Statistical Considerations for Detection of Bladder Cancer by Microsatellite Analysis (MSA) of Urinary Sediment: Multi-Institutional Study

Presentation at the EDRN FDA Education Workshop
February 15, 2007

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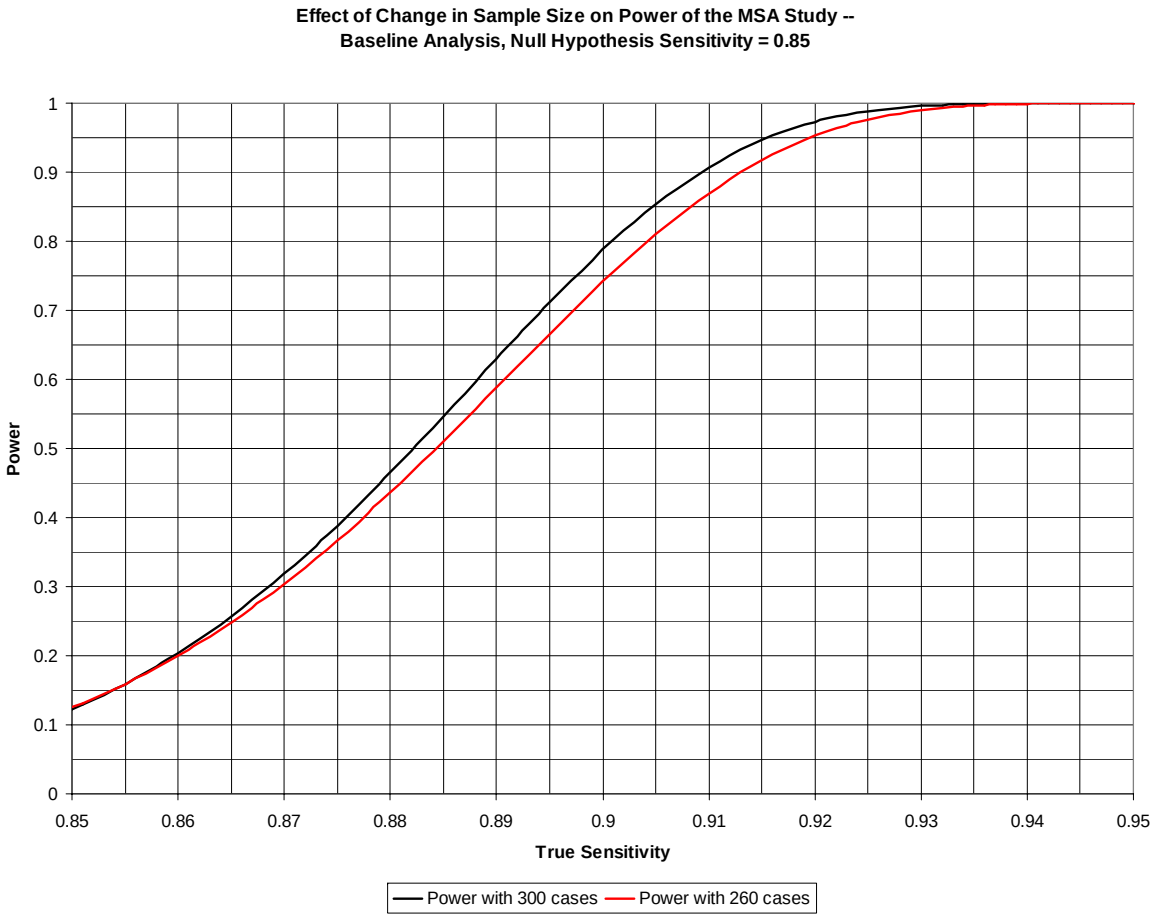
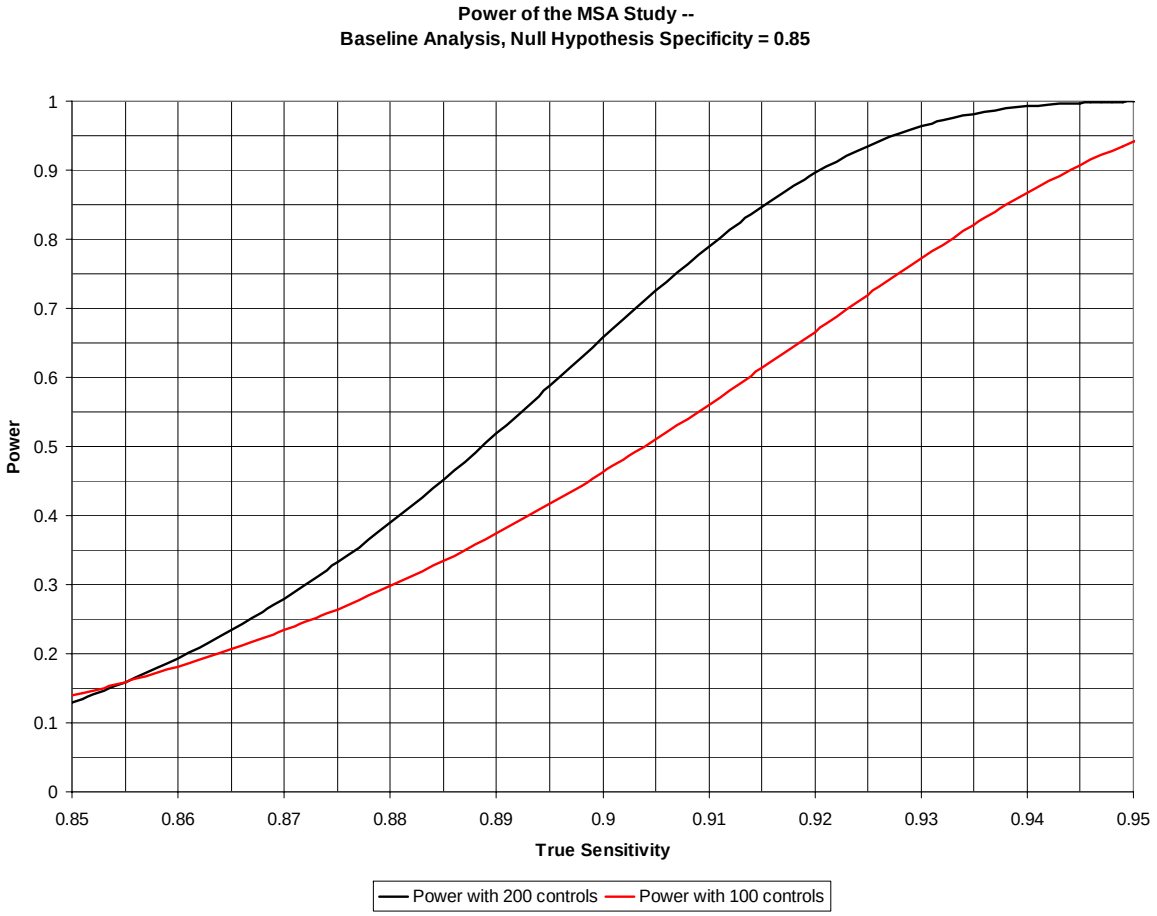
Study Design

