Joint Propensity Scores for the Analysis of Real-World Data with Biomarker Driven Treatment Selection

Debbie Jakubowski and Michael Crager

Genomic Health, Inc.

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Setting for causal analysis for a treatment

- A cohort of patients with
  - A record of treatment received
  - Various other measures and assessments
  - An outcome of interest

Estimands in causal analysis

- Average treatment effect (ATE)
  - Reflects whole population
  - Expected treatment effect if population had been randomized to treatment

- Average treatment effect in the treated (ATT)
  - Reflects the population of patients selected for treatment
  - Expected treatment effect if the population selected for treatment had been randomized to treatment

Propensity score for treatment use

$$PS_T(\mathbf{z}_T) = \Pr(I_T = 1 | \mathbf{z}_T)$$

I_T = Indicator for treatment actually received

$\mathbf{z}_T$ = Vector of confounding covariates

- Is a balancing score
  - Weighted mean of each covariate is approximately equal across treatments

Setting for causal analysis for a treatment and a biomarker

- A cohort of patients with
  - A record of treatment received
  - An indication of whether a particular biomarker test was used and its result
    - Biomarker use influences treatment use
  - Various other measures and assessments
  - An outcome of interest

Propensity scores for biomarker test use

$$PS_B(\mathbf{z}_B) = \Pr(I_B = 1 | \mathbf{z}_B)$$

I_B = Indicator for biomarker test use

$\mathbf{z}_B$ = Vector of confounding covariates

- Is a balancing score
  - Weighted mean of each covariate is approximately equal for patients who used or did not use biomarker test

Conditional propensity score for treatment use given biomarker test use

$$PS_{T|B=1}\left(\mathbf{z}_T, \mathbf{z}_B\right) = \Pr\left(I_T = 1 \,|\, \mathbf{z}_T, I_B = 1\right)$$

- Is a balancing score
  - Weighted mean of each covariate is approximately equal across treatments given biomarker tes use

Joint propensity score for treatment and biomarker test use

$$PS_{T,B}\left(x,y;\mathbf{z}_T,\mathbf{z}_B\right)=\Pr\left(I_T=x,I_B=y\,|\,\mathbf{z}_T,\mathbf{z}_B\right) \qquad x,y\in\{0,1\}$$

$$=\Pr\left(I_T=x\,|\,\mathbf{z}_T,I_B=y\right)\Pr\left(I_B=y\,|\,\mathbf{z}_B\right)$$

$$PS_{T,B}\left(1,1;\mathbf{z}_T,\mathbf{z}_B\right)=PS_{T|B=1}\left(\mathbf{z}_T,\mathbf{z}_B\right)PS_B\left(\mathbf{z}_B\right)$$

- Is a balancing score
  - Weighted mean of each covariate is approximately equal across combinations of treatment and biomarker test use

Methods for using propensity scores in analysis

- Propensity score matching
  - Pair each treated patient with an untreated patient having a similar propensity score
  - May not be able to use all patients

- Estimates ATT not ATE

- Stratification by propensity score
  - Divide range of the propensity score into bins

- Use propensity score as a covariate

- Approximately unbiased estimates for
  - Linear models
- Biased estimates for
  - Cox regression of survival data
  - Logistic regression of categorical data

- Inverse probability of treatment weighting (IPTW)

- Approximately unbiased estimates for
  - Linear models
  - Cox regression of survival data
  - Logistic regression of categorical data

Ref: Austin (2014)

Inverse joint propensity weighting with focus on tested population

Weight for treated patients	Weight for untreated patients	Estimand
$1/\widehat{\Pr}(I_{Ti}=1, I_{Bi}=1 \mid \mathbf{z}_{Ti}, \mathbf{z}_{Bi})$	$1/\{1-\widehat{\Pr}(I_{Ti}=1, I_{Bi}=1 \mid \mathbf{z}_{Ti}, \mathbf{z}_{Bi})\}$	ATE as a function of test result in the tested
$1/\widehat{\Pr}(I_{Ti}=1, I_{Bi}=1 \mid \mathbf{z}_{Ti}, \mathbf{z}_{Bi})$	$1/\widehat{\Pr}(I_{Ti}=0, I_{Bi}=1 \mid \mathbf{z}_{Ti}, \mathbf{z}_{Bi})$	ATE as a function of test result in the whole population

$\mathbf{z}_{Ti}$ = covariate vector for treatment for patient i

$\mathbf{z}_{Bi}$ = covariate vector for biomarker for patient i

Stabilized inverse joint propensity weighting with focus on tested population

Weight for treated patients	Weight for untreated patients	Estimand
$\frac{\widehat{\Pr}(I_T = 1, I_B = 1)}{\widehat{\Pr}(I_T = 1, I_B = 1 \mid \mathbf{z}_{Ti}, \mathbf{z}_{Bi})}$	$\frac{1 - \widehat{\Pr}(I_T = 1, I_B = 1)}{1 - \widehat{\Pr}(I_T = 1, I_B = 1 \mid \mathbf{z}_{Ti}, \mathbf{z}_{Bi})}$	ATE as a function of test result in the tested
$\frac{\widehat{\Pr}(I_T = 1, I_B = 1)}{\widehat{\Pr}(I_T = 1, I_B = 1 \mid \mathbf{z}_{Ti}, \mathbf{z}_{Bi})}$	$\frac{\widehat{\Pr}(I_T = 0, I_B = 1)}{\widehat{\Pr}(I_T = 0, I_B = 1 \mid \mathbf{z}_{Ti}, \mathbf{z}_{Bi})}$	ATE as a function of test result in the whole population

$\mathbf{z}_{Ti}$ = covariate vector for treatment for patient i

$\mathbf{z}_{Bi}$ = covariate vector for biomarker for patient i

Principles

- Develop and lock propensity score model without looking at outcome data
- Consider prior knowledge when selecting covariates for treatment or biomarker use
  - Do not rely solely on significance testing
- Check to see if propensity score model balances covariates
  - Absolute standardized difference between treatment groups (calculated using weights) < 10%

$$d = \frac{\bar{x}_{\text{treatment}} - \bar{x}_{\text{control}}}{\sqrt{\frac{s^2_{\text{treatment}} + s^2_{\text{control}}}{2}}}$$

Ref: Austin (2009)

Cohort from the Surveillance, Epidemiology and End Results (SEER) data base (National Cancer Institute)

- Oncotype DX Breast Cancer Recurrence Score® results provided to SEER registries using SEER methods (Petkov 2016)

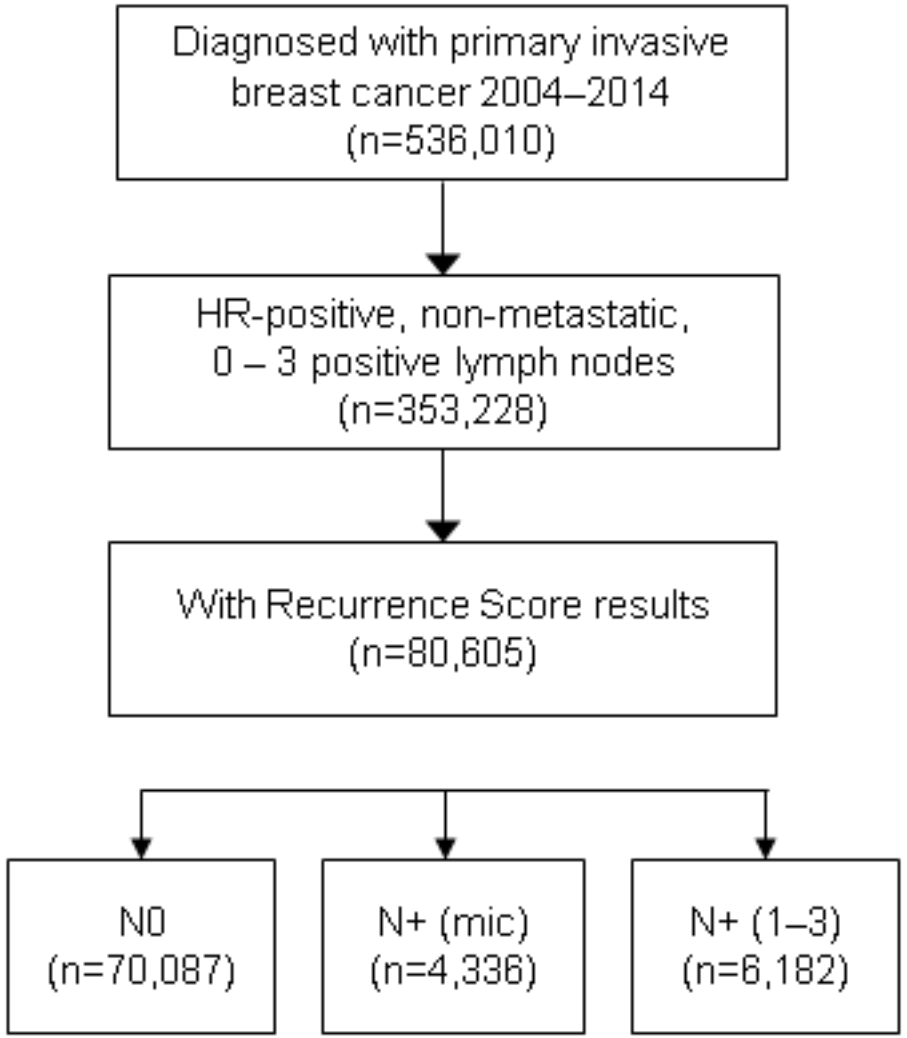
- Eligibility requirements:
  - Breast cancer diagnosis Jan 2004 - Dec 2014
  - Node-negative (N0), micromets (N1mic) or 1-3 positive nodes (N1-3), HR+, HER2-negative
  - No prior malignancy or multiple tumors

