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Prostate cancer screening in the Tyrol, Austria: experience and results

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Abstract

This article summarises the experience and results of different prostate carcinoma screening projects using total prostate specific antigen (PSA) and per cent free PSA as the initial test. Of the 21 078 volunteers 1618 (8%) had elevated PSA levels. Of these men 778 (48%) underwent biopsies; 197 (25%) biopsies were positive for prostate carcinoma and 135 (17%) underwent radical prostatectomy. 95 were found to be organ-confined. A PSA cut-off of 2.5 ng/ml in men aged 45–49 years and of 3.5 ng/ml in men aged 50–59 years resulted in an 8% increase in the detection rate of organ-confined disease. 284/2272 men (13%) had elevated PSA levels and prostate carcinoma was detected in 62 men (3%). All patients underwent radical prostatectomy and histological examination revealed organ-confined tumour in all but 8 men. 98/340 men (29%) had biopsies positive for carcinoma; 28 of these patients (29%) had carcinoma that originated in the transition zone only. In the retrospective study receiver operating characteristic curve analysis showed that by using a per cent free PSA of less than 18% as a biopsy criterion, 30% of the negative biopsies could be eliminated although 94% of all carcinomas would still be detected. In the first prospective study, 106/158 men (67%) with elevated PSA levels below 10.0 ng/ml were further evaluated and 37 (35%) prostate carcinomas were detected. By using a per cent free PSA of <22% as a biopsy criterion, 30% of the negative biopsies could be eliminated although 98% of the carcinomas would still be detected. In the second prospective study, 120/465 men (26%) with total PSA levels between 1.25 and 6.49 ng/ml and a per cent free PSA < 18% were further evaluated and 27 (23%) were found to have prostate carcinomas. Receiver operating characteristic curve analysis for PSA transition zone (TZ) density showed that by using a transition zone density of >22 ng/ml/cc as a biopsy criterion, 24.4% of negative biopsies could be avoided without missing a single carcinoma. In the prescreening era the incidence of T1a Grade 1 and 2 carcinomas was 3.1% and the incidence of T1a and T1b Grade 3 carcinoma was 2.3% whereas in the years after the establishment of PSA-based screening the incidence was 4.6 and 1.8% respectively. The rate of organ-confined tumours increased from 28.7% in 1993 to 65.7% in 1997. In this evaluation a new approach, to proceed with a prostate biopsy based upon the individual risk of having prostate cancer rather than a single PSA cut-off point was developed. High total PSA levels, PSA density and PSA transition zone density correlated significantly with high Gleason scores, capsular penetration, a high percentage of cancer in the prostatectomy specimen and a high cancer volume. In this evaluation all of the 95 patients with PSA levels below 3.99 ng/ml who underwent radical prostatectomy showed clinically significant, organ-confined prostate cancer with negative surgical margins. The results of this evaluation suggest that older men have larger tumour volumes compared with younger men with the same PSA levels. These data suggest that PSA-based screening with low PSA cut-off values increase the detection rate of clinically significant, organ confined and potentially curable prostate cancer. Per cent free PSA and PSA transition zone density provide an additional diagnostic benefit over total PSA. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Prostate specific antigen; Free prostate specific antigen; Prostate specific antigen transition zone density; Transitional zone cancer; Stage migration; Organ confined tumours; PSA-screening; Probability of prostate cancer

1. Introduction

Several studies have demonstrated that PSA-based screening is the most effective screening method, however, most of these studies were done in men referred to urological care settings because of signs and symptoms [1–3]. It is only recently that largescale screening studies have been conducted in asymptomatic men within a limited timeframe [4]. A mass screening project was carried out in the Tyrol, one of nine federal states of the Republic of Austria. The Tyrol is an alpine region in the Western parts of Austria with 631 410 inhabitants (324 161 females; 307 249 males) in an area of 12.647 km^2. The region is dominated by the mountains of the

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Central Alps, and the distances to Innsbruck, the capital, where the central healthcare unit is located, are not too long. This geographical situation as well as the willingness of the general population to participate in preventive medical programmes caused us to launch a state-wide mass screening programme with PSA as the initial test for early detection of prostate cancer. Of the 307 249 male inhabitants, 65 000 were between 45 and 74 years of age. We recommended that men within this age range should undergo screening, and information to this effect was distributed to all Tyrolean males by press, radio and television.

The screening project was carried out in collaboration with general practitioners, medical officers, urologists and the Tyrolean Blood Bank of the Red Cross. All coworkers were fully informed about the guidelines for withdrawal, storage and shipping of the blood samples. PSA was assessed immediately upon arrival of the blood or serum samples. All volunteers and/or referring physicians were informed in writing about the results. In case of elevated PSA levels the volunteers were invited to undergo further urological evaluation, while men with normal PSA levels were invited to have a repeat PSA test 1 year later.

2. Projects

1. Results of a mass screening with PSA as the initial test in 21 078 volunteers.
2. Comparison of the usefulness of normal and age-referenced PSA cut-offs in 1618 men.
3. PSA-based screening of 227 asymptomatic blood donors.
4. Incidence and significance of transitional zone cancer in 340 men with negative digital rectal examination (DRE) findings.
5. Determination of the ratio of free/total PSA in screening volunteers to define the optimal range of total PSA and determine the appropriate cut-off points for percentage free PSA within this range.
6. Evaluation of the diagnostic benefit of PSA transition zone biopsy in 308 screening volunteers.
7. Reduction in the incidence of incidental prostate cancer by PSA screening in 1543 men undergoing transurethral resection of the prostate.
8. Stage migration in a 5-year PSA-based mass screening programme.
9. The probability of having prostate cancer given the patient's age, serum PSA value and DRE findings.
10. Correlation between preoperative predictors and pathological features in radical prostatectomy specimens.
11. Correlation of total PSA with pathological stage and tumour volume in patients undergoing radical prostatectomy with low PSA cut-off levels.
12. PSA-based screening with very low PSA cut-off values: correlation between age and clinical and pathological features in the 40–59 year age group.

2.1. The Tyrol project

This mass screening project was conducted between October 1993 and September 1994 with PSA as the initial test for early detection of prostate cancer. About 65 000 Tyrolean males between 45 and 75 years of age were invited to participate in this screening programme free of charge.

21 078 male volunteers (32%) responded to press releases, and radio and TV programmes asking healthy men to participate in a PSA screening test for prostate cancer. None of these had a history of prostate cancer and males with history of prostatitis were excluded from the study.

All volunteers underwent determination of serum PSA concentration (Abott IMX assay) in the same laboratory using age-referenced PSA levels [5].

Age-referenced PSA levels were defined according to the recommendations made by Oesterling (2.5 ng/ml for men aged 45–49 years, 3.5 ng/ml for men aged 50–59 years, 4.5 ng/ml for men aged 60–69 years, and 6.5 ng/ml for men aