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abstract **Purpose** Generalized competing event (GCE) models improve stratification of patients according to their risk of cancer events relative to competing causes of mortality. The potential impact of such methods on clinical trial power and cost, however, is uncertain. We sought to test the hypothesis that GCE models can reduce estimated clinical trial cost in elderly patients with cancer.

Methods Patients with nonmetastatic head and neck (n = 9,677), breast (n = 22,929), or prostate cancer (n = 51,713) were sampled from the SEER-Medicare database. Using multivariable Cox proportional hazards models, we compared risk scores for all-cause mortality (ACM) and cancer-specific mortality (CSM) with GCE-based risk scores for each disease. We applied a cost function to estimate the cost and duration of clinical trials with a primary end point of overall survival in each population and in high-risk subpopulations. We conducted sensitivity analyses to examine model uncertainty.

Results For the purpose of enriching subpopulations, GCE models reduced estimated clinical trial cost compared with Cox models of ACM and CSM in all disease sites. The relative cost reductions with GCE models compared with ACM and CSM models, respectively, were −68.4% and −14.4% in prostate cancer, −38.8% and −18.3% in breast cancer, and −17.1% and −4.1% in head and neck cancer. Cost savings in breast and prostate cancers were on the order of millions of dollars. The GCE model also reduced relative clinical trial duration compared with CSM and ACM models for all disease sites. The optimal risk score cutoff for clinical trial enrollment occurred near the top tertile for all disease sites.

Conclusion GCE models have significant potential to improve clinical trial efficiency and reduce cost, with a potentially large impact in prostate and breast cancers.

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INTRODUCTION

Randomized clinical trials are time intensive and costly research endeavors. The cost of conducting clinical trials in oncology has been rising because of higher operational and administrative overhead and increasing drug development costs.¹⁻³ The expense of conducting clinical trials has led to the adoption of risk-averse research strategies, globalization of clinical trials to low-cost countries, and delayed scientific and clinical progress.⁴⁻⁶ Given the scarcity of research resources, funding agencies, regulatory bodies, and researchers have called for disruptive innovation in the design and conduct of clinical trials.⁷⁻¹⁰

Generalized competing event (GCE) models are a novel strategy to reduce clinical trial cost and improve efficiency.^{11,12} This method seeks to enrich clinical trial populations by identifying

patients with the highest probability of experiencing an event of interest (eg, cancer recurrence or mortality) relative to competing events (eg, non-cancer or treatment-related mortality).¹³⁻¹⁵ Although inclusion and exclusion criteria achieve this implicitly to some degree, GCE models achieve this more directly by separating the cause-specific effects of known predictors, then aggregating them into an individualized risk score.

Previous studies have found that GCE models are superior to conventional Cox proportional hazards (PH) regression models for stratifying elderly patients with cancer according to the hazard for cancer mortality relative to all-cause mortality (ACM; ω ratio).^{11,12} However, the potential impact of this strategy on clinical trial cost remains uncertain, because power and study duration depend on factors such as cancer event rates and accrual rates, independent of the ratio of cancer

to noncancer events. We sought to estimate trial cost using GCE models compared with conventional methods of risk stratification in elderly patients with cancer at risk for competing events.

METHODS

Population and Sampling Methods

The population included patients with nonmetastatic cancer of the prostate, head and neck, or breast identified in the SEER-Medicare linked database. The SEER registries include 26% of the US cancer population, and Medicare provides health insurance for those age ≥ 65 years. The sample and covariates used for risk-stratification models were described previously.¹² Briefly, the study included 51,713 patients with localized prostate cancer diagnosed from 2000 to 2009, 9,677 patients with nonmetastatic head and neck cancer diagnosed from 1996 to 2009, and 22,929 patients with nonmetastatic breast cancer diagnosed from 2004 to 2009. Patients with prostate cancer were treated with definitive radiotherapy; we excluded 16,546 patients treated with radical prostatectomy because too few of these patients died as a result of cancer (141 deaths; $< 1\%$). Patients with head and neck cancer were treated with radiotherapy with or without surgery and/or chemotherapy. Those with breast cancer were treated with mastectomy or lumpectomy with or without radiotherapy and/or chemotherapy.