- Endpoint: breast cancer mortality
  - Follow-up through Dec 2015

- Chemotherapy (CT) use reported as yes vs. no/unknown

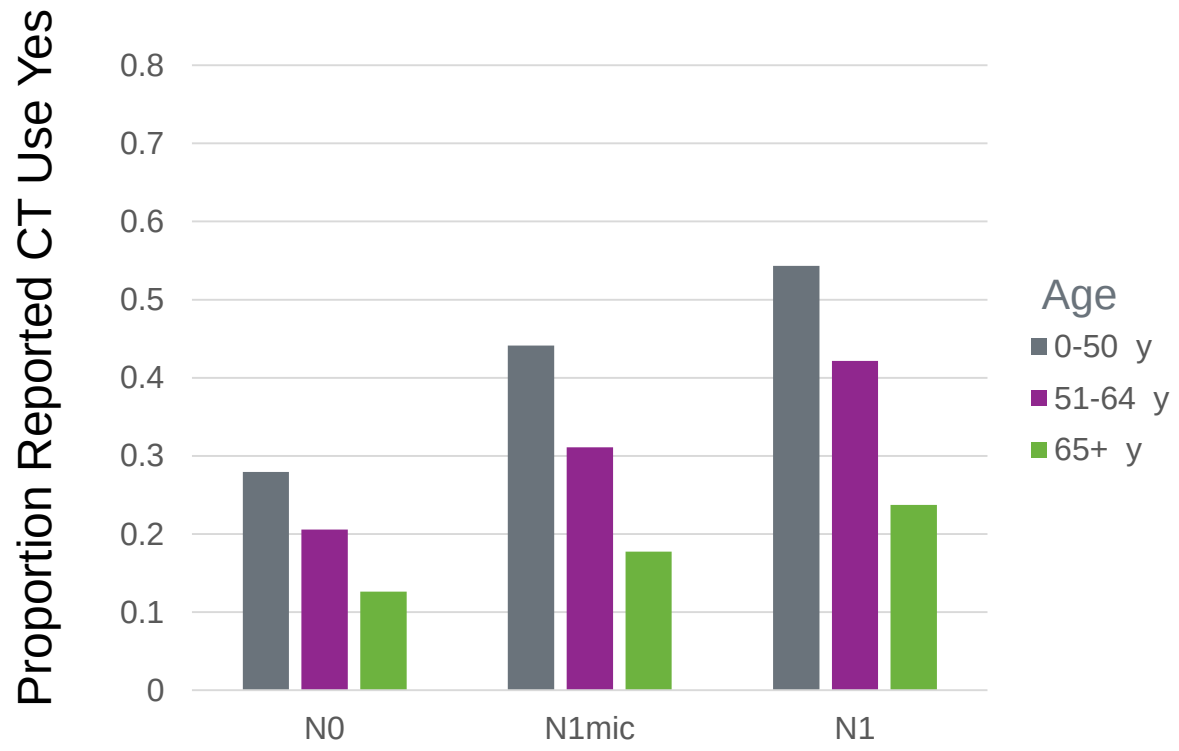
Ref: Hortobagyi et al (2018)

SEER study population



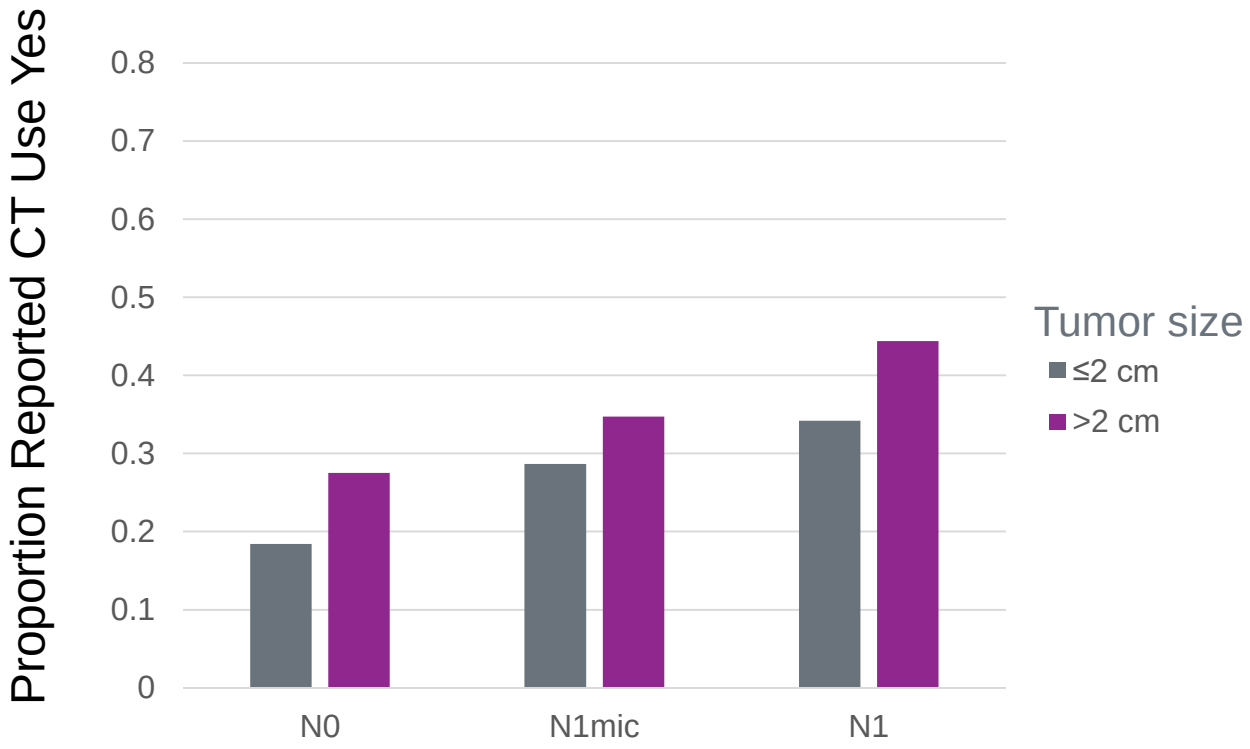
Ref: Hortobagyi et al (2018)

CT use in Breast Recurrence Score®-tested patients by nodal status and age (N=80,605)



