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European Association of Urology

Words of Wisdom

Re: Predictors of Subsequent Prostate Cancer in Men with a Prostate-Specific Antigen (PSA) of 2.6 to 4.0 ng/mL and an Initially Negative Biopsy
Scott E. Eggener, Kimberly A. Roehl, William J. Catalona

J Urol 2006;174:500–4.

Expert's opinion:
1,202 men with an elevated PSA > 2.5 ng/mL and a prior negative biopsy of the prostate were studied. 191 men were lost to follow-up, 1,011 remained and were re-screened with 6–12 months intervals. Biopsies were recommended at re-screening if PSA was 2.6 ng/mL or higher or if rectal examination (DRE) was suspicious. 136 prostate cancers were found (13.5%). The research question: which other factors may more accurately predict the presence of prostate cancer? Age, DRE, family history, prostatic volume, PSA density, free PSA, and PSA velocity were studied together with parameters obtained at the first screen, such as high grade PIN. It turned out that only high grade PIN at initial biopsy, a PSA of 3.6–4.0 ng/mL at the first screen, an abnormal DRE, a positive family history, and a PSAV of >0 remained predictive in a multivariate analysis.

Expert's summary:
This study has the intention to tell us as practising urologists how best to identify or exclude prostate cancer in men who had a previous negative biopsy after being screened with PSA and DRE. Does the paper provide this information? This reviewer is doubtful. Why?

To evaluate a diagnostic test it is necessary that the decisive procedure, in this case a prostate biopsy, is carried out in all or almost all study participants based upon the test under study. If that is not the case assignment or attribution bias results [1,2]. Here follows a constructed example. 500 of 1,000 men age 55–70 undergo a PSA test. 300 have a biopsy indication, 150 are in fact biopsied, 50 PC are found a positive predictive value (PPV) of 33%. Is it safe to assume that 100 PC would be found if all 300 men who tested positive had been biopsied? Probably not. Let us assume that most of the 150 refusers had a large prostate, all had a negative family history, none had high grade PIN, almost all had a normal DRE when they were re-examined. While the number of biopsy indications based on PSA was identical between the compliant and non-compliant group, if all non-compliers were in fact biopsied, it is likely that only 25 cancers might have been found. This would have changed the detection rate from 50 of 1000 (0.5%) to 75 of 1000 (0.75%). At the same time the PPV would have changed from 33% to 25% (75 of 300 biopsied men).

Specific comments:

- The authors state that "biopsy was recommended if PSA continued to be >2.5 ng/mL". No clear indication is given of the proportion of men who were in fact biopsied (Fig. 1 suggests that this was the case for all participants).
- Table 4 indicates that all 136 cancers were found with PSA values >2.5 ng/mL. None of the significant predictors approaches the relative sensitivity of this PSA cut-off value in this specific setting.
- The role of PSAV: 120 cancers were found in the subset of 995 men evaluable for PSAV (12.1%). A PSAV > 0 was found to be an independent predictor (OR 1.7 (1.1–2.6), $p = 0.02$). This means that any rise was better than no rise or a decrease of PSA (see Table).

	PSA N (%)	No PC (%)	Total (%)
PSAV > 0	72 (60.0)	378 (43.2)	450 (45.2)
PSAV < 0	48 (40.0)	497 (56.8)	545 (54.8)
Total	120	875	995

0302-2838/$ – see back matter doi:10.1016/j.eururo.2006.04.023

Apparently 40% of the participants had a lower PSA at the second than at the first screen. This is in line with observations of others [3]. Were these men all biopsied even if the PSA was <2.5 ng/mL at the time of the second screen and if PSAV was higher than 0? Table 5 of the paper shows that increasing the PSAV cut-off leads to the loss of cancers diagnosed again confirming observations of others [4]. Why is the term PSAV > 0 chosen in place of simply differentiating between a decrease or an increase of PSA? A loss of sensitivity by using higher PSAV cut-offs than zero might be acceptable but only if more aggressive cancers could be selectively identified in this way. The paper reports that this is not the case.

In conclusion: The answer to the issue of the best way of following men with a previous negative biopsy is still open. Apparently all cancers are identified in the PSA range >2.5 ng/mL. Any algorithm to be derived from this report would lead to the decrease of numbers of cancers diagnosed (72 of 120 with PSAV > 0; 57 of 120 with PSAV > 0.3). This might be acceptable if such a procedure would selectively identify less or more aggressive cancers. This however is not the case.

References

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Fritz H. Schröder
Erasmus MC, University Medical Centre, Rotterdam, The Netherlands

DOI: 10.1016/j.eururo.2006.04.024

Re: Chemoprevention of Human Prostate Cancer by Oral Administration of Green Tea Catechins in Volunteers with High-grade Prostate Intraepithelial Neoplasia: A Preliminary Report from a One-Year-Proof-of-Principle Study

Bettuzi S, Brausi M, Rizzi F, Castgnetti G, Peracchia G, Corti A

Cancer Res 2006; 66:1234–40.

Expert's summary:

The effect of green tea catechins in prevention and treatment of prostate cancer has been studied extensively. The reviewed article is the first report on significant clinical efficacy in the treatment of high-grade prostate intraepithelial neurology (PIN) of the prostate. Usually 30% of patients with high-grade PIN develop prostate cancer in the further course of their disease. Two groups with high-grade PIN ($n = 30$) were randomized to 3 doses of 200 mg green tea capsules versus a placebo arm. After 1 year, one tumor was diagnosed in the green tea arm, and nine cancers were found in the placebo arm.

Expert's comments:

Since the presentation of the Prostate Cancer Prevention Trial, the chance of influencing the ''natural history'' of prostate cancer has become a very interesting topic [1,2]. On the other hand, the impact of the green tea catechins (GTC) on prostate cancer prevention has been studied intensively during the last few years [3]. Bettuzi et al. presents the first study that demonstrated a significant influence of GTC on the development of prostate cancer in a high-risk group. I am impressed by the clear design of the study and the impressive result concerning the cancer incidence (3% vs 30%). In addition to the preventive administration of 5-alpha-reductase inhibitors, there is now significant evidence that prostate antigen screening (PSA) may not be the only method for early detection of a disease that we then may treat unnecessarily [4]. In contrast, we might be able to offer our patients at risk something to really turn back the wheel of cancer promotion.

Since we in Europe most probably will not be able to change our life and nutrition style (i.e., preference for Asian food) considerably, chemoprevention may be the only way to influence the incidence of prostate cancer significantly. Moreover, this chance may reduce the objections against PSA screening in Europe.

On the other hand, GTC and 5-alpha-reductase inhibitors are not the only drugs proposed as chemopreventive agents for prostate cancer. Ongoing