

C-reactive protein is significantly associated with prostate-specific antigen and metastatic disease in prostate cancer

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Accepted for publication 3 January 2005

OBJECTIVE

To further analyse the relationship of c-reactive protein (CRP) levels to prostate cancer, by measuring CRP in men with prostate cancer and benign prostatic hypertrophy (BPH), as chronic inflammation has long been linked to cancers with an infectious cause and CRP is a nonspecific marker for inflammation, associated with prostate cancer incidence and progression.

PATIENTS AND METHODS

Data from 114 men, most of whom had had radioactive seeds implanted, were evaluated from November 1990 to April 2002. In addition, 27 men were included who had

biopsy-confirmed BPH. CRP was assessed with an automated chemiluminometric high-sensitivity assay kit.

RESULTS

There was no significant difference in CRP levels in men with localized prostate cancer or BPH but levels were significantly higher in men with bone metastases. There was also a significant correlation of CRP level with prostate-specific antigen (PSA) in those with cancer. Because PSA is correlated with disease stage, multiple linear regression was used with CRP as the dependent variable, and PSA and disease stage as independent variables. The regression was significant overall ($P < 0.001$) and the effect of disease stage on

CRP ($P < 0.001$) was independent of the effect of PSA level ($P = 0.001$).

CONCLUSION

The strong association of CRP with PSA, independent of tumour stage, suggests that inflammation might be fundamental in prostate cancer, and that chronic inflammation may be a legitimate target for prostate cancer chemoprevention and treatment.

KEYWORDS

prostate cancer, bone metastases, inflammation, c-reactive protein

INTRODUCTION

Chronic inflammation has long been linked to cancers with an infectious cause, e.g. of the stomach and liver, and colon cancer is common in patients with inflammatory bowel disease [1]. Inflammation might contribute to prostate carcinogenesis, and is frequently present in prostate biopsies, radical prostatectomy specimens and tissue resected to treat BPH. Inflammatory infiltrates are often found in and around foci of atrophy that are characterized by an increased proliferative index. These foci, called proliferative inflammatory atrophy, may be precursors of early prostate cancer or may indicate an intraprostatic environment favourable to cancer development [1].

C-reactive protein (CRP) is a general marker for inflammation and has been associated with prostate cancer, e.g. elevated CRP is a marker of a poor prognosis [2,3] and is high in men with bone metastases [4]. However, no

association has been reported between plasma CRP levels and subsequent prostate cancer [5]. To further analyse the relationship of CRP levels with prostate cancer we measured CRP in men with prostate cancer or BPH.

PATIENTS AND METHODS

Data were assessed from 114 men, most of whom had had radioactive seeds implanted from November 1990 to April 2002 (mean age 65 years, SD 7.2); 27 men with biopsy-confirmed BPH were also included in the analysis. CRP was assessed using an automated chemiluminometric high-sensitivity assay kit (#LK-CR1, Diagnostic Products Corporation, Los Angeles, California).

RESULTS

There was no significant difference among CRP levels in men with localized prostate

cancer or BPH, but levels were significantly higher in men with bone metastases (Fig. 1). There was also a significant correlation between CRP and PSA levels in patients with cancer (Fig. 2). Because PSA levels correlate with disease stage, multiple linear regression was used with CRP as the dependent variable, and PSA and disease stage as independent variables. The regression was significant overall ($P < 0.001$) and the effect of disease stage on CRP ($P < 0.001$) was independent of the effect of PSA level on CRP ($P = 0.001$).

