

Reporting of Tumor Marker Studies

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Current State of Tumor Markers

“There are few tumor markers that are clinically useful in predicting therapeutic response or patient outcomes despite nearly ~~20~~²⁷ years of advances in molecular biology.”

Hammond and Taube, *Seminars in Oncology*, 2002

available at www.sciencedirect.comjournal homepage: www.ejconline.com

Almost all articles on cancer prognostic markers report statistically significant results

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ABSTRACT

We aimed to understand the extent of the pursuit for statistically significant results in the prognostic literature of cancer. We evaluated 340 articles included in prognostic marker meta-analyses (Database 1) and 1575 articles on cancer prognostic markers published in 2005 (Database 2). For each article, we examined whether the abstract reported any statistically significant prognostic effect for any marker and any outcome ('positive' articles). 'Negative' articles were further examined for statements made by the investigators to overcome the absence of prognostic statistical significance. We also examined how the articles of Database 1 had presented the relative risks that were included in the respective meta-analyses. 'Positive' prognostic articles comprised 90.6% and 95.8% in Databases 1 and 2, respectively. Most of the 'negative' prognostic articles claimed significance for other analyses, expanded on non-significant trends or offered apologies that were occasionally remote from the original study aims. Only five articles in Database 1 (1.5%) and 21 in Database 2 (1.3%) were fully 'negative' for all presented results in the abstract and without efforts to expand on non-significant trends or to defend the importance of the marker with other arguments. Of the statistically non-significant relative risks in the meta-analyses, 25% had been presented as statistically significant in the primary papers using different analyses compared with the respective meta-analysis. We conclude that almost all articles on cancer prognostic marker studies highlight some statistically significant results. Under strong reporting bias, statistical significance loses its discriminating ability for the importance of prognostic markers.

Tumor Marker Study Deficiencies

- Unclear objectives
- Poor design
 - Poorly defined or unrepresentative cohort
 - Biased case selection
 - Design inappropriate for question/claims
 - Underpowered
- Unknown assay technical performance
- Unknown specimen quality
- Analysis problems
 - Multiple testing – multiple markers, patient subsets, endpoints, etc.
 - Cutpoint optimization
 - Model overfitting
- Poor reporting
- Publication bias

American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer

Lyndsay Harris, Herbert Fritsche, Robert Menzel, Larry Norton, Peter Ravdin, Sheila Taube, Mark R. Somerfield, Daniel F. Hayes, and Robert C. Bast Jr

The Update Committee's literature review focused attention on available systematic reviews and meta-analyses . . . although primary data were also reviewed. By and large, however, the primary literature is characterized by studies that included **small patient numbers**, that are **retrospective**, and that commonly perform **multiple analyses until one reveals a statistically significant result**. Furthermore, many tumor marker studies **fail to include descriptions of how patients were treated or analyses of the marker in different treatment subgroups**. The Update Committee hopes that adherence to . . . **REMARK criteria** will provide more informative data sets in the future.

REMARK

REporting recommendations for tumor MARKer prognostic studies

Lisa M. McShane , Douglas G. Altman , Willi Sauerbrei , Sheila E. Taube , Massimo Gion , Gary M. Clark for the Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics

- Proposed at 1st NCI-EORTC Meeting on Cancer Diagnostics (Nyborg, Denmark, July 2000)
- Consultation with/endorsement by PACCT
- Published (2005): BJC, EJC, JCO, JNCI, NCPO
- Re-published (2006): BCRT, Exp Oncol

Goals of REMARK

- Recommend elements and formats for presentation to facilitate
 - Evaluation of **appropriateness** of study design, methods, and analysis
 - Evaluation of **quality** of study design, methods, and analysis
 - **Comparisons** across studies, including formal meta-analyses
- Ultimately improve study quality?

Target Studies

- Studies relating marker values to clinical events
 - Initially single prognostic marker, but largely relevant to predictive markers and > 1 marker
- Many points also relevant to exploratory studies not examining clinical outcome
 - Patient characteristics
 - Specimen characteristics
 - Assay methods
- Not geared to studies *developing* multiplex classifiers/risk scores, but applicable to studies *assessing* them

REMARK Guidelines Structure

- **INTRODUCTION**
- **MATERIALS AND METHODS**
- **RESULTS**
- **DISCUSSION**

Introduction

- State all marker(s) examined
- Study objectives
- Pre-specified hypotheses

Materials and Methods

Patients

- Inclusion/exclusion
- Source (e.g., hospital, community clinic)
- Disease subtypes & stages
- Treatments & how chosen (e.g., randomization, rule-based, physician choice)

Materials and Methods

Specimen characteristics

- Format (e.g., serum, FFPE or fresh/frozen tissue)
- Collection
- Preservation
- Storage

Materials and Methods

Assay methods

- Provide or reference detailed protocol
 - Reagents or kits
 - Quantitation method (e.g., manual, image analysis)
 - Scoring & reporting
- QC procedures & reproducibility
- Blinded to patient characteristics and clinical endpoints

Design Considerations for Tumor Marker Studies?



