

pattern 4/5, more than two cores involved with PCa, or >50% cancer in any core.

In the RP specimens, a total of 48% showed primary or secondary Gleason pattern 4/5, 35% extracapsular extension, and 2% seminal vesical invasion. Mean total tumour volume was 1.3 cm³; 27% of the tumours were potentially clinically insignificant. All tumours with a dominant nodule >1 cm³ were located in the anterior region of the prostate.

Expert's comments:

AS may prove to be a realistic option for decreasing the overtreatment of low-risk PCa. The definitive results from trials randomising for treatment (including AS), such as Prostate Testing for Cancer and Treatment (ProtecT) and Surveillance Therapy Against Radical Treatment (START), are not yet available; however, intermediate outcomes, such as findings at RP after initial expectant management in single-arm observational studies, may be indicative of the performance and safety of AS protocols. Upgrading between initial biopsy and deferred RP in an AS setting may be caused by true tumour progression during expectant management but is mainly caused by initial undersampling of the tumour.

When comparing the outcomes after deferred RP of men who started on AS with men with similar tumours who received immediate surgery, two important aspects should be considered. First, men with similar tumours at the moment of diagnosis who received direct treatment instead of delayed surgery also show adverse outcomes to some extent. Conti et al, when retrospectively applying the inclusion criteria of the AS study of Duffield et al in a large RP cohort, found a Gleason score >6 in 23%, extracapsular extension in 7%, and seminal vesical invasion in 2%. In this nonrandomised setting, the potential differences between the cohorts in terms of, for example, the number of biopsies taken and the a priori risks also should be considered.

Second, the RP specimens from patients for whom treatment was delayed may comprise a group for whom poorer characteristics are artificially enhanced. In the AS cohort of the study by Duffield et al, active therapy-free survival has previously been reported to be around 80% after 2.5 yr of follow-up (the mean delay from diagnosis to RP in the men analysed in the current report) [2]. For every

man who stopped AS and switched to radical therapy, four others remained on AS. Because the adverse findings during follow-up (upgrading in repeat biopsies) are associated with more adverse findings at RP, the men who have remained on AS might have had relatively more favourable results if they had received surgery immediately.

Tumours that fulfil the pathologic criteria for indolent disease are the most appropriate malignancies to include in an AS protocol because they will probably never cause any symptoms. Tumours with slightly more adverse characteristics also may show a favourable course for patients with limited life expectancy. Future research is necessary to study the most appropriate biopsy sampling schemes regarding number, location, and frequency within an AS setting. With this in mind, it should be considered that regions of the prostate that are relatively undersampled might harbour the largest tumours. The necessity for more perfect sampling of the tumour, however, could be questioned within an expectant management setting: Men diagnosed with PCa based on a limited number of six biopsy cores also showed very favourable mortality outcomes after initial expectant management [3].

Conflicts of interest: The author has nothing to disclose.

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Roderick C.N. van den Bergh
 Department of Urology, Erasmus University Medical Centre,
 Rotterdam, The Netherlands
 E-mail address: r.vandenbergh@erasmusmc.nl

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Re: Periprostatic Adipose Tissue as a Modulator of Prostate Cancer Aggressiveness

Finley DS, Calvert VS, Inokuchi J, et al

J Urol 2009;182:11621–7

Expert's summary:

The authors studied the role of interleukin-6 (IL-6) production in prostate cancer (PCa) using periprostatic adipose tissue removed during prostatic surgery. Adipose tissue was cultured for 24 h, and the concentration of 29 cytokines was determined by immunoassay in conditioned medium and in serum samples from the same patients. Tissue expression of

IL-6 was also studied by immunohistochemistry. Furthermore, the effect on IL-6 signaling network was studied using the reverse-phase protein microarray technique.

The IL-6 concentrations in conditioned media were >100-fold of those in serum, and concentrations were significantly higher in conditioned medium from fat tissue of patients with high-grade PCa than from those with low-grade PCa. In contrast, there was no correlation between the serum levels and tumor grade. Analysis of cell-signaling pathways showed that phosphorylation of signal transducer and activator of transcription 3 (STAT3), which is regulated by IL-6, increased in periprostatic adipose tissue with increasing tumor grade.

Expert's comments:

Obesity, especially when estimated on the basis of body mass index, is associated with a moderately increased risk of PCa, and especially of advanced disease [1]. This association may be explained by various mechanisms, such as endocrine effects of obesity causing changes in androgen and estrogen metabolism and effects on adipokines, insulin, and insulin-like growth factors. Adipose tissue also produces several cytokines, and IL-6 particularly has been found to be involved in PCa growth and progression [2,3]. Most of these studies have been performed on PCa cell lines derived from metastatic disease, and it is not clear whether IL-6 also contributes to the development of cancer [2].

The finding of high local production of IL-6 in periprostatic tissue and the increase in patients with high-grade cancer is intriguing. It may indicate that chronic exposure of the prostate to high concentrations of IL-6 contributes to tumor aggressiveness, but Finley et al do not exclude the possibility that the tumor induces IL-6 production in surrounding tissues.

This study may provide new insights into the role of IL-6 in the development of aggressive PCa [2], but a number of questions still need to be answered. It would be interesting to know what induces the high expression of IL-6 in adipose tissue from patients with aggressive PCa. Although the concentrations of IL-6 in periprostatic tissue are much higher than in plasma, it is not clear whether IL-6 can exert an effect locally by diffusing into the prostate. It seems more likely that IL-6 reaches the prostate through circulation. The contribution of periprostatic adipose tissue to the circulating concentrations of IL-6 is probably small in comparison to other sources.

Other studies have shown elevated serum IL-6 levels in advanced disease, but in the study of Finley et al, the serum concentrations were not related to tumor grade. Thus, the clinical relevance of IL-6 production in periprostatic adipose tissue requires further study. Interestingly, as Finley et al acknowledge, obesity is known to cause increased serum concentrations of IL-6. Increased IL-6 concentrations in the prostate may also result from local

production, which can be induced by infections and inflammation in the prostate [3].

IL-6 may induce PCa progression in several ways: It can contribute to neuroendocrine differentiation, induce intra-prostatic androgen production, and activate the androgen receptor. These mechanisms are thought to contribute to development of hormone-refractory PCa [2]. Furthermore, IL-6 may induce expression of serine peptidase inhibitor, Kazal type 1 (SPINK1) [4], increased tissue expression of which is a prognostic factor for adverse outcome in PCa [5]. Thus, there is increasing evidence for the role of IL-6 in PCa development and progression to therapy-resistant disease.

High IL-6 production is intriguing. Even if the mechanisms that link this finding to aggressive PCa need to be determined, the results of Finley et al provide further impetus for studies of the role of IL-6 in PCa. Elucidation of these results may contribute to development of novel therapies for PCa.

Conflicts of interest: The author has nothing to disclose.

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Ulf-Håkan Stenman

*Clinical Chemistry – Hormone & Tumor Marker Laboratory,
Helsinki University – Central Hospital, 00290 Helsinki, Finland*

E-mail address: Ulf-Hakan.Stenman@hus.fi

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Re: Effects of Simvastatin, Acetylsalicylic Acid, and Rosiglitazone on Proliferation of Normal and Cancerous Prostate Epithelial Cells at Therapeutic Concentrations

Murtola TJ, Pennanen P, Syväälä H, Bläuer M, Ylikomi T, Tammela TLJ

Prostate 2009;69:1017–23

Experts' summary:

Murtola et al investigated the treatment of multiple prostate cell lines using acetylsalicylic acid, a commonly used nonsteroidal anti-inflammatory drug (NSAIDs); simvastatin, a common cholesterol-lowering drug; and rosiglitazone, an antidiabetic drug with anti-inflammatory properties. All compounds were used at concentrations representative of typical plasma concentrations as well as at

concentrations slightly higher than physiologic. Using three established primary epithelial cell lines, two immortalized normal prostate lines, and two cell lines representative of advanced stage prostate cancer (PCa), the authors found that acetylsalicylic acid and simvastatin had the greatest effect on inhibiting cell growth, whereas rosiglitazone had little to no effect. More specifically, acetylsalicylic acid and simvastatin were most effective in the primary and immortalized cells and not in the cancerous lines. Therefore, the authors concluded that in vitro, statins and acetylsalicylic acid are most effective for treatment of early stage PCa but have no effect on advanced stage disease.

Experts' comments:

The use of statins as prevention or treatment of PCa raises as many questions as it does hopes [1]. As HMG-CoA reductase