Analysis

We initially divided patients by comorbidity count (0, 1, 2, and 3+) and compared baseline characteristics using the analysis of variance test for continuous variables and the chi-square test for categorical variables.

We then computed cumulative incidence of other-cause mortality at two-year intervals after treatment by comorbidity count across age at diagnosis (< 60, 60-70, >70). Other-cause mortality was modeled with the proportional subdistribution hazards regression as described by Fine and Gray [16], treating prostate cancer death as a competing risk. We included comorbidity count, age at diagnosis, race, study site, D'Amico tumor risk strata, and primary treatment type as covariates. An interaction term between age and comorbidity count was included to allow age-specific effects of comorbidity counts on survival. Prostate Cancer-specific mortality (PCSM) was modeled using a similar approach. Overall mortality was modeled using Cox proportional hazard regression with the same covariate structure as above models.

Kaplan Meier estimates of PCSM and other-cause mortality were computed for groups defined by D'Amico tumor risk categories and comorbidity count and are presented graphically for each tumor risk-comorbidity pair.

A significance level of 0.05 denoted statistical significance, and all tests were two-sided. Statistical analyses were performed using R 2.14 [17] with cmprsk package [18] for Fine and Gray modeling.

RESULTS

Sample characteristics by comorbidity count are reported in Table 1. Advanced age, African American race and higher tumor risk level were associated with higher comorbidity count.

Cumulative incidences of overall, other-cause, and PCSM by comorbidity count and D'Amico tumor risk category are shown in Figure 1A and Figure 1B. Other-cause mortality was 28%, 35%, 52%, and 60% at fourteen years after diagnosis for men with comorbidity counts of 0, 1, 2, and 3+, respectively. Prostate cancer mortality was 5%, 8%, and 23% for men with low-, intermediate-, and high-risk disease, respectively.

Table 2 presents the cumulative incidence of other-cause mortality by comorbidity count and age. Other-cause mortality associated with comorbidity count markedly increased with older age. For men with comorbidity counts of 0, 1, 2, and 3+, cumulative incidence of other-cause mortality at fourteen years was: 9%, 18%, 30%, and 35% for those younger than 60; 26%, 26%, 48%, and 52% for those aged 60-70; and 49%, 57%, 66%, and 74% for those older than 70 years at diagnosis.

Kaplan Meier curves illustrating the longitudinal cumulative incidence of other-cause and cancer-specific mortality by comorbidity count and D'Amico tumor risk level, after stratification by age at diagnosis, are shown in Figures 2A-C. Overall, cumulative incidence of other-cause mortality increased with higher comorbidity count for each age subgroup, and cumulative incidence of PCSM increased with higher tumor risk level.

Men older than 60 had a higher incidence of other-cause mortality associated with comorbidity count than men younger than 60. High tumor risk was associated with a markedly higher cumulative incidence of prostate cancer mortality compared with lowand intermediate-risk tumors.

DISCUSSION

This study presents longitudinal, population-based estimates of other-cause mortality for men with early-stage prostate cancer based on age and a count of 12 common comorbidities at diagnosis. The intent of this work is to operationalize our competing risks model data for use at the point-of-care as part of shared decision making. Older men with multiple comorbidities had a high risk of other-cause mortality; men aged 60-70 and older than 70 with 3 or more comorbidities had a cumulative incidence of other-cause mortality of 52% and 74% at fourteen years after diagnosis, respectively. When deciding between aggressive and non-aggressive initial treatment, these older, sicker men and their physicians should carefully weigh the patient's higher likelihood of dying of other causes against the potential risk of cancer mortality based on tumor risk level. In contrast, men younger than 60 had a greatly diminished absolute impact of comorbidity on other-cause mortality. Younger men may be appropriate candidates for aggressive therapy despite a heavy comorbidity burden, given their substantial long-term longevity.

Our data suggest that older men with multiple comorbidities may be best served by conservative management of D'Amico low-risk but not high-risk tumors. In our population

of men who were often treated with curative intent, fourteen-year cumulative incidence of prostate cancer mortality for men with low-risk disease was 5%. This low incidence of cancer-specific mortality is similar to that observed in studies of patients with similar risk tumors managed conservatively [1,19,20]. Considering the high likelihood of other-cause mortality and low likelihood of prostate cancer mortality, older men with low risk disease and multiple comorbidities may most benefit from conservative management of their tumors in order to avoid morbidities associated with aggressive treatment. In contrast, fourteen-year cancer-specific mortality for men with high-risk disease was 23%. Given that high-risk tumors pose a significant threat to short-term survival, older men with multiple comorbidities may be candidates for aggressive treatment of these tumors despite potential side effects.