Risk Stratification

Patients were stratified according to the risk for cancer-specific mortality (CSM) and ACM based on demographic, tumor, and treatment characteristics (Appendix). CSM was defined as death as a result of the primary cancer diagnosis (ie, prostate, head and neck, or breast cancer). Competing mortality (CM) was defined as either noncancer mortality or second cancer mortality. ACM was defined as death resulting from any cause. We used cumulative incidence functions to calculate outcome event probabilities.^{16,17}

Risk models for CSM and ACM were developed and internally validated using the Cox PH model.¹⁸ All covariates that were significant ($P < .05$) were retained in the models. Using the same covariates as the Cox models, we created risk models for CSM and CM using Fine-Gray regression.¹⁹ The GCE risk model was created by

subtracting the CM risk score (ie, linear predictor) from the CSM risk score to stratify patients according to ω (Appendix).¹² High ω values indicated subpopulations with lower incidence of competing risks and thus with potentially greater likelihood of benefiting from cancer therapies. To determine the optimal cutoff points for clinical trial enrollment based on the GCE risk score, we calculated cost and duration at various thresholds for each cancer type.

Cost Model

We applied a previously developed model to estimate the cost and duration of clinical trials with a primary end point of ACM (ie, overall survival).²⁰ The model incorporates both fixed (startup and yearly maintenance) and variable (accrual and follow-up) costs:

$$C(t) = Cs + Cmt + \beta Ca\tau + \beta Cf(\lambda\tau - e^{-\lambda t}[e^{\lambda\tau} - 1])/\lambda^2$$

where Cs is the startup cost, Cm is the fixed cost per year, t is the trial duration in years, β is the accrual rate, Ca is the cost per individual of accrual, τ is the length of accrual in years, Cf is the cost per patient-year of follow-up, and λ is the event hazard. The cost function assumes a constant accrual rate and an exponentially distributed survival function. Inputs to the cost function were based on cost estimates cited in the oncology literature, including startup cost of \$8,000, annual maintenance cost of \$80,000, per-patient treatment cost of \$5,000, and annual per-patient follow-up cost of \$200.³ The annual follow-up cost was modest because most estimates of per-patient treatment cost include corresponding follow-up. Loss to follow-up was not accounted for, because it would affect both standard risk and GCE methods. An important caveat is that these cost estimates are historical and may not account for recent rises in health care costs. Therefore, relative cost differences between models are more meaningful than absolute trial cost.

Power Analysis

Sample size calculations assumed two-sided type I error (α) of 0.05 and type II error (β) of

0.20, exponential event distribution, equal-sized arms, and cause-specific hazard ratio of 1.0 for CM (ie, null effect).²¹ The cause-specific hazard ratio for CSM was 0.25 for prostate and breast cancers and 0.5 for head and neck cancer. The primary end point was overall survival. We assumed accrual and follow-up times of 3 years for head and neck cancer, 5 years for breast cancer, and 6 years for prostate cancer. Evaluation was at 5 years for head and neck cancer, 5 years for breast cancer, and 10 years for prostate cancer. The values were chosen to be representative of typical clinical trials in each disease site; because longer follow-up is typically required to determine treatment effects in prostate cancer, a longer evaluation time point of 10 years was chosen. Cumulative incidences for cause-specific and overall survival were taken from SEER-Medicare data.

The effect on overall survival was computed according to the following equation²²⁻²⁴:

$$\theta = \omega * \theta_1 + (1 - \omega) * (\theta_2) = \omega * \theta_1 + (1 - \omega)$$

where θ is the effect of therapy on overall survival, θ_1 is the effect on CSM, and θ_2 is the effect on CM, which was set at 1.0.

On the basis of the observed survival rates in the unselected SEER-Medicare cohort and representative accrual and follow-up times, hazard ratios for overall survival, and evaluation times, we calculated sample size, cost, and trial duration for the unselected cohort in each cancer. Cost and trial duration were then estimated for hypothetical trials conducted in subpopulations defined by the top tertile of each risk score and for each decile of the GCE-based risk score. Accrual rate in the selected subgroups was a

proportional fraction of accrual rate in the whole cohort. For instance, a 33% enriched subgroup would accrue at 33% of the rate for conducting the trial in the whole cohort of patients. Accrual duration was calculated as sample size divided by accrual rate.

We conducted one-way sensitivity analyses to determine the effect of parameter variation on clinical trial cost. Per-patient treatment cost was varied from \$2,500 to \$10,000, and cause-specific hazard ratio was varied from 0.10 to 0.90. Clinical trial cost was calculated for each disease site using all three risk models in the sensitivity analysis.

Assumptions and parameter inputs for risk stratification, cost model, and power analysis are summarized in Appendix Table A1. SEER-Medicare data were extracted using SAS software (SAS Institute, Cary, NC), and all statistical analyses were performed in R (www.r-project.org).

RESULTS

For the whole sample, the cumulative incidence of noncancer mortality was higher than cancer mortality in prostate, head and neck, and breast cancers. The 5-year cumulative incidences of CSM versus ACM for head and neck and breast cancers were 24.2% versus 59.3% and 4.8% versus 20.1%, respectively; the 10-year cumulative incidence of CSM versus ACM for prostate cancer was 4.7% versus 40.2%, respectively.

The ω value was lowest for patients with prostate cancer at 0.115 at 10 years, followed by patients with breast cancer at 0.238 at 5 years and patients with head and neck cancer at 0.380 at 5 years. Note this ratio was approximately

Table 1. Effect of Various Prostate Cancer Risk Models on Clinical Trial Cost and Duration in High-Risk Subpopulations

Risk Group	10-Year PCM (%) [*] (95% CI)	10-Year ACM (%) [*] (95% CI)	10-Year Ratio of PCM Hazard to ACM Hazard (ω)	Treatment Effect Size	Sample Size	Relative Accrual Rate	Trial Duration (years)	Trial Cost (\$; millions)
Cox model of ACM	6.0 (5.4 to 6.8)	60.0 (58.1 to 62.0)	0.092	0.931	11,369	0.333	24.7	61.15
Cox model of PCM	8.7 (7.6 to 9.8)	53.7 (51.1 to 56.2)	0.159	0.881	4,117	0.333	12.8	22.58
GCE method	8.6 (7.6 to 9.7)	44.1 (41.7 to 46.4)	0.190	0.857	3,462	0.333	11.7	19.33
Unselected total cohort	4.7 (4.3 to 5.0)	40.2 (39.4 to 41.1)	0.115	0.914	10,922	1.0	12.0	59.76

NOTE. Relative to the unselected SEER-Medicare cohort of 51,713 patients, risk models selected the top tertile of patients.

Abbreviations: ACM, all-cause mortality; GCE, generalized competing event; PCM, prostate cancer mortality.

^{*}Cumulative incidence method.

Table 2. Effect of Various Breast Cancer Risk Models on Clinical Trial Cost and Duration in High-Risk Subpopulations

Risk Group	5-Year BCM* % (95% CI)	5-Year ACM* % (95% CI)	5-Year Ratio of Hazard for BCM to Hazard for ACM (ω)	Treatment Effect Size	Sample Size	Relative Accrual Rate	Trial Duration (years)	Trial Cost (\$; millions)
Cox model of ACM	10.2 (9.4 to 11.0)	41.6 (40.2 to 43.0)	0.238	0.822	1,582	0.333	12.6	9.51
Cox model of BCM	10.9 (10.1 to 11.7)	36.9 (35.6 to 38.3)	0.289	0.783	1,157	0.333	10.6	7.12
GCE method	8.5 (7.8 to 9.3)	20.0 (19.0 to 21.2)	0.422	0.684	889	0.333	9.3	5.82
Unselected total cohort	4.8 (4.5 to 5.2)	20.1 (19.4 to 20.8)	0.238	0.822	3,107	1.0	10.0	18.57

NOTE. Relative to the unselected SEER-Medicare cohort of 22,929 patients, risk models selected the top tertile of patients.

Abbreviations: ACM, all-cause mortality; BCM, breast cancer mortality; GCE, generalized competing event.

*Cumulative incidence method.

constant over time for prostate and breast cancers but decreased with time for head and neck cancer. When the highest tertile of each risk score was selected as a cutoff for clinical trial enrollment, the CSM and GCE models increased ω scores in all disease sites (Tables 1, 2, and 3). GCE models optimized ω in the highest tertile of the risk score for each disease. For ACM, CSM, and GCE risk methods, the ω scores were 0.092 versus 0.159 versus 0.190 for prostate cancer, 0.238 versus 0.289 versus 0.422 for breast cancer, and 0.384 versus 0.423 versus 0.454 for head and neck cancer.

For the purpose of enriching subpopulations, GCE models reduced estimated clinical trial cost compared with Cox models of ACM and CSM in all disease sites. The relative cost reductions with GCE models compared with ACM and CSM models were –68.4% and –14.4% in prostate cancer, –38.8% and –18.3% in breast cancer, and –17.1% and –4.1% in head and neck

cancer (Tables 1 to 3). The potential cost savings in breast and prostate cancers were on the order of millions of dollars. The GCE model also reduced clinical trial duration compared with CSM and ACM models for all disease sites. All risk models increased trial duration in head and neck cancer, but the GCE model had a lower trial duration than the CSM and ACM models. When the per-patient treatment cost and cause-specific hazard ratios were varied in the sensitivity analyses, the GCE model reduced clinical trial cost compared with the CSM and ACM at all parameter inputs (Appendix Tables A2 to A7).