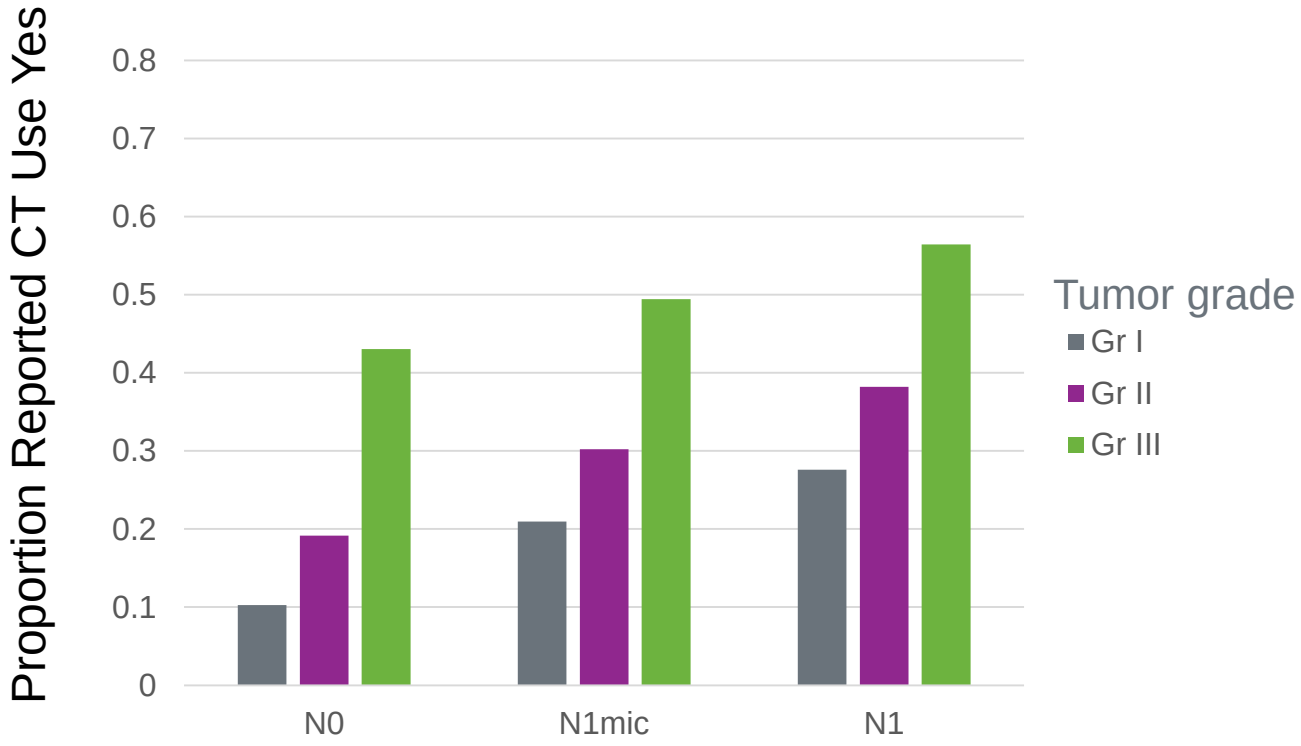
Ref: Hortobagyi et al (2018)

CT use in Breast Recurrence Score-tested patients by nodal status and tumor size (N=80,605)



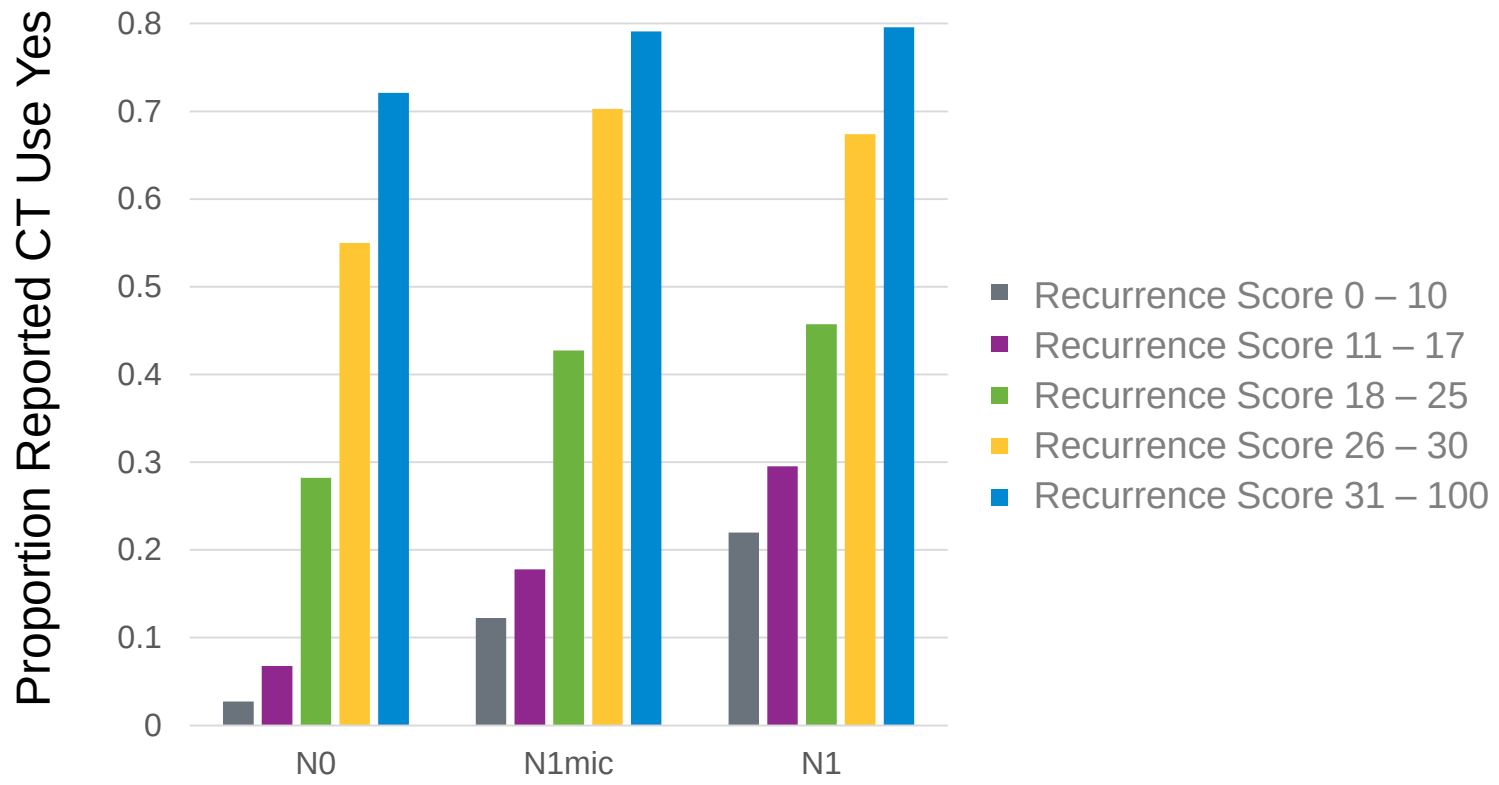
Ref: Hortobagyi et al (2018)