Older men with multiple comorbidities should weigh the risks and benefits of aggressive treatment of intermediate-risk tumors, since the lack of clinical benefit in this group is less certain. The fourteen-year cancer-specific mortality in our study for all men with intermediate-risk tumors was only 8%, but the majority of men were treated aggressively with surgery or radiation. While the best evidence suggests that among all men with intermediate-risk disease aggressive treatment may be beneficial, these benefits may be attenuated in older, sicker men. In the PIVOT randomized controlled trial of radical prostatectomy versus watchful waiting, the intermediate-risk subgroup that underwent surgery had a benefit in terms of all-cause mortality (Absolute Risk Reduction (ARR) 12.6, 95%CI 0.2—24.5, p=0.04) and a non-significant reduction in cancer-specific mortality (ARR 4.6, 95%CI -2.5—12.1, p=0.1) [21]. Despite these apparent benefits, a recent SEER-Medicare study showed that the ARR in cancer mortality associated with aggressive treatment of tumors with Gleason scores ≤ 7 diminishes with increasing comorbidity; in fact, men older than 66 with Charlson scores of 2 and 3+ had only 1.9% and -0.5% ARR with aggressive treatment, respectively [22]. Given the relatively small absolute reductions in cancer-specific mortality and the substantial risk of other-cause mortality for older men with multiple comorbidities, it may still be wiser for these men to avoid aggressive treatment for intermediate-risk disease.

One explanation for the current lack of strong guidelines regarding life expectancy in guiding treatment recommendations is the wide variation in reported survival outcomes associated with comorbidity scores, which may be attributable to spectrum bias. Since men who receive surgery are generally healthier than those who receive radiation (who are healthier than those who choose watchful waiting), mortality outcomes associated with comorbidity scores will be markedly different when considered in populations treated solely with surgery, radiation, or watchful waiting. For example, a widely cited, SEER-based study of 1,611 men found that 10-year overall mortality rates for men treated with surgery, radiation or watchful waiting were 26%, 47%, 53% for men with CCI scores of 2+, respectively [23]. These trends can also be observed when comparing other large, retrospective studies of men either treated conservatively or aggressively for early-stage disease [24-26]. We strongly feel that our population-based approach that includes all men regardless of treatment type minimizes selection bias and more accurately models the relevant clinical scenario: an average man considering treatment for newly diagnosed, clinically localized prostate cancer.

Our study has several limitations that deserve mention. First, the majority of men in our sample were treated aggressively for prostate cancer, which may reduce the incidence of PCSM compared with men who are treated conservatively. However, our reported incidence of cancer-specific mortality is comparable to that observed in retrospective and prospective studies of conservatively treated men with risk-matched disease [1,19, 20]. Second, misclassification of cause of death may lead to imprecision in cause-specific mortality estimates, but SEER definitions for cause of death have been shown to be accurate [27, 28]. Third, since our patient cohort consists of men diagnosed with prostate cancer in 1994–95, it is possible that recent advances in surgery or radiation therapy may result in lower cancer-specific and overall mortality in a more contemporary cohort. Fourth, our comorbidity scale has important limitations that should be recognized when applying this information in practice. (1) Comorbidity information was obtained by patient self-report and not confirmed by physician interview or medical record validation. However, studies have shown that patient self-report of comorbidities is fairly reliable [29]. (2) Although our comorbidity categories subsume a large spectrum of diseases, there is no distinction in our scoring system between mild or severe manifestation of disease, which reduces specificity of our comorbidity assessment. (3) Some major comorbidities that are not included in our count data may contribute significantly to prediction of survival, such as a diagnosis of another malignancy. Although these imperfections will lead to variance in mortality predictions, we feel that the data offered here can provide a reasonable estimate of average prognosis by age and comorbidity; the data are meant to augment but not substitute for physician judgment.