The optimal risk score cutoff for clinical trial enrollment was similar and occurred near the top tertile for prostate, breast, and head and neck cancers (Fig 1). We identified the optimal risk score cutoff as that which yielded the lowest cost without substantially prolonging trial duration. For breast and prostate cancers, increased selection reduced clinical trial cost even until

Table 3. Effect of Various Head and Neck Cancer Risk Models on Clinical Trial Cost and Duration in High-Risk Subpopulations

Risk Group	5-Year HNCRM* % (95% CI)	5-Year ACM % (95% CI)	5-Year Ratio of HNCRM Hazard to ACM Hazard (ω)	Treatment Effect Size	Sample Size	Relative Accrual Rate	Trial Duration (years)	Trial Cost (\$; millions)
Cox model of ACM	34.8 (33.1 to 36.5)	79.6 (78.1 to 81.1)	0.384	0.808	965	0.333	9.3	5.70
Cox model of HNCRM	35.5 (33.8 to 37.2)	75.9 (74.2 to 77.5)	0.423	0.788	827	0.333	8.4	4.93
GCE method	34.1 (32.4 to 35.8)	69.2 (67.5 to 70.9)	0.454	0.773	787	0.333	8.1	4.73
Unselected total cohort	24.2 (23.4 to 25.1)	59.3 (58.2 to 60.3)	0.380	0.810	1,376	1.0	6.0	7.67

NOTE. Relative to the unselected SEER-Medicare cohort of 9,677 patients, risk models selected the top tertile of patients.

Abbreviations: ACM, all-cause mortality; GCE, generalized competing event; HNCRM, head and neck cancer mortality.

*Cumulative incidence method.

Fig 1. (A, D, G) Clinical trial cost, (B, E, H) ω values, and (C, F, I) clinical trial duration as a function of risk score cutoff using different risk-stratification models in (A-C) prostate cancer, (D-F) breast cancer, and (G-I) head and neck cancer. ω values were calculated at 10 years for prostate cancer and 5 years for breast and head and neck cancers. Data points associated with increased selectivity resulting in trial durations > 20 years are not displayed, because they were considered impractical. ACM, all-cause mortality; CSM, cancer-specific mortality; GCE, generalized competing event.

the final ω decile of patient selection. In head and neck cancer, increased selectivity resulted in a U-shaped cost curve because of increasing cost with longer accrual (ie, increasing selectivity beyond the 70th percentile led to smaller benefits in ω , so cost savings related to reductions in sample size were outweighed by the cost of longer trial duration).

DISCUSSION

Elderly patients with cancer and those with comorbidities are at high risk for noncancer

mortality that often exceeds the risk of CSM, diminishing the benefit of intensive cancer treatment. Using GCE methods to identify subpopulations at increased risk for cancer mortality relative to noncancer mortality is a strategy to improve selection of patients most likely to benefit from more intensive cancer treatment. In addition, we found a large potential for GCE methods to reduce trial cost and duration relative to conventional risk-stratification methods. We observed the largest benefit in breast and prostate cancers, in which the predominant cause of death was noncancer mortality. The

benefit of GCE was comparatively smaller in head and neck cancer because of a lower incidence of noncancer mortality relative to cancer mortality.

Enrolling patients at high risk for noncancer mortality relative to cancer mortality (ie, low ω) in treatment intensification trials places them at risk for treatment-related adverse events, without necessarily contributing significant information regarding treatment effects.²³ Moreover, such patients increase the sample size and event rate—giving the illusion of greater statistical power while adding little to the actual statistical power—which leads to increased trial cost, duration, and inefficiency.^{14,23-25} Tailoring trials better designed to address such patients' needs is more consistent with the emphasis on personalized medicine.^{26,27} Our findings also support the general concept of using risk scores, rather than binary thresholds based on single covariates, for individualizing treatment decisions and evaluating trial eligibility, because risk scores can distill the effects from a large set of predictive factors into a single metric. Risk scores can also be used for postrandomization patient stratification between treatment arms to ensure balance of baseline risk factors.¹⁵

Strengths of our study include large patient samples in three different diseases with detailed patient demographic, tumor, and comorbidity data. Cause of death information allowed for the creation of CSM and CM risk scores. Risk models were internally validated and applied to a previously developed cost model that accounts for both clinical trial cost and duration. Because of the large SEER-Medicare sample, we were able to conduct a detailed analysis of cost and duration to identify optimal cutoffs for clinical trial enrollment.