CT use in Breast Recurrence Score-tested patients by nodal status and tumor grade (N=80,605)



Ref: Hortobagyi et al (2018)

CT use in Breast Recurrence Score-tested patients by nodal status and Recurrence Score group (N=80,605)



Ref: Hortobagyi et al (2018)

Propensity model covariates for CT use and for Recurrence Score use

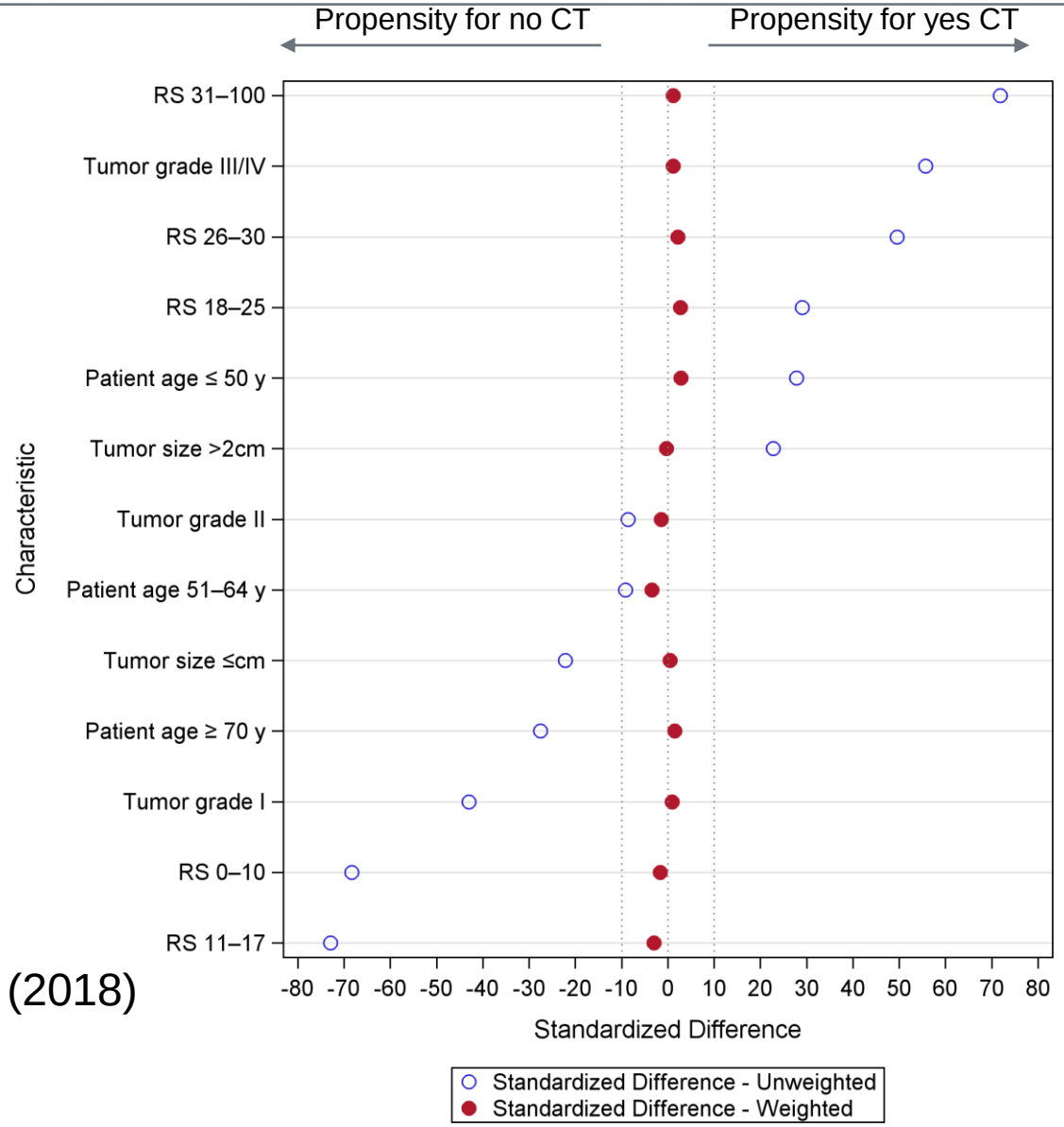
- Tumor size
- Tumor grade
- Race and ethnicity
- Type of surgery
- Histologic subtype
- State of residence
- Socioeconomic status
- Patient age
- Year of diagnosis

Interactions of other variable with these

- RS (propensity for CT only)

Model separately by nodal status => relationship of covariates with Recurrence Score test use and CT use may differ among nodal status groups

Propensity model adjustment for imbalances in baseline covariates N=70,087 patients with N0 disease



Ref: Hortobagyi et al (2018)

Analysis Methods

- Cox proportional hazards regression
  - Inverse joint propensity score weighting
  - Variance estimation using robust method of Lin and Wei (1989)