CONCLUSIONS

Our data operationalizes population-based estimates of long-term, other-cause mortality for use by clinicians at the point-of-care as part of shared decision making. Given the comparatively low incidence of cancer-specific mortality and the high likelihood of treatment-related morbidity, these data suggest that older, sicker men should pursue conservative management of low-risk disease. Men younger than 60 have less absolute risk of mortality associated with comorbidity, so they may be appropriate candidates for potentially curative aggressive treatment despite a heavy comorbidity burden. Men with high-risk tumors as defined by D'Amico criteria should consider aggressive treatment regardless of chronic comorbidity burden, given that these tumors pose a substantial threat to survival within the first ten years after diagnosis.

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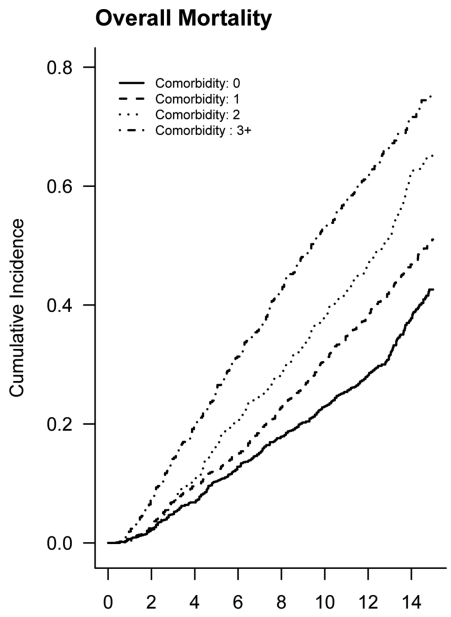
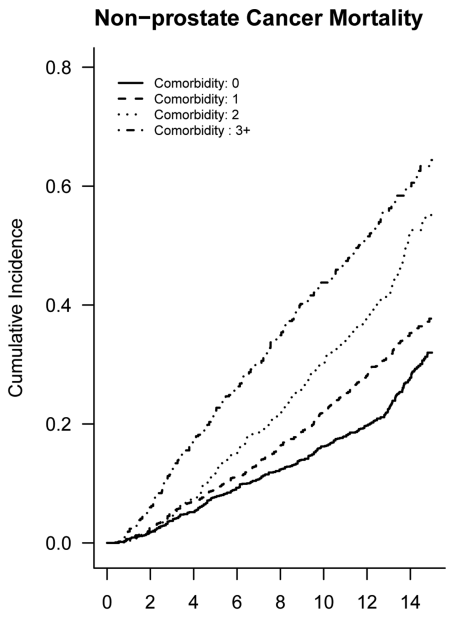
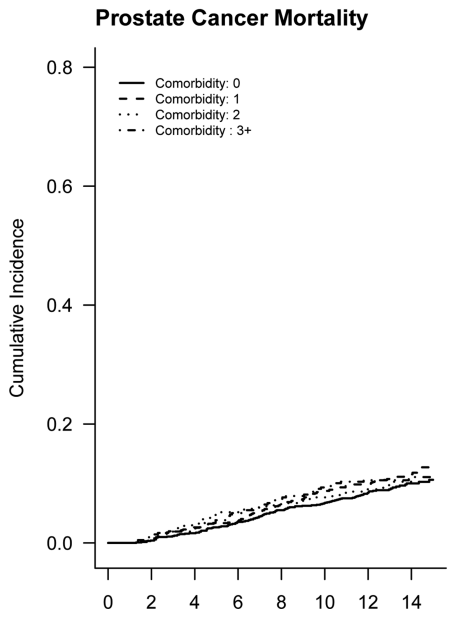






