Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review


CRD summary
This generally well-conducted review concluded that there was a paucity of good quality data making the results inconclusive. However, prostate specific antigen velocity stood out in terms of the strength of evidence supporting its prognostic value in localised prostate cancer. Given the limitations of the included studies, the authors made suitably cautious conclusions.

Authors' objectives
To assess the prognostic value of novel biomarkers in localised prostate cancer and to attempt to identify the best prognostic model.

Searching
MEDLINE, EMBASE, Cochrane Library, DARE, BIOSIS Previews, the Science Citation Index, NHS EED, Health Technology Assessment Database, CINAHL, Current Controlled Trials Meta-Register and the National Research Register were searched from 1970 to April 2007 for English language studies. The search strategy was reported. Bibliographies of relevant articles were also scanned, and health services research related sources on the Internet consulted. Studies with no abstract at initial sift, and studies available only as abstracts, were excluded.

Study selection
Any study with at least five years follow-up, that recruited at least 200 men with a diagnosis of early localised prostate cancer and evaluated either an individual novel disease-specific marker, or a model combining two or more factors, to predict a prostate cancer outcome, were eligible for inclusion. Included studies were required to report statistical differences between prognostic groups. Included studies also had to contain at least 80% diagnosed patients within the total study population. Studies of epidemiological markers, measures of co-morbidity or classical markers (such as T-stage, Gleason score or prostate specific antigen (PSA)) were excluded. Outcomes of interest were survival and recurrence.

Where reported, the age of men ranged from 33 to 95 years, the proportion of men with positive surgical margins ranged from 0% to 53%, the median PSA ranged from 4.3 to 22.3 ng/mL and the median or mean follow-up ranged from 60.6 months to 10.6 years.

Abstracts were read by at least two reviewers. Disagreements were resolved by consensus. The method used to select full papers was not reported.

Assessment of study quality
Study quality was assessed in terms of population, drop-outs, prognostic factor measurement, outcome measurement, measurement and adjustment for confounding and the analysis used. Details of the criteria used during the assessment and justification for their use were reported. Criteria were classified as being reported, partially reported or not reported.

At least two reviewers assessed the quality of each study; disagreements were resolved by consensus.

Data extraction
Results from univariate and multivariate analyses were extracted, with the p-values where statistically significant associations were reported. Two reviewers extracted data. Differences were resolved by consensus.

Methods of synthesis
Studies were combined in a narrative synthesis. Study details and results were tabulated, and differences between studies discussed in the text.

### Results of the review

Thirty studies met the inclusion criteria. All studies of individual prognostic markers recruited representative populations. Eleven studies did not report on exclusions at final follow-up. Four studies did not provide a clear definition of the prognostic factors being measured. Three studies did not define the outcome. Seven studies did not report the inclusion of classical markers to assess confounders. Two studies did not provide sufficient data to assess the adequacy of the analysis. Overall, the quality of the studies of prognostic models was considered to be good, and better than those of novel markers, but potential bias from attrition and the inclusion of classical markers to assess confounders was poorly addressed.

**Novel prognostic markers (28 studies, 17 markers):**

Results from multivariate analyses showed statistically significant associations between: acid phosphatase and local relapse (one study) or biochemical recurrence (one study), but not mortality (three studies) or local recurrence (one study); the proportion of high grade tumour and death or progression (two studies); Gleason score of 7 and death or recurrence (two studies); prostate specific antigen (PSA) kinetics two studies) and death; DNA ploidy and progression and prostate cancer related death (three studies); and CYP3A4 genotypes and progression (one study). The association between androgen receptor and the proportion of cancer in sample with outcomes was variable across studies.

Markers showing no association in multivariate analyses with survival, recurrence or progression include: β-catenin (one study); creatinine (two studies); genetic variation in vitamin D receptor (when genotype classified according to the number of B alleles; one study); KKI67 LI, Bel-2, p53, syndecan-1 or CD10 (one study); Stat5 (signal transducer and activator of transcription-5) activation status (one study); and tumour size (five studies).

**Prognostic models (five studies, eight models):**

Only two studies reported a measure of model performance, with C-statistics of 0.73 and 0.72 (95% confidence intervals were not reported, therefore statistical significance could not be ascertained).

### Authors' conclusions

The paucity of good quality data means the results are generally inconclusive. Prostate specific antigen (PSA) velocity stood out in terms of the strength of evidence supporting its prognostic value in localised prostate cancer.

### CRD commentary

The authors addressed a clear review question, supported by appropriate inclusion criteria. Several relevant sources were searched. However, the restriction to English language studies, the exclusion of any study where no abstract was available or where a study was only available as an abstract, could mean studies were missed. The screening of abstracts, data extraction and quality assessment were all conducted in duplicate. It was unclear whether similar methods to avoid error and bias were employed during the screening of full papers. Appropriate criteria were used to assess quality, and the result for each criterion provided for each study. The decision to combine studies in a narrative synthesis seemed appropriate given the heterogeneity between studies. This was a generally well-conducted review, but, as acknowledged by the authors, the conclusions drawn are limited by the paucity of good quality data.

### Implications of the review for practice and research

**Practice:** The authors did not state implications for practice.

**Research:** The authors stated that cohort studies to identify the most promising prognostic markers are needed, which can then be evaluated in a randomised controlled trial. The authors also recommended: prospective recording of data, preferably combined with storage of biopsy and pathological material; use of larger cohorts of patients through multicentre collaborations; consistency of definitions across study centres; and improved reporting.

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