DISCUSSION

A causal role for chronic or recurrent inflammation or infection in the development of prostate cancer has yet to be confirmed, but inflammation might contribute to carcinogenesis by several potentially interrelated mechanisms [6]. These include: (i) the elaboration of cytokines and growth factors that favour tumour cell growth; (ii)

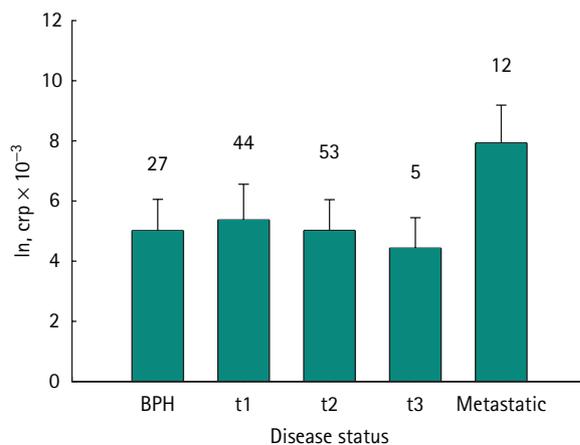


FIG. 1. The mean (SD) CRP levels in men with prostate cancer and BPH; the levels were natural-log transformed to normalize the data. There was no significant difference among CRP levels in men with localized prostate cancer and BPH but levels were significantly higher in men with bone metastases ($P < 0.05$, Tukey B post hoc test). The number of cases in each group is indicated above the corresponding error bar.

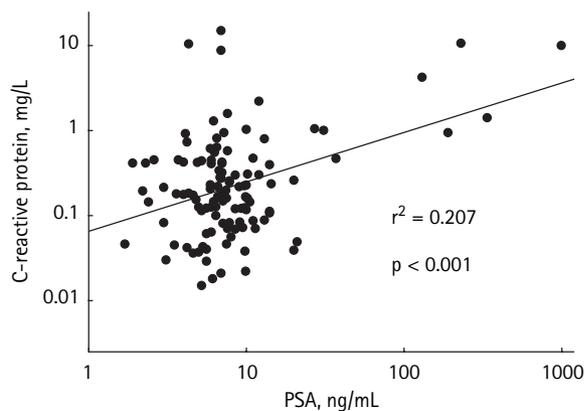


FIG. 2. CRP and PSA levels in men with prostate cancer.

the induction of cyclooxygenase-2 in macrophages and epithelial cells; and (iii) the generation of mutagenic reactive oxygen and nitrogen species. Chronic inflammation in the form of stromal and epithelial infiltrates of lymphocytes and histiocytes is extremely common in the peripheral zone of the prostate, where most cancers arise. Although there are differences in histology and terminology for these inflammatory and atrophic lesions, as a group they often show evidence of epithelial proliferation. Heterogeneous expression of the *GSTP1* gene in such lesions has been proposed as evidence for susceptibility to oxidative damage, thereby providing fertile ground for carcinogenesis.

The elevated CRP in metastatic prostate cancer has been attributed to progressive nutritional decline in patients with advanced disease [4], but the strong association of CRP with PSA, independent of disease stage, suggests that inflammation might be fundamental in the disease process. Indeed, animal and laboratory studies suggest that regular use of NSAIDs may reduce the risk of

prostate cancer, while epidemiological studies indicate that there is an inverse association between aspirin and other NSAID use and the incidence of prostate cancer [7,8].

Inflammation might also be integral to the development of bone metastases from prostate cancer. Cells that participate in inflammation and immunity can stimulate osteoclast formation and lead to bone destruction. Tumour cells probably subvert normal osseous metabolism to lodge in bone and cause metastases [9]. Moreover, NSAID use is associated with a delay in distant metastases, a decrease in second cancers, and an improvement in overall survival in men with prostate cancer [10].

Chronic inflammation may be a legitimate target for prostate cancer chemoprevention and treatment, as studies on aspirin and NSAID use indicate. The present finding of a significant correlation of CRP and PSA levels suggests that more study may further illuminate the causal role of inflammation in prostate cancer.

CONFLICT OF INTEREST

None declared.

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Abbreviations: CRP, C-reactive protein.

expression of the receptor on the cell surface is not important. Perhaps there may be some confusion as to the role of trastuzumab. Our approach involves the antibody merely as a carrier delivering the nuclide at the cell surface, not primarily acting alone or combined with chemotherapy, as in the treatment of breast cancer. In fact, the most recent work at our laboratory has been with other antibodies targeting the receptor.