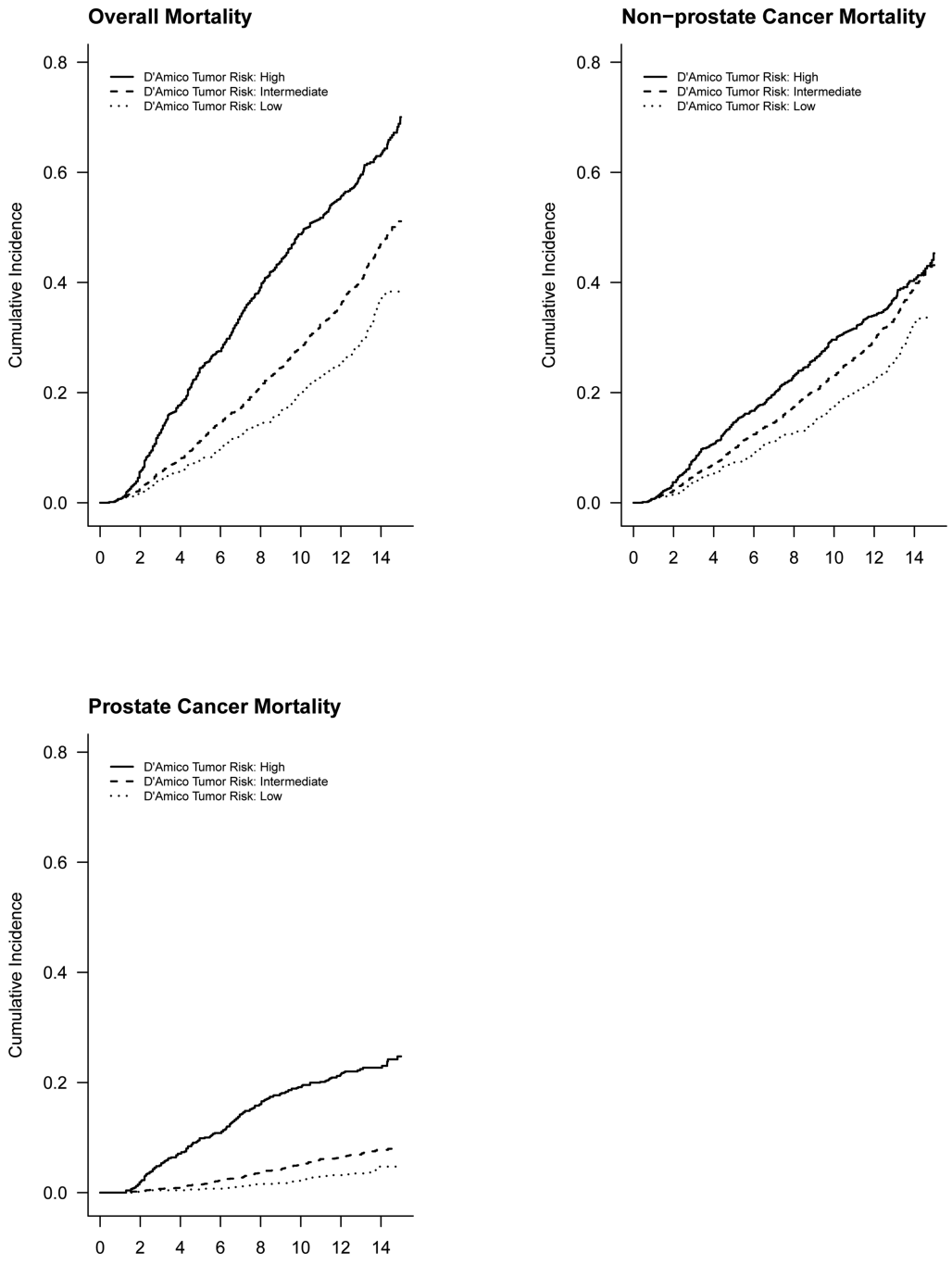
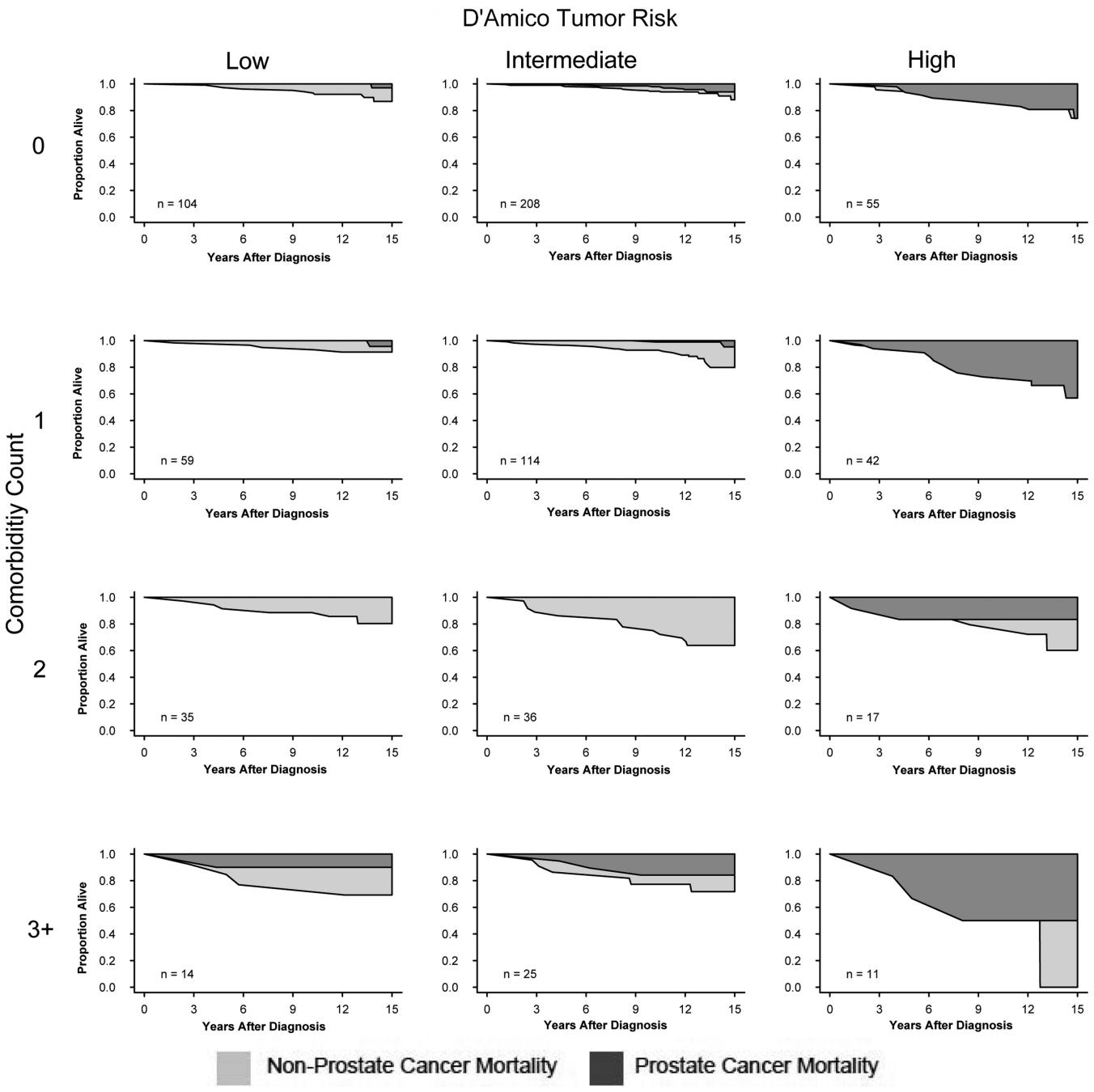