This study has some limitations. First, we used a cost model, rather than measuring actual clinical trial cost, to investigate the effects of a GCE approach relative to conventional risk stratification. Actual trial cost is extremely difficult to calculate and ascribe accurately to subpopulations, making it challenging to test the effects of varying risk-stratification models directly. However, our sensitivity analysis indicated that the conclusion that a GCE model reduces clinical trial cost and duration was stable under varying assumptions regarding cost and power parameters. Second, our risk-stratification models depend on the proportional hazards assumption, but this assumption is routinely accepted in the design and analysis of clinical trial data. We also assumed constant accrual for the cost models, which may not always be the case in practice. Other important assumptions and parameter inputs facilitated this work (Appendix Table A1), and because some of these assumptions simplify the complexities of conducting clinical trials, it remains unclear whether GCE models would reduce trial cost in actual practice. Finally, the potential cost reductions with GCE modeling do not necessarily apply to populations with other types of cancers or with low incidences of competing events. Also, the benefit of therapies in enriched populations will be attenuated in patients with more comorbidities, so caution is needed if extrapolating the findings.

In summary, we found that GCE models reduced estimated clinical trial cost compared with standard risk-stratification methods in elderly patients with prostate, breast, or head and neck cancer. GCE-based risk stratification represents an evidence-based method to improve clinical trial efficiency and reduce cost in competing risks populations.

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Data analysis and interpretation: All authors

Manuscript writing: All authors

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Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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REFERENCES

1. DiMasi JA, Hansen RW, Grabowski HG: The price of innovation: New estimates of drug development costs. *J Health Econ* 22:151-185, 2003
2. Adams CP, Brantner VV: Spending on new drug development. *Health Econ* 19:130-141, 2010
3. Institute of Medicine: A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program. Washington, DC, National Academies Press, 2010
4. Glickman SW, McHutchison JG, Peterson ED, et al: Ethical and scientific implications of the globalization of clinical research. *N Engl J Med* 360:816-823, 2009
5. Johnston SC, Hauser SL: Clinical trials: Rising costs limit innovation. *Ann Neurol* 62:A6-A7, 2007
6. Wood AJ: A proposal for radical changes in the drug-approval process. *N Engl J Med* 355:618-623, 2006
7. DeMets DL, Califf RM: A historical perspective on clinical trials innovation and leadership: Where have the academics gone? *JAMA* 305:713-714, 2011
8. Food and Drug Administration: Critical path opportunities report, 2006. http://www.fda.gov/oc/initiatives/criticalpath/report/opp_report.pdf
9. Stewart DJ, Whitney SN, Kurzrock R: Equipoise lost: Ethics, costs, and the regulation of cancer clinical research. *J Clin Oncol* 28:2925-2935, 2010
10. Temple RJ: Enrichment designs: Efficiency in development of cancer treatments. *J Clin Oncol* 23:4838-4839, 2005
11. Carmona R, Gulaya S, Murphy JD, et al: Validated competing event model for the stage I-II endometrial cancer population. *Int J Radiat Oncol Biol Phys* 89:888-898, 2014
12. Carmona R, Zakeri K, Green G, et al: Improved method to stratify elderly patients with cancer at risk for competing events. *J Clin Oncol* 34:1270-1277, 2016
13. Mell LK, Dignam JJ, Salama JK, et al: Predictors of competing mortality in advanced head and neck cancer. *J Clin Oncol* 28:15-20, 2010
14. Rose BS, Jeong JH, Nath SK, et al: Population-based study of competing mortality in head and neck cancer. *J Clin Oncol* 29:3503-3509, 2011
15. Zakeri K, Rose BS, Gulaya S, et al: Competing event risk stratification may improve the design and efficiency of clinical trials: Secondary analysis of SWOG 8794. *Contemp Clin Trials* 34:74-79, 2013

16. Korn EL, Dorey FJ: Applications of crude incidence curves. *Stat Med* 11:813-829, 1992
17. 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
18. Cox DR: Regression models and life tables. *J R Stat Soc Series B Stat Methodol* B34:187-220, 1972
19. Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 94:496-509, 1999
20. Piantadosi S, Patterson B: A method for predicting accrual, cost, and paper flow in clinical trials. *Control Clin Trials* 8:202-215, 1987
21. Pintilie M: Dealing with competing risks: Testing covariates and calculating sample size. *Stat Med* 21:3317-3324, 2002
22. Mell LK, Lau SK, Rose BS, et al: Reporting of cause-specific treatment effects in cancer clinical trials with competing risks: A systematic review. *Contemp Clin Trials* 33:920-924, 2012
23. Zakeri K, Rose BS, D'Amico AV, et al: Competing events and costs of clinical trials: Analysis of a randomized trial in prostate cancer. *Radiother Oncol* 115:114-119, 2015
24. Mell LK, Jeong JH: Pitfalls of using composite primary end points in the presence of competing risks. *J Clin Oncol* 28:4297-4299, 2010
25. Gómez G, Lagakos SW: Statistical considerations when using a composite endpoint for comparing treatment groups. *Stat Med* 32:719-738, 2013
26. Mega JL, Sabatine MS, Antman EM: Population and personalized medicine in the modern era. *JAMA* 312:1969-1970, 2014
27. Mell LK, Zakeri K, Rose BS: On lumping, splitting, and the nosology of clinical trial populations and end points. *J Clin Oncol* 32:1089-1090, 2014

