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Prostate-specific Antigen in Serum from Blood Donors with Subsequent Prostate Cancer Diagnosis

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PROSTATE-SPECIFIC ANTIGEN (PSA) is a serine protease produced exclusively by prostatic epithelial cells. It is present in prostatic tissue and in seminal plasma as a single chain 33 kDa glycoprotein [1], while in serum it is mainly bound to serine protease inhibitors [2, 3]. Elevated serum levels are seen in 25–90% of patients with prostate cancer, and in 20–50% of patients with benign hyperplasia [4–6]. Because of the specificity, PSA provides a unique marker for function of the prostate and is regarded as the most sensitive serum marker available for monitoring the progression of prostate cancer and response to therapy. The value for early detection and staging of the cancer, however, is not yet elucidated. As nearly two thirds of prostate cancers have spread beyond the prostate when first identified, there is a need for improved methods of detecting prostate cancer while it is still confined to the gland. It has been shown that rectal examinations combined with PSA measurements increase the rate of detection of prostate cancer [7].

Most investigations concerning serum PSA and cancer are performed after a tumour has been diagnosed. The aim of our work was to study PSA values in stored sera collected from blood donors who later had prostate cancer diagnosed, and compare these with matched controls. The samples were obtained from the Janus serum bank [8], a collection of sera from various populations comprising persons not known to have cancer at the time of sampling. Persons who later developed cancer, the cases, were reported to the Cancer Registry. Control samples were from the same population with no diagnosis of neoplasia, matched according to sex, age, time of sampling and condition of storage.

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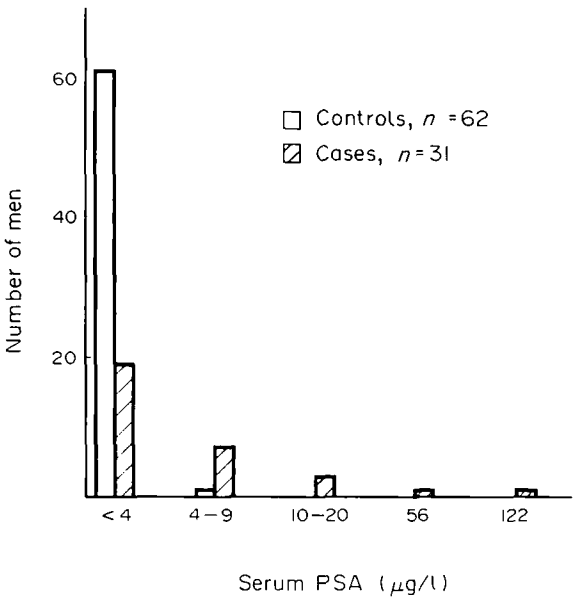

Fig. 1. Distribution of PSA values in stored sera from patients who later had a diagnosis of prostate cancer and from matched controls. All samples from the 31 cases were drawn 4–180 months prior to diagnosis. The 62 male controls were matched according to age and time of sampling. All sera were obtained from the Janus serum blood bank.

This study comprises samples from 31 cases (age 55–97 years at diagnosis) and 62 controls, all men donating blood to the Red Cross Blood Centre, Oslo. Case and control sera were identified, coded and analysed to determine PSA values in a "blind" fashion. The applied PSA assay, developed in our laboratory, was a two-site immunoradiometric assay based on monoclonal antibodies against PSA and magnetisable polymer particles as the solid phase [9]. The sensitivity of the assay is 0.5 μg/l (0 + 2 S.D.) and the interassay coefficient of variation is below 10% in the range of the standard curve, 0–150 μg/l. Statistical analysis of the datasets was carried out using the Egret program [10].

PSA was ≤ 4 μg/l in 61 of the 62 controls, while one had serum PSA of 5 μg/l. In 12 of the 31 cases PSA was > 4 μg/l

Table 1. PSA values and time before diagnosis in the 12 cases with premorbid serum PSA > 4 μg/l

Cases		PSA measurements	
No.	Age at diagnosis	PSA (μg/l)	Years before diagnosis
1	64	7	0.3
2	65	15	0.3
3	62	5	0.8
4	57	122	0.9
5	61	56	1.0
6	56	20	1.3
7	62	6	4.0
8	72	7	7.3
9	73	20	8.7
10	63	6	12.2
11	55	9	12.6
12	79	7	13.3

(5–126 μg/l), Fig. 1. The time from the sampling to diagnosis ranged from 4 to 176 months. 7 of the 31 persons who developed cancer had samples taken less than 2 years prior to diagnosis; 6 of these had PSA values > 4 μg/l, Table 1.