- Weighted Kaplan-Meier curves

Truncating weights

- Goal: avoid variance inflation due to a few patients with extreme weights

- Truncation of stabilized weights
  - Set weights < 5^{th} percentile to 5^{th} percentile
  - Set weights > 95^{th} percentile to 95^{th} percentile

Ref: Lee, Lessler and Stuart (2011), Austin and Stuart (2015)

Significance tests for interaction with chemotherapy treatment N=70,087 patients with N0 disease

Cox proportional hazards regression with inverse joint propensity weighting

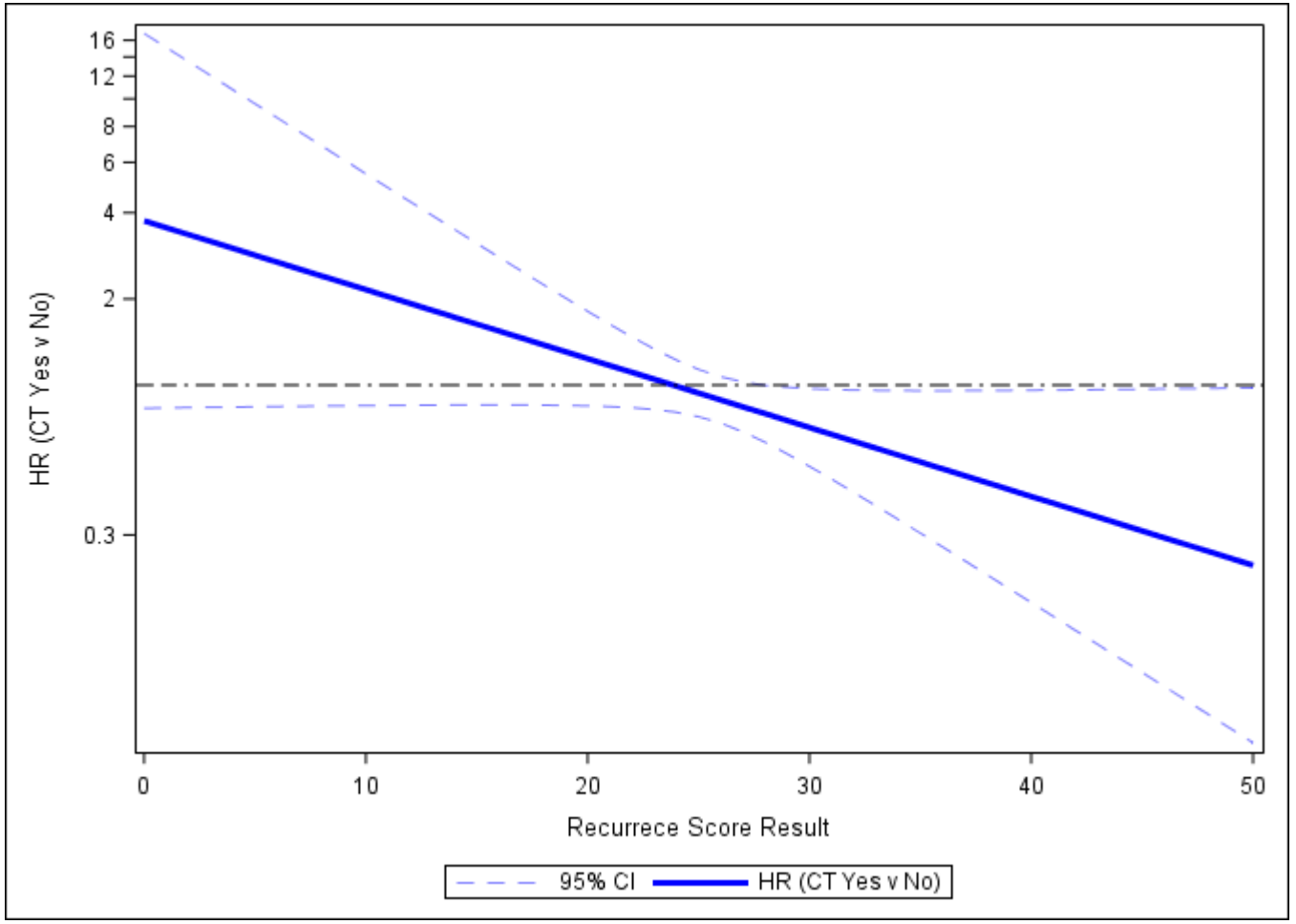
Interaction	HR (95% CI)	p-value
Age (≤ 50 y vs > 50 years) with CT	0.581 (0.303,1.116)	.103
Tumor Size (≤ 2 cm vs > 2 cm) with CT	1.579 (0.821,3.040)	.171
Tumor Grade (II vs I, III vs I) with CT	0.299 (0.085,1.053)	.083
	0.252 (0.074,0.858)	
RS (RS 26-100 vs. RS 0-25) with CT	0.432 (0.229,0.812)	.009

Each interaction added separately to model adjusting for Recurrence Score group (RS 26-100 vs. RS 0-25), tumor size (≤2 cm vs >2 cm), age (≤50 y vs >50 y), tumor grade (II vs I, III vs I), and chemotherapy use (yes vs. no/unknown).