There are 89 frozen specimens available.

- Retrospective specimens
 - Limited numbers
 - Heterogeneous (unless from trials)
 - Patient characteristics
 - Treatments
 - Variable data quality

Materials and Methods

Study design

- Case selection
 - Prospective or retrospective
 - Stratification or matching (e.g., based on outcome)
 - Time period
 - Follow-up

Materials and Methods

Study design (cont.)

- Define clinical endpoints
- Candidate variables
- Rationale for sample size (e.g., statistical power)

Over-analysis Problems

If you torture the data long enough
it will confess to anything.

Source unknown

Materials and Methods

Statistical analysis methods

- Model building & assumptions
- Variable selection
- Missing data handling
- Coding of marker values in analyses (e.g., continuous vs. categorized)
- Internal or external validation

Results

Data

- Flow of patients through study
- Numbers and events at each analysis stage and in each subgroup
- Reasons for patient/specimen dropout

Results

Data (cont.)

- Demographic characteristics (at least age and sex) distribution
- Standard (disease-specific) prognostic variable distributions
- Tumor marker distribution
- Numbers of missing values

Results

Analysis and presentation

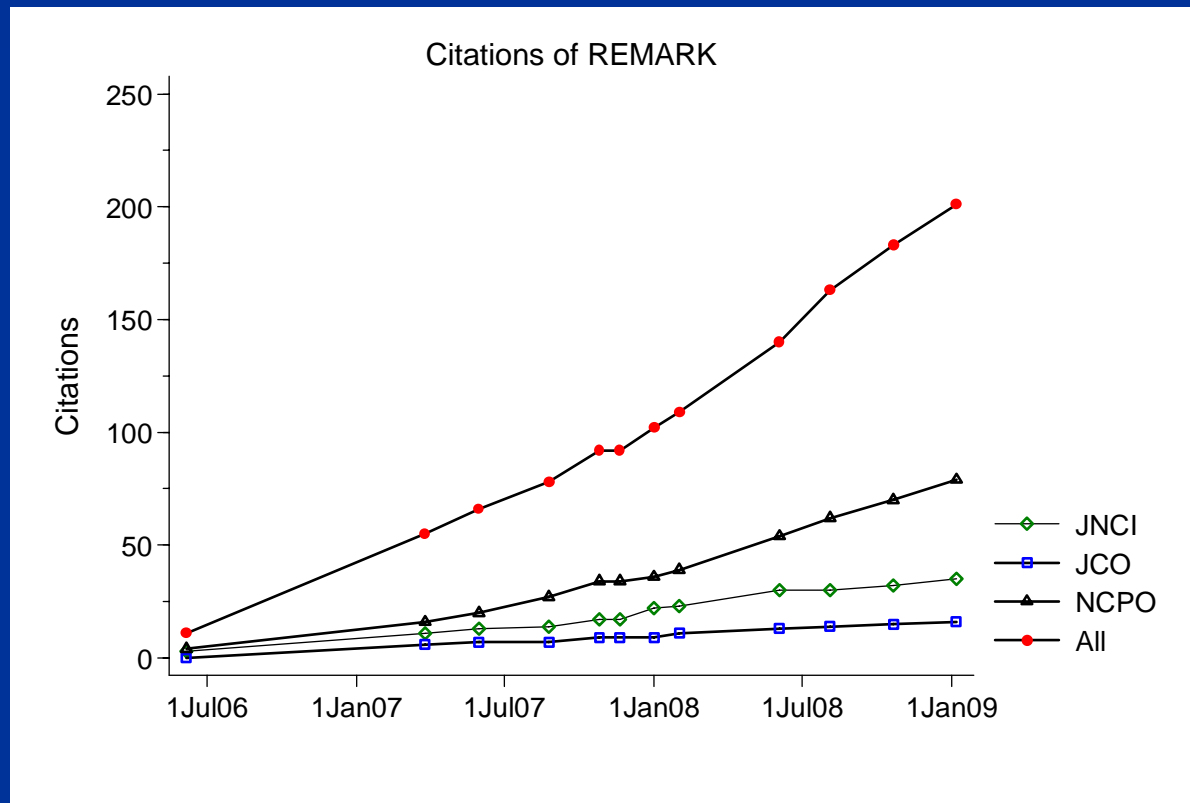
- Univariate analyses
 - Marker vs. standard prognostic variables
 - Marker vs. outcome
 - Estimated effect (e.g., hazard ratio and survival probability)
 - Kaplan-Meier plots
- Multivariable analyses
 - Marker effect on outcome adjusted for standard prognostic variables

Discussion

- Interpretation in context of the pre-specified hypotheses
- Relevance to other studies
- Limitations
- Future research
- Clinical value

Awareness of REMARK

- Mentioned in instructions to authors and/or reviewers: JCO, BCRT, CCR
- Citations



(Graph courtesy of Doug Altman)

Current & Future Work

- Nearing completion of companion explanatory document – elaboration and examples
- Formal assessment of impact – before vs. after assessment of reporting quality

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