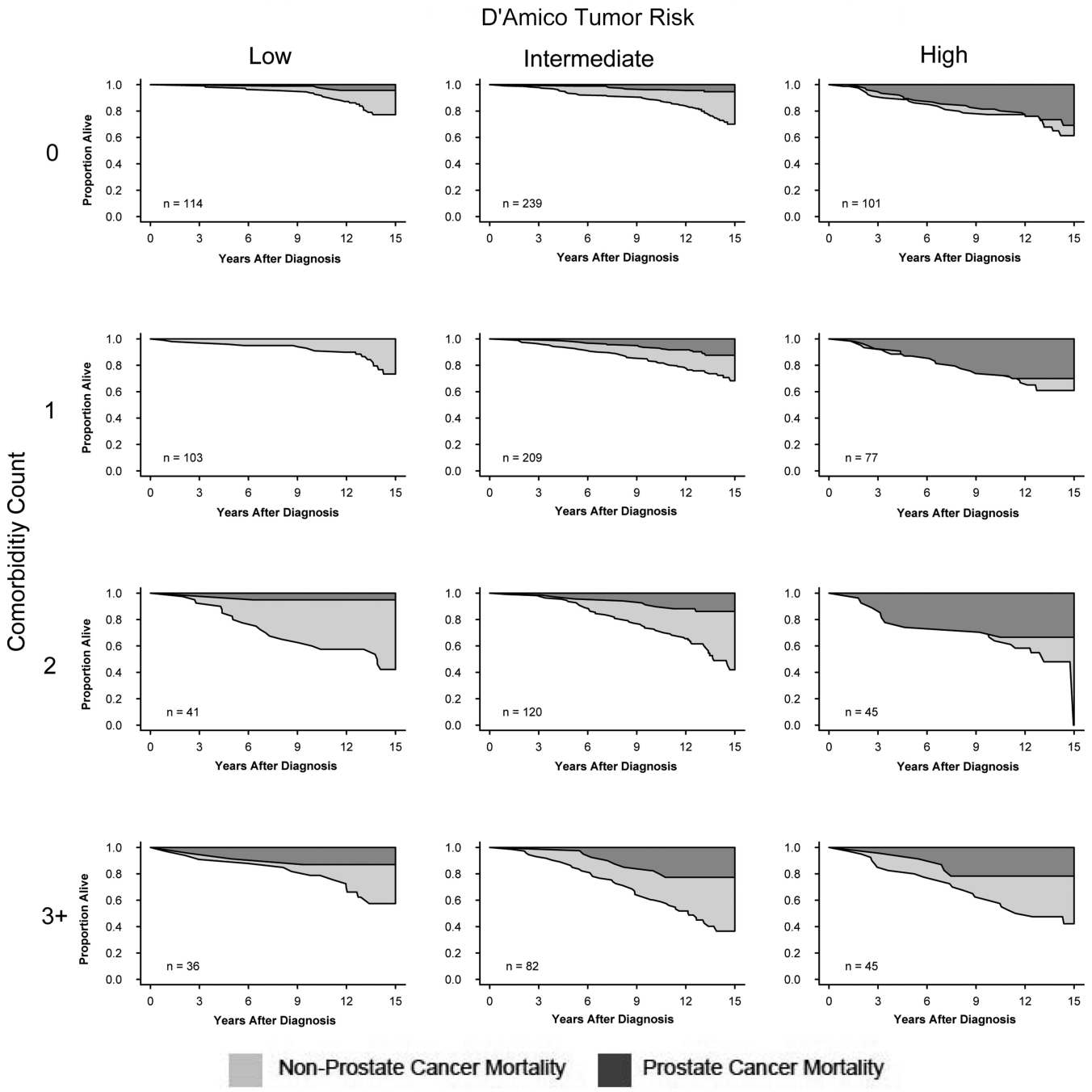