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**C-REACTIVE PROTEIN IS SIGNIFICANTLY
ASSOCIATED WITH PROSTATE-SPECIFIC
ANTIGEN AND METASTATIC DISEASE IN
PROSTATE CANCER**

Sir,
I read with interest this paper [1] investigating the relationship between PSA, stage of prostate cancer and the important but non-specific inflammatory marker, C-reactive protein (CRP). The authors state in the final paragraph of their discussion: "The present finding of a significant correlation of CRP and PSA levels suggests that more study may further illuminate the causal role of inflammation in prostate cancer." The authors have used the statistical technique of multiple regression, as opposed to correlation. These are closely related; however, using multiple regression may have been unnecessary in this context. The latter technique gives a precise relationship between two variables, PSA and CRP in this instance, which is expressed as a regression equation. This has the implied use for predicting the dependent variable, CRP in this case, when the independent variables are known (PSA and disease stage). I would suggest that there is no use of such prediction in routine clinical use, as CRP is a commonly measured serum variable. The authors quote an r^2 value of 0.207 in Figure 2, relating to the multiple regression model illustrated. This indicates that the multiple regression analysis shown only explains 20.7% of the observations made by the authors, i.e. 79.3% of the data is not modelled by the regression analysis described. This suggests that the multiple regression shown may be inappropriate for the data.

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REPLY

Dr. Abedin writes that we implied that the multiple regression we used would allow the prediction of the dependent variable, CRP, and that this would be clinically useful. We implied nothing of the sort in our article, nor did we say anything about clinical utility. Dr. Abedin is reading into our work something that simply is not there. We did feel that the r^2 value of 0.207, contrary to Dr. Abedin's assertion, was useful for the reader to know because it shows that the PSA level explained 20.7% of CRP level; therefore, regression was the appropriate analysis to use. (Dr. Abedin incorrectly states that the r^2 value of 0.207 was from a multiple regression; in fact, it was from the simple regression shown in Figure 2.) Prostate cancer and PSA levels are complicated biological phenomena, poorly understood, and obviously do not correlate perfectly with inflammation, CRP, or, probably, anything else.

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LAPAROSCOPY FOR IMPALPABLE TESTES

Sir,
I read with interest this article by Patil *et al* [1]. However, their statement that orchidopexy does not reduce the risk of malignant transformation may not be entirely true. Swerdlow *et al* [2], in a retrospective cohort study of 1075 boys with cryptorchidism, showed that the relative risk of testicular cancer decreases significantly at 15 years after orchidopexy. Furthermore, a population-based case-control study of 794 men with a testicular germ cell tumour suggested that orchidopexy before age 10 years eliminates the excess risk of testicular cancer associated with undescended testis [3]. Undoubtedly intra-abdominal testes confer a greater risk of

dysgenesis [4] but I think these data allow one to be more positive if discussing the future risk of testicular cancer with the parents of a cryptorchid boy.

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**THE ROLE OF URINARY URGENCY AND ITS
MEASUREMENT IN THE OVERACTIVE
BLADDER SYMPTOM SYNDROME:
CURRENT CONCEPTS AND FUTURE
PROSPECTS**

Sir,
I read this article [1] with interest and congratulate the eminent authors for tackling this issue. We have in common our concern to improve the treatment for this symptom syndrome, but I may have additional insight to offer, as I suffer from it. I began research into lower urinary tract physiology before I had any urological problems, but over the years my bladder has become seriously overactive, something that appears to happen to many who contracted poliomyelitis as young adults. Although I can only speak for what applies to me, I find that the authors are wrong in some of their assessments, and offer the following observations.

The definition of urgency as 'a sudden compelling desire to pass urine, which is difficult to defer' is accurate, and I agree with this. However, over the issue of whether urge and urgency are a continuum, or urgency is pathological and not experienced by normal people, in my experience it is the former. I seem to remember from childhood friends