Ref: Hortobagyi et al (2018)

Hazard ratio for chemotherapy benefit as a function of Recurrence Score result

Cox proportional hazards regression with inverse joint propensity weighting (N=70,087)



1.0 = No CT Benefit

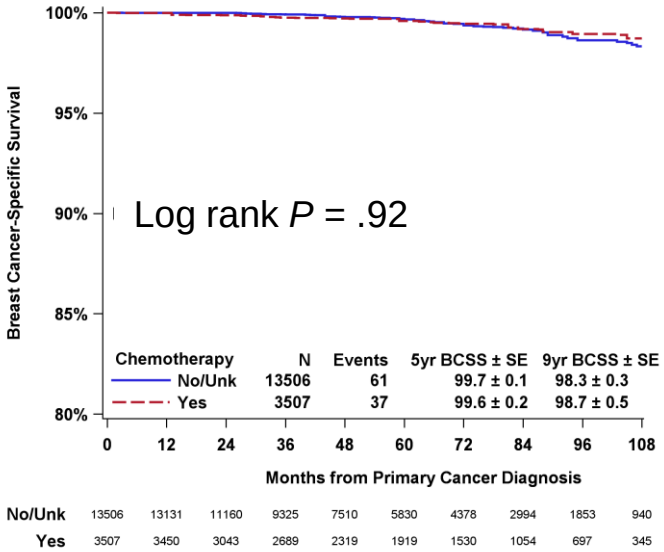
Increasing CT Benefit

Ref: Hortobagyi et al (2018)

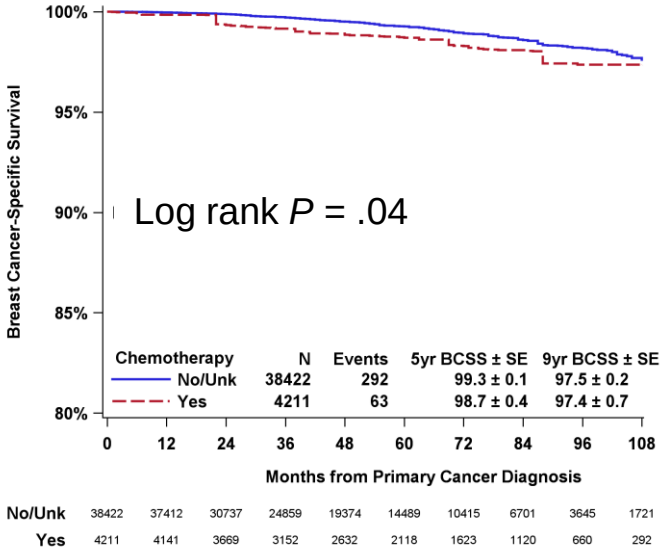
Breast cancer-specific survival in N0 disease, Kaplan-Meier estimates with inverse joint propensity weighting (N=70,087)