Prostate cancer risk scores:

Cox all-cause mortality risk score = $0.056 \times (\text{age}) + -0.165 \times (\text{brachytherapy}) + -0.167 \times (\text{married}) + 0.150 \times (\text{T2}) + 0.331 \times (\text{T3}) + 0.312 \times (\text{high grade}) + 0.496 \times (\text{CCI} = 1) + 0.741 \times (\text{CCI} = 2) + 1.370 \times (\text{CCI} > 2) + 0.007 \times (\text{PSA}) + 0.033 \times (\text{East}) + 0.160 \times (\text{Midwest}) + 0.393 \times (\text{South})$.

Cox prostate cancer-specific mortality risk score = $0.035 \times (\text{age}) + -0.065 \times (\text{brachytherapy}) + 0.097 \times (\text{married}) + 0.544 \times (\text{T2}) + 1.015 \times (\text{T3}) + 1.320 \times (\text{high grade}) + -0.035 \times (\text{CCI} = 1) + 0.464 \times (\text{CCI} = 2) + 0.552 \times (\text{CCI} > 2) + 0.012 \times (\text{PSA}) + -0.240 \times (\text{East}) + 0.045 \times (\text{Midwest}) + 0.201 \times (\text{South})$.

Generalized competing event risk score = $-0.029 \times (\text{age}) + 0.142 \times (\text{brachytherapy}) + 0.309 \times (\text{married}) + 0.437 \times (\text{T2}) + 0.867 \times (\text{T3}) + 1.073 \times (\text{high grade}) + -0.631 \times (\text{CCI} = 1) + -0.375 \times (\text{CCI} = 2) + -1.0456 \times (\text{CCI} \geq 3) + 0.006 \times (\text{PSA}) + -0.304 \times (\text{East}) + -0.125 \times (\text{Midwest}) + -0.255 \times (\text{South})$.

where age in years at diagnosis and prostate-specific antigen (PSA) are continuous variables. The following variables are defined by the presence (value = 1) or absence (value = 0) of the indicated condition: married, receipt of brachytherapy, tumor stage (T2 and T3), high grade of Gleason 4 or 5, Charlson comorbidity index (CCI), and region (East, Midwest, South).

Breast cancer risk scores:

Cox all-cause mortality risk score = $0.061 \times (\text{age}) + -0.214 \times (\text{married}) + -0.136 \times (\text{Midwest}) + -0.218 \times (\text{East}) + 0.154 \times (\text{South}) + -0.072 \times (\text{high SES}) + 0.466 \times (\text{CCI} = 1) + 0.825 \times (\text{CCI} = 2) + 1.213 \times (\text{CCI} \geq 3) + 0.185 \times (\text{high grade}) + 0.361 \times (\text{regional stage}) + 0.898 \times (\text{size} > 5) + 0.403 \times (\text{size 2-5}) + 0.094 \times (\text{size unknown}) + -0.342 \times (\text{ER positive}) + -0.031 \times (\text{ER unknown}) + -0.170 \times (\text{PR positive}) + -0.349 \times (\text{PR unknown}) + 0.064 \times (\text{left side}) + 0.454 \times (\text{axillary node not examined}) + -0.434 \times (\text{radiotherapy}) + 0.377 \times (\text{teaching hospital}) + -0.206 \times (\text{SLNB}) + 0.132 \times (\text{chemotherapy})$.

Cox breast cancer-specific mortality risk score = $0.022 \times (\text{age}) + -0.242 \times (\text{married}) + 0.005 \times (\text{Midwest}) + -0.126 \times (\text{East}) + 0.299 \times (\text{South}) + 0.052 \times (\text{high SES}) + 0.363 \times (\text{CCI} = 1) + 0.361 \times (\text{CCI} = 2) + 0.667 \times (\text{CCI} \geq 3) + 0.673 \times (\text{high grade}) + 0.689 \times (\text{regional stage}) + 1.586 \times (\text{size} > 5) + 0.867 \times (\text{size 2-5}) + 0.643 \times (\text{size unknown}) + -0.628 \times (\text{ER positive}) + 3.453 \times (\text{ER unknown}) + -0.363 \times (\text{PR positive}) + -4.018 \times (\text{PR unknown}) + 0.140 \times (\text{left side}) + 0.715 \times (\text{axillary node not examined}) + -0.477 \times (\text{radiotherapy}) + 0.267 \times (\text{teaching hospital}) + -0.307 \times (\text{SLNB}) + 0.096 \times (\text{chemotherapy})$.

Generalized competing event risk score = $-0.059 \times (\text{age}) + -0.031 \times (\text{married}) + 0.232 \times (\text{Midwest}) + 0.096 \times (\text{East}) + 0.172 \times (\text{South}) + 0.172 \times (\text{high SES}) + -0.180 \times (\text{CCI} = 1) + -0.671 \times (\text{CCI} = 2) + 0.941 \times (\text{CCI} \geq 3) + 0.728 \times (\text{high grade}) + 0.601 \times (\text{regional stage}) + 1.146 \times (\text{size} > 5) + 0.605 \times (\text{size 2-5}) + 0.790 \times (\text{size unknown}) + -0.472 \times (\text{ER positive}) + 1.972 \times (\text{ER unknown}) + -0.266 \times (\text{PR positive}) + -2.309 \times (\text{PR unknown}) + 0.119 \times (\text{left side}) + 0.284 \times (\text{axillary node not examined}) + -0.032 \times (\text{radiotherapy}) + -0.187 \times (\text{teaching hospital}) + -0.129 \times (\text{SLNB}) + 0.008 \times (\text{chemotherapy})$; where age in years at diagnosis is continuous. The following variables are defined by the presence (value = 1) or absence (value = 0) of the indicated condition: married, high socioeconomic status (SES), CCI, high grade, regional stage, tumor size in centimeters, estrogen receptor (ER) status, progesterone receptor (PR) status, left breast tumor location, sentinel lymph node biopsy (SLNB), absence of axillary node examination, receipt of radiotherapy, receipt of chemotherapy, treatment at teaching hospital, and region (East, Midwest, South).

Head and neck cancer risk scores:

Cox all-cause mortality risk score = $0.044 \times (\text{age}) + -0.222 \times (\text{married}) + -0.052 \times (\text{female}) + -0.299 \times (\text{postoperative radiotherapy}) + 0.393 \times (\text{hypopharynx}) + 0.213 \times (\text{nasopharynx}) + 0.469 \times (\text{oral cavity}) + 0.276 \times (\text{CCI} = 1) + 0.530 \times (\text{CCI} = 2) + 0.676 \times (\text{CCI} = 3) + 0.886 \times (\text{CCI} \geq 4) + 0.122 \times (\text{low SES}) + 0.573 \times (\text{advanced stage})$.

Cox head and neck cancer-specific mortality risk score = $0.036 \times (\text{age}) + -0.204 \times (\text{married}) + 0.128 \times (\text{female}) + -0.483 \times (\text{postoperative radiotherapy}) + 0.494 \times (\text{hypopharynx}) + 0.508 \times (\text{nasopharynx}) + 0.568 \times (\text{oral cavity}) + 0.141 \times (\text{CCI} = 1) + 0.344 \times (\text{CCI} = 2) + 0.412 \times (\text{CCI} = 3) + 0.675 \times (\text{CCI} \geq 4) + 0.098 \times (\text{low SES}) + 0.912 \times (\text{advanced stage})$.

Generalized competing event risk score = $-0.007 \times (\text{age}) + 0.025 \times (\text{married}) + 0.370 \times (\text{female}) + -0.394 \times (\text{postoperative radiotherapy}) + 0.316 \times (\text{hypopharynx}) + 0.690 \times (\text{nasopharynx}) + 0.220 \times (\text{oral cavity}) + -0.198 \times (\text{CCI} = 1) + -0.270 \times (\text{CCI} = 2) + -0.495 \times (\text{CCI} = 3) + -0.273 \times (\text{CCI} \geq 4) + -0.038 \times (\text{low SES}) + 0.689 \times (\text{advanced stage})$; where age in years at diagnosis is continuous. The following variables are defined by the presence (value = 1) or absence (value = 0) of the indicated condition: married, female sex, receipt of postoperative radiotherapy, site of primary tumor (hypopharynx, nasopharynx, or oral cavity), CCI, low SES, and advanced stage.

Table A1. Assumptions and Parameter Inputs for the Models

Model	Assumptions and Parameter Inputs
Risk stratification	Proportional hazards assumption
Cost model	Constant patient accrual
	Accrual rate in subgroups is a proportional fraction of accrual rate in the whole cohort (eg, 33% subgroup would accrue at 33% of the rate for conducting the trial in the whole cohort)
	Exponentially distributed survival function
	Trial startup cost of \$8,000
	Annual maintenance cost of \$80,000
	Per-patient treatment cost of \$5,000
	Annual per-patient follow-up cost of \$200
Power analysis	Equal-sized arms
	20% type II error and 5% type I error
	No treatment effect on competing mortality
	Cancer-specific treatment effects of 0.25, 0.25, and 0.5 for prostate, breast, and head and neck cancers
	Accrual and follow-up times of 3, 5, and 6 years for head and neck, breast, and prostate cancers
	Evaluation at 5, 5, and 10 years for head and neck, breast, and prostate cancers
	Cumulative incidences for cancer-specific and overall survival were taken from SEER-Medicare data in subgroups and whole cohort

Table A2. Clinical Trial Costs in Top Tertile of Patients With Prostate Cancer Defined by the Three Risk Models

Cost Per Accrual (\$)	Trial Cost (\$; millions)		
	Cox Model of ACM	Cox Model of PCM	GCE Method
2,500	32.61	13.08	10.55
4,500	55.27	21.87	17.39
6,500	77.93	30.65	24.23
8,500	100.59	39.44	31.08
10,000	117.58	46.03	36.21

NOTE. With varying cost per accrual from \$2,500 to \$10,000.

Abbreviations: ACM, all-cause mortality; GCE, generalized competing event; PCM, prostate cancer mortality.

Table A3. Clinical Trial Costs in Top Tertile of Patients With Breast Cancer Defined by the Three Risk Models

Cost Per Accrual (\$)	Trial Cost (\$; millions)		
	Cox Model of ACM	Cox Model of BCM	GCE Method
2,500	5.57	4.21	3.54
4,500	8.74	6.51	5.28
6,500	11.91	8.81	7.02
8,500	15.08	11.11	8.76
10,000	17.45	12.84	10.07

NOTE. With varying cost per accrual from \$2,500 to \$10,000.

Abbreviations: ACM, all-cause mortality; BCM, breast cancer mortality; GCE, generalized competing event.

Table A4. Clinical Trial Costs in Top Tertile of Patients With Head and Neck Cancer Defined by the Three Risk Models

Cost Per Accrual (\$)	Trial Cost (\$; millions)		
	Cox Model of ACM	Cox Model of HNCM	GCE Method
2,500	3.27	2.88	2.76
4,500	5.19	4.55	4.33
6,500	7.11	6.21	5.91
8,500	9.03	7.88	7.48
10,000	10.46	9.12	8.66

NOTE. With varying cost per accrual from \$2,500 to \$10,000.

Abbreviations: ACM, all-cause mortality; GCE, generalized competing event; HNCM, head and neck cancer mortality.

Table A5. Clinical Trial Costs in Top Tertile of Patients With Prostate Cancer Defined by the Three Risk Models

HR for Cancer Mortality	Trial Cost (\$; millions)		
	Cox Model of ACM	Cox Model of PCM	GCE Method
0.10	38.86	15.97	13.60
0.26	57.87	23.81	20.31
0.42	94.92	39.13	33.43
0.58	182.52	75.50	64.60
0.74	480.59	199.60	171.15
0.90	—*	1,369.33	1,176.64

NOTE. With varying the HR for cancer mortality from 0.10 to 0.90.

Abbreviations: ACM, all-cause mortality; GCE, generalized competing event; HR, hazard ratio; PCM, prostate cancer mortality.

*Too high to calculate.

Table A6. Clinical Trial Costs in Top Tertile of Patients With Breast Cancer Defined by the Three Risk Models

HR for Cancer Mortality	Trial Cost (\$; millions)		
	Cox Model of ACM Trial Cost	Cox Model of BCM Trial Cost	GCE Method Trial Cost
0.10	6.55	4.95	3.97
0.26	9.77	7.39	6.02
0.42	16.11	12.21	10.12
0.58	31.22	23.70	20.03
0.74	74.83	63.25	54.45
0.90	574.20	438.93	383.12

NOTE. With varying the HR for cancer mortality from 0.10 to 0.90.

Abbreviations: ACM, all-cause mortality; BCM, breast cancer mortality; GCE, generalized competing event; HR, hazard ratio.

Table A7. Clinical Trial Costs in Top Tertile of Patients With Head and Neck Cancer Defined by the Three Risk Models

HR for Cancer Mortality	Trial Cost (\$; millions)		
	Cox Model of ACM	Cox Model of HNCM	GCE Method
0.10	1.69	1.48	1.43
0.26	2.51	2.20	2.13
0.42	4.14	3.63	3.52
0.58	8.09	7.09	6.88
0.74	21.82	19.13	18.59
0.90	153.54	134.97	131.27

NOTE. With varying the HR for cancer mortality from 0.10 to 0.90.

Abbreviations: ACM, all-cause mortality; GCE, generalized competing event; HNCM, head and neck cancer mortality; HR, hazard ratio.