Figure 1.

A-B. Competing Risks Cumulative Incidence Curves for Overall, Other-cause, and Cancer-Specific Mortality by (a) Comorbidity Count and (b) D'Amico Tumor Risk





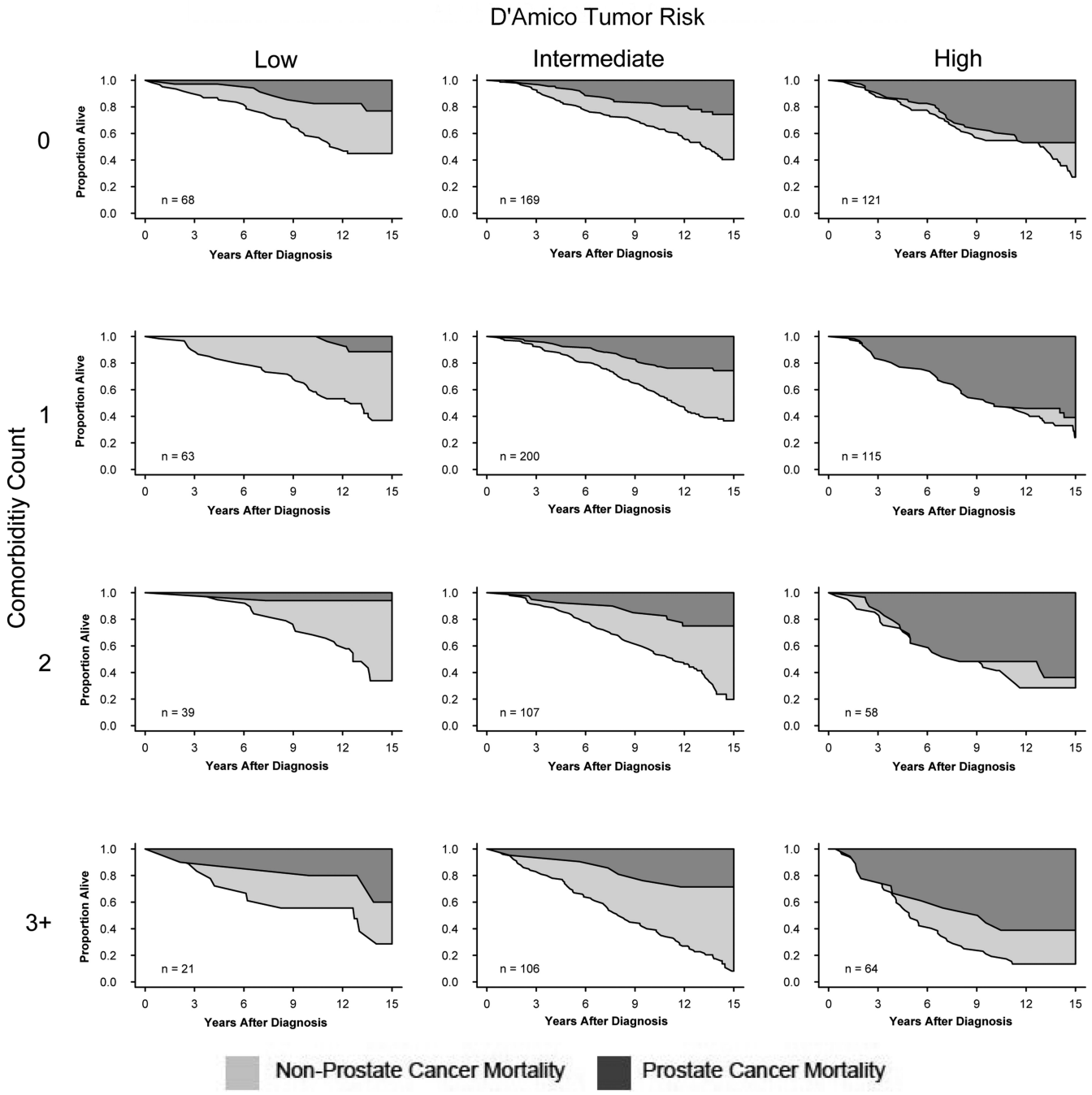


Figure 2.

Mortality by D'Amico Tumor Risk and Comorbidity Count, for Men Aged (a) < 60 years, (b) 60-70 years, and (c) > 70 years at Diagnosis.

Table 1

PCOS patient characteristics by comorbidity count, % (No of patients)

	Comorbidity count 0 (N = 1,221)	Comorbidity count 1 (N = 1,020)	Comorbidity count 2 (N = 523)	Comorbidity count 3+ (N = 419)	p-value*
% Total (N)	38% (1,221)	32% (1,020)	16% (523)	13% (419)	
Age at diagnosis	65 (58, 71)	67 (61, 73)	68 (62, 73)	69 (64, 74)	< 0.001
≤55	57% (203)	29% (101)	8% (29)	6% (21)	
56-65	42% (446)	32% (341)	15% (165)	11% (113)	
66-75	34% (436)	32% (418)	19% (243)	16% (203)	
≥76	29% (136)	34% (160)	19% (86)	18% (82)	
Race					< 0.001
Non-Hispanic white	40% (885)	32% (716)	15% (326)	13% (278)	
African American	31% (169)	30% (162)	22% (121)	16% (88)	
Hispanic	38% (167)	32% (142)	17% (076)	12% (53)	
PSA at diagnosis Missing PSA	8.0 (5.3, 13.7) 35% (69)	8.0 (5.5, 13.6) 34% (67)	8.0 (5.6, 14.1) 19% (38)	9.8 (5.6, 17.9) 13% (26)	0.04 0.61
Clinical T stage					0.7
T1	40% (340)	32% (271)	17% (143)	12% (99)	
T1/T2	37% (367)	33% (321)	15% (152)	14% (144)	
T2	38% (467)	32% (382)	17% (204)	13% (156)	
T3	34% (47)	34% (46)	17% (24)	15% (20)	
Gleason score					0.90
≤ 6	39% (753)	33% (637)	16% (319)	12% (254)	
7	39% (321)	30% (273)	18% (144)	13% (114)	
≥ 8	38% (139)	33% (98)	15% (55)	15% (47)	
Missing GS	34 % (8)	30% (12)	18% (5)	18% (4)	0.64
D'Amico tumor risk					0.08
Low	41% (286)	32% (225)	17% (115)	10% (71)	
Intermediate	38% (616)	33% (523)	16% (263)	13% (213)	
High	37% (277)	31% (234)	16% (120)	16% (120)	
Missing tumor risk	35% (42)	32% (38)	21% (25)	12% (15)	0.60
Primary treatment					< 0.001
Radical Prostatectomy	46% (735)	31% (499)	15% (240)	8% (135)	
External Beam Radiation	32% (245)	34% (254)	18% (137)	16% (121)	
ADT****	29% (85)	33% (99)	18% (54)	20% (60)	
Watchful waiting/Active Surveillance	30% (156)	32% (168)	18% (92)	20% (103)	