Recurrence Score 0 – 25

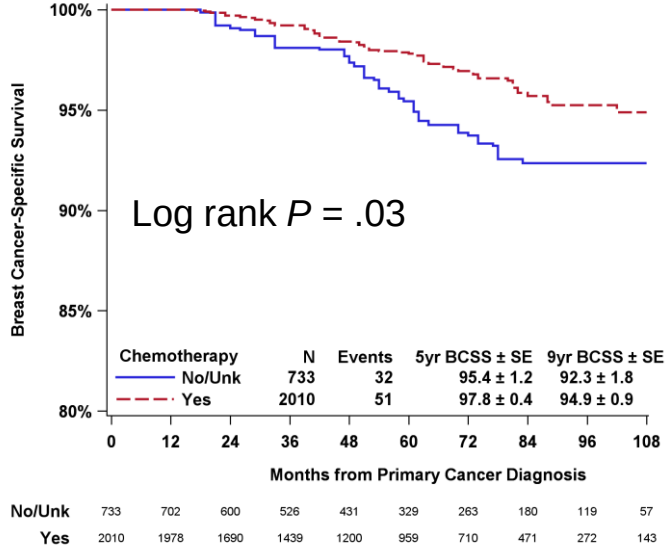
Age ≤50y

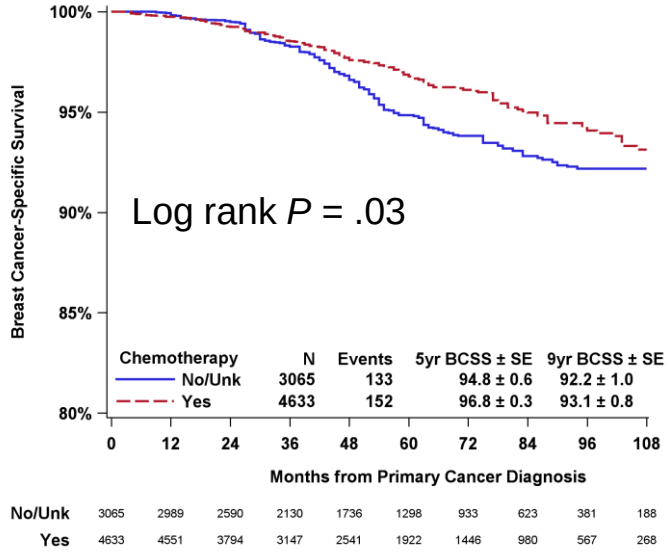


Age >50y



Recurrence Score 26 – 100

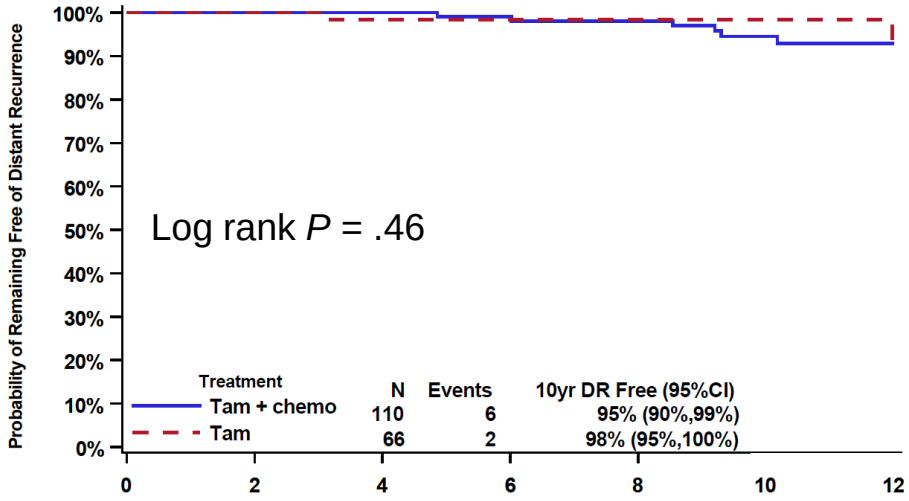




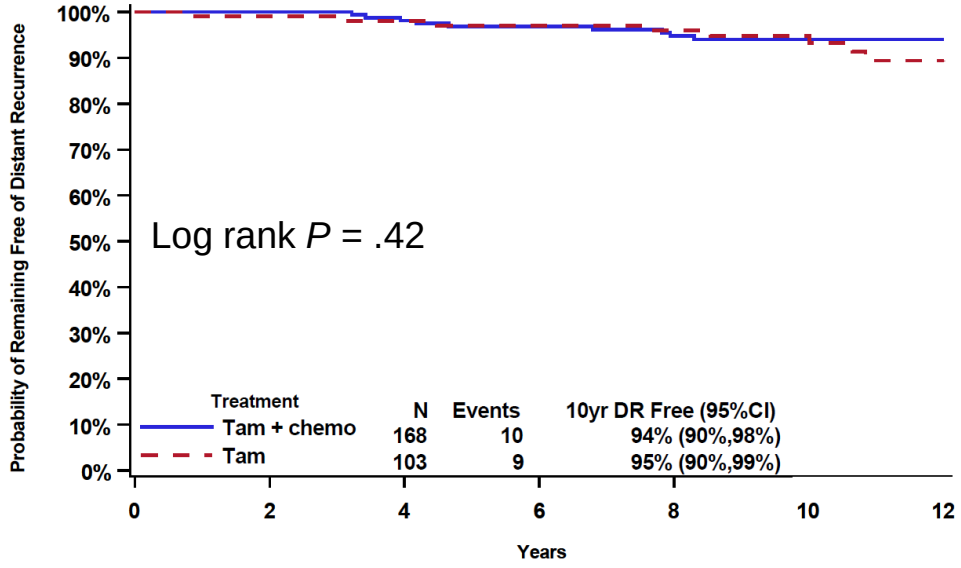
Ref: Hortobagyi et al (2018)

Results are consistent with randomized clinical trial results
Example: National Surgical Adjuvant Breast and Bowel Project (NSABP) Trial B-20

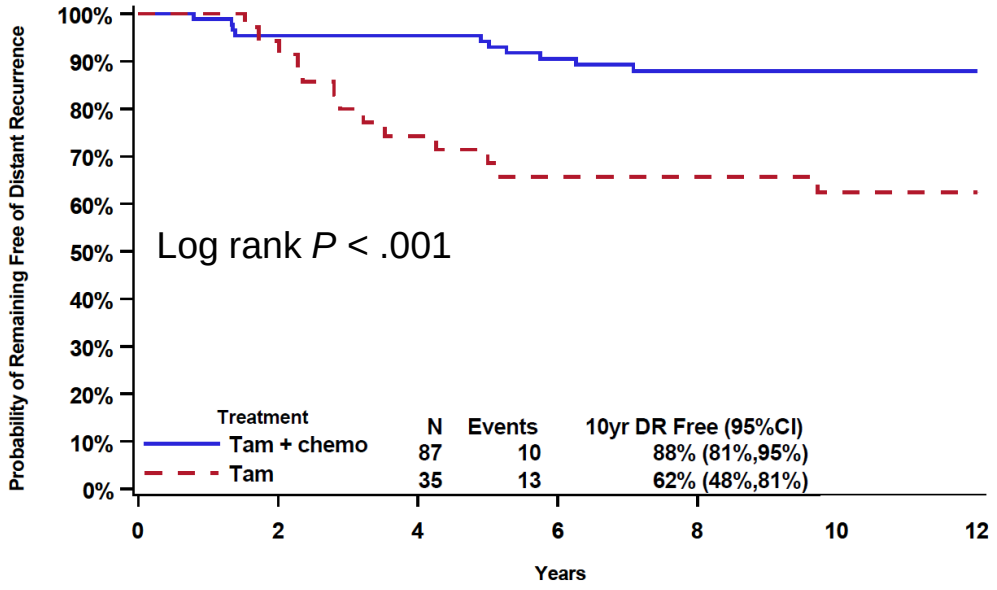
Recurrence Score < 11



Recurrence Score 11 – 25



Recurrence Score > 25



Test for interaction between Recurrence Score group and treatment: p=.014

Ref: Geyer et al. 2018

Discussion

- Causal analysis using propensity scores
  - Reduces bias due to non-random use of treatment and biomarkers
  - Increases variability of treatment main effect and interaction estimates

- All causal analyses assume no unmeasured confounders
  - Results should be interpreted with caution

Discussion

From Karim and Booth (2019):

“[Real-world data (RWD) comparative effectiveness] studies are best suited for settings in which there is existing evidence that a given treatment is efficacious . . . In settings where RCTs do not exist or may not be feasible, RWD can be informative; however, these studies should be interpreted with caution.”

Discussion

- Real-world evidence can help supplement evidence from randomized controlled trials
  - Evaluate treatment effects or interactions in actual use populations
  - Address effectiveness in patient populations under-represented in clinical trials
    - Example: young and old patients

- Analysis of real-word data related to biomarker-directed treatment should account for joint propensity for biomarker and treatment use

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