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## Original Paper

# Frequent Detection of Mutations in the 5′ Flanking Region of the Prostate-specific Antigen Gene in Female Breast Cancer

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**Prostate-specific antigen (PSA) is expressed in normal, hyperplastic and cancerous female breast tissue. Expression is regulated by steroid hormones. Some breast tumours produce very high levels of PSA, while others do not express any PSA. In this study, we selected three primary breast tumours which overexpressed PSA (PSA protein concentration in tumour cytosols >4300 ng/l) and three tumours which were negative for PSA (<1 ng/l). We extracted DNA and sequenced all five exons of the *PSA* gene. No mutations were found in the PSA coding sequence in any of the tumours. We identified only two polymorphic sites in exon 2. We also sequenced parts of the 5′ flanking region of the *PSA* gene in five tumours. All tumour DNAs contained abnormalities which consisted of point mutations and deletions of 1–7 base pairs. Except for one tumour which had only a 3 base pair deletion, all other tumours had multiple abnormalities (up to seven in one tumour). The deletions occurred adjacent to direct repeats similarly to deletions seen in the *p53* gene. Our data suggest that the coding sequence of *PSA* is not mutated in breast cancer. However, the 1.4 kb 5′-flanking region was mutated in all five tumours tested. The importance of this observation in relation to *PSA* gene regulation and breast cancer pathobiology remain to be determined. © 1997 Elsevier Science Ltd.**

**Key words: prostate-specific antigen, *PSA* gene mutations, breast cancer, steroid hormone-regulated genes, *PSA* gene regulation in breast cancer**
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## INTRODUCTION

THE GROWTH and differentiation of the mammary gland is a result of complex interactions of a number of endocrine hormones which act alone and in combination. The development and progression of breast cancer is also strongly influenced by hormonal status, yet the molecular mechanisms underlying the complex patterns of multihormone regulation of mammary epithelium are not well understood. This understanding can be greatly facilitated by analysing a suitable multihormone regulated gene.

The *PSA* gene codes for a serine protease which is a member of the kallikrein gene family, KLK3 [1,2]. It is a 240 amino acid glycoprotein (33 kDa) and is found in the serum as a 33 kDa monomer, as a 100 kDa complex with $\alpha_1$-antichymotrypsin and as an 800 kDa complex with $\alpha_2$-macroglobulin [3]. Prostate-specific antigen (PSA) has been known as an important clinical marker in prostate disease for many years [4,5]; however, a growing body of literature has described a number of non-prostatic sources of PSA [6–9]. PSA was originally described as expressed in the epithelial lining of the ducts of the prostate gland [10] and has recently been found in ovarian, breast, colon, liver, kidney, adrenal and parotid tumours, as well as many of the cell lines corresponding to these tumours [11,12]. Approximately 30% of breast cancer cytosolic extracts have measurable PSA levels and PSA has been associated with hormone-responsive tumours and early stage disease. Finally, a number of human breast cancer cell lines have been described to express this glycoprotein in a hormone-dependent manner [13,14].

In prostate cancer, high PSA levels are associated with a poor prognosis and disease relapse [3,10] but PSA has been considered a favourable prognostic indicator for breast cancer [15]. In some breast cancer patients, a high level of PSA has been found in the serum, while in other patients there is no

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