Percentages are reported across rows and may not sum to 100% due to rounding.

Age and PSA are summarized with median and quartiles.

** Aggressive = surgery or radiation therapy

*** Non-aggressive= androgen deprivation therapy, watchful waiting, or active surveillance without treatment

* Chi-squared tests except Kruskal-Wallis tests for age and PSA.

**** ADT = Androgen deprivation therapy

Table 2

Mortality Tables: Longitudinal Cumulative Incidence of Other-Cause Mortality by Comorbidity Count*, Stratified by Age at Diagnosis, % (95% Confidence Interval)

(a) Age < 60	Years after diagnosis						
Comorbidity Count	**2**	**4**	**6**	**8**	**10**	**12**	**14**
0	1 (0,1)	1 (0,2)	3 (1,5)	3 (2,5)	6 (3,8)	7 (4,9)	9 (6,13)
1	2 (0,4)	2 (0,4)	3 (1,6)	7 (4,10)	8 (5,12)	12 (8,17)	18 (12,24)
2	0 (0,0)	6 (1,10)	10 (4,16)	13 (6,20)	17 (9,25)	22 (14,31)	30 (19,40)
3+	0 (0,0)	12 (3,20)	15 (5,25)	17 (7,28)	25 (13,37)	25 (13,37)	35 (21,50)

(b) Ages 60-70	Years after diagnosis						
Comorbidity Count	**2**	**4**	**6**	**8**	**10**	**12**	**14**
0	1 (0,2)	4 (2,5)	7 (5,9)	9 (7,12)	12 (9,14)	16 (13,19)	26 (22,30)
1	2 (1,4)	5 (3,7)	8 (5,10)	11 (8,14)	14 (11,18)	19 (16,23)	26 (21,30)
2	1 (0,3)	6 (3,9)	13 (9,17)	19 (14,24)	26 (21,32)	34 (28,39)	48 (41,56)
3+	5 (2,8)	14 (9,19)	20 (15,26)	29 (22,35)	37 (30,44)	44 (37,51)	52 (45,60)

(c) Age > 70	Years after diagnosis						
Comorbidity Count	**2**	**4**	**6**	**8**	**10**	**12**	**14**
0	5 (2,7)	12 (8,15)	20 (16,25)	28 (23,32)	35 (30,41)	41 (35,46)	49 (43,55)
1	3 (2,5)	13 (9,16)	21 (17,25)	30 (25,34)	40 (35,45)	49 (44,54)	57 (52,63)
2	3 (1,6)	10 (6,15)	20 (15,26)	30 (23,37)	42 (35,49)	51 (44,59)	66 (58,74)
3+	9 (5,14)	22 (16,29)	36 (29,43)	47 (40,55)	57 (50,64)	67 (60,74)	74 (67,81)

* Comorbidity Count is calculated as a count of the following twelve major comorbidities at diagnosis: Diabetes, bleeding gastrointestinal ulcer, chronic lung disease, congestive heart failure (CHF), stroke, myocardial infarction, angina/chest pain, cirrhosis/liver disease, arthritis, inflammatory bowel disease/colitis/Crohn's disease, hypertension, and depression/anxiety.