With a matched analysis an odds-ratio of 24 was obtained comparing those who had PSA > 4 μg/l with the persons having PSA ≤ 4 μg/l, (95% confidence interval, 3.1–185; $P = 0.002$). This means that men with serum PSA > 4 μg/l have a 24 times higher risk of having a prostatic cancer diagnosis compared with those who have values ≤ 4 μg/l. One person who developed cancer had samples taken twice. The concentration was increasing with PSA values of 8 and 20 μg/l in samples taken 26 and 15 months prior to diagnosis, respectively.

This study was performed to evaluate the usefulness of the Janus serum bank and to look for appearance of PSA in serum prior to diagnosis of prostatic cancer. The validity of such investigations depends on appropriate control groups. The Red Cross blood donors allow this possibility. The long interval from sampling to diagnosis, may reflect that prostatic cancer usually affects men at advanced age, and they simply stop donating blood before this age.

Our essential finding is the difference in PSA levels between the case and the control group, leading to a significantly increased probability of later getting a diagnosis of prostate cancer if the PSA value is > 4 μg/l. Our data support previous results [7] that elevated serum PSA identifies patients at high risk, and that this cancer can be detected by PSA measurements years before the clinical diagnosis is established.

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Haemorrhagic Cystitis Requiring Cystectomy After Cyclophosphamide and Radiotherapy

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HAEMORRHAGIC CYSTITIS is a well recognised complication of cyclophosphamide therapy. Hepatic microsomal activation of the parent compound leads to the production of active alkylating metabolites and acrolein, and urinary excretion of these products causes damage to the urothelium. Following intravenous doses of 1 g/m^2 or less of cyclophosphamide, the maintenance of a urine output of at least 100 ml/h prevents urotoxicity; with larger doses or with pre-existing urinary disease, uroprotection with mesna is recommended. The late effects of cyclophosphamide on the bladder include fibrosis and secondary carcinoma. We present a case in which substantial bleeding from the bladder, precipitated by irradiation, occurred 5 years after chemotherapy for non-Hodgkin's lymphoma.

A 35-year-old woman presented with a painful mass in the distal femur, biopsy of which revealed diffuse centrocytic centroblastic non-Hodgkin's lymphoma. Computerised tomography (CT) suggeted a nodal mass on the right side of the pelvis. A bone marrow trephine biopsy from the ilium was normal, and the patient had no systemic symptoms. Chemotherapy was commenced comprising cyclophosphamide 1 g/m^2, epirubicin 60 mg/m^2, and vincristine 1.6 mg/m^2, q3/52, and oral prednisolone 50 mg daily. After two courses of chemotherapy there was dramatic resolution of the primary lesion. Concomitant radiotherapy and chemotherapy was administered over 1 month: the patient received 300 mg/m^2 cyclophosphamide and 1.6 mg/m^2 vincristine at weekly intervals, and radiotherapy, 45 Gy in 20 daily fractions, to the distal femur. This was followed by a further four courses of cyclophosphamide, epirubicin and vincristine. A CT scan showed complete resolution of the primary tumour but the mass in the right pelvis was unchanged, and was attributed to a simple ovarian cyst.

Over 2 years the patient remained well, but during the next 6 months the pelvic mass increased in size, reaching 5 × 7.5 × 10.5 cm before laporotomy was performed. At operation tumour was found replacing the right ovary, and the histology of this was identical to her original lymphoma. The left ovary and uterus were free of tumour and a paraaortic node biopsy was negative, but peritoneal washings contained malignant lymphoid cells. Postoperative radiotherapy was delivered to the whole abdomen and pelvis: the abdominal cavity received a dose of 22.5 Gy in 20 daily fractions, with renal shielding after 13.5 Gy, and the pelvis received 45 Gy in 30 daily fractions. Two years later the patient was admitted with profuse

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