- Prospective study
- Primary outcomes: Sensitivity and specificity of an MSA panel of 16 markers to detect recurrent bladder cancer in the two years following resection of incident bladder cancer
- Secondary outcome: Sensitivity and specificity of the MSA panel to detect incident bladder cancer
- Study populations:
  - 260 bladder cancer cases, with baseline and follow-up every three months for 2 years (9 total contacts)
  - 100 healthy normal controls – Group 1
  - 100 controls with potentially confounding conditions: 25 BPH, 25 bladder infections, 25 hematuria, 25 foreign bodies (e.g., stones, stents) – Group 2
- Specimens collected: blood (baseline only for cases), urine
- Data collected:
  - Cystoscopy (except in healthy normal controls)
  - Urine cytology
  - Pathology (whenever biopsy is done)

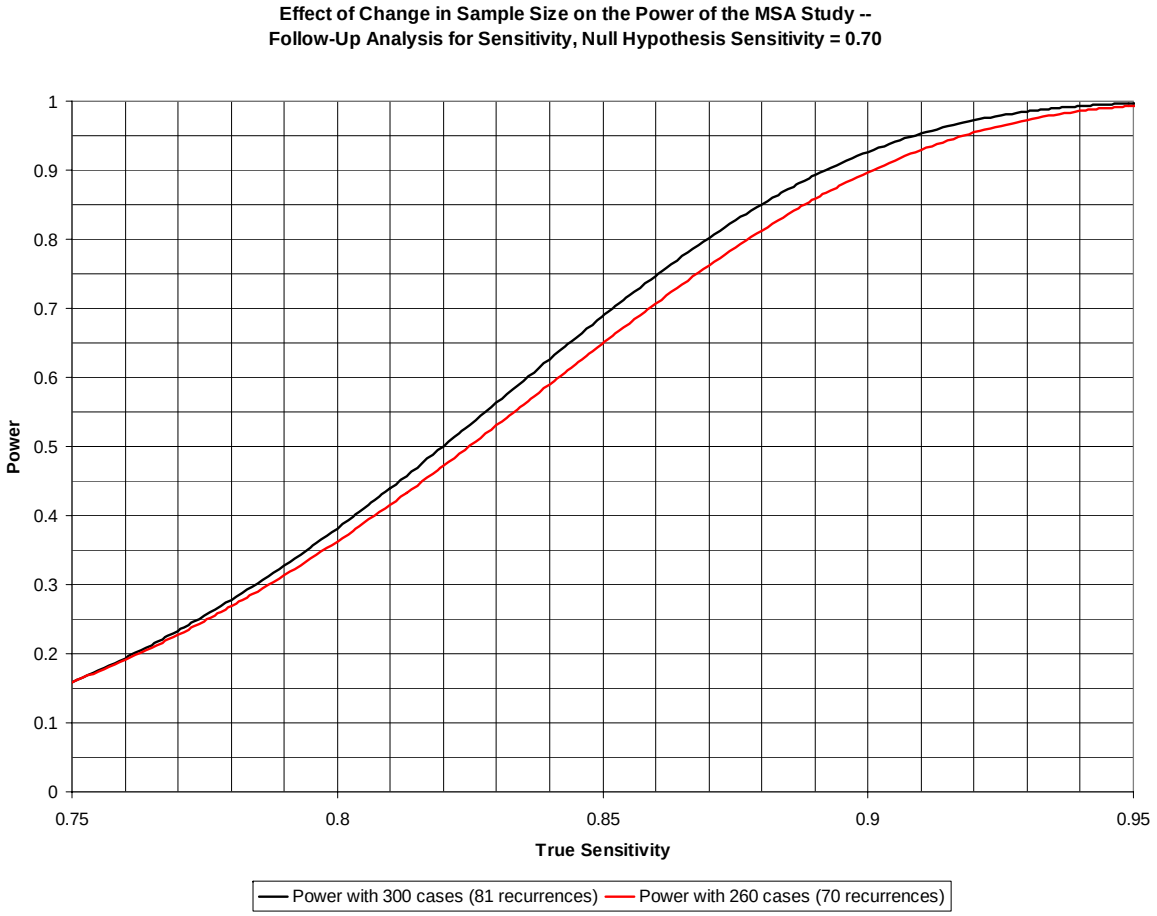
Study Power: Baseline Sensitivity



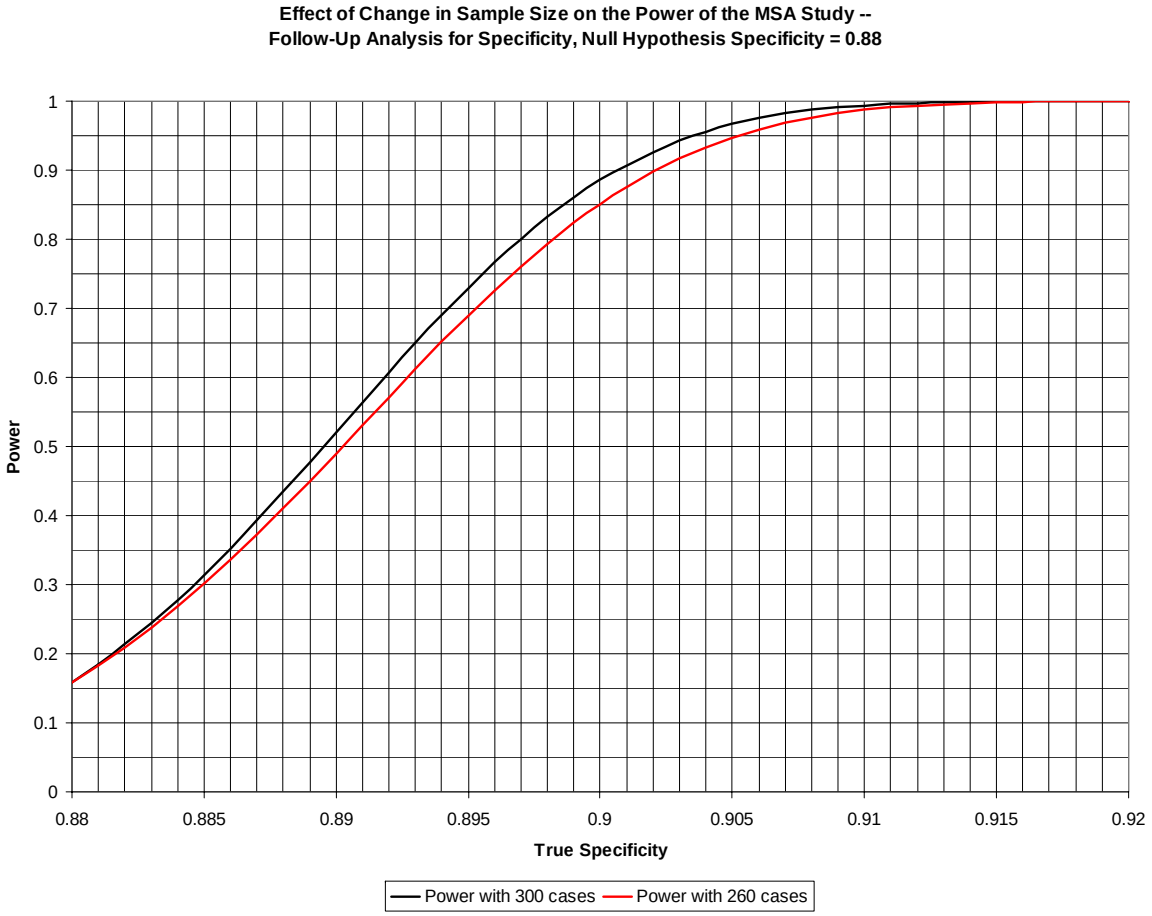
Study Power:
Baseline Specificity



Study Power:
Follow-Up Sensitivity



Study Power:
Follow-Up Specificity



Analysis Plan—Baseline Data

- Sensitivity [P(M+|D+)] and Specificity [P(M-|D-)] for the pre-defined marker panel
  - D- defined as no disease indicated by cystoscopy (group 1 controls all considered D-)
  - Specificity calculated separately for group 1 and group 2 controls
- Secondary analyses
  - Weighted estimate of group 2 specificity that weights to the anticipated prevalence of the conditions in the screening population
- Exploratory subgroup analyses
  - Sensitivity and specificity by sex
  - Specificity by type of potentially confounding condition
- Exploratory marker combination analyses
  - Optimization of panel rule (markers included, cutpoints, combination rule) with training and test sets

Analysis Plan—Follow-Up Data

- Sensitivity and specificity for the pre-defined marker panel
  - Based on concurrent marker status, fit using GEE methods
  - Anticipatory estimate:
    - Se(t-s) = P[M+(t-s)|D+(t)], Sp(t-s) = P[M-(t-s)|D-(t)]
    - Fit using GEE methods
    - Goal to determine the value of s that provides satisfactory sensitivity while maintaining high specificity
- Exploratory marker combination analyses
  - If an improved marker panel is developed in the baseline analysis, that panel will be examined for concurrent and anticipatory sensitivity and specificity in the follow-up data
  - Exploratory analyses of marker combinations similar to those done in the baseline analyses can be conducted here using concurrent marker status as the outcome and with participants randomly divided into training and test sets

Analysis Plan—Other Analyses

- Potential bias—the participating sites are include several with a strong referral component. We will examine whether the baseline risk factor distribution of study participants matches those in bladder cancer cases from large population-based studies conducted by ACS and the National Center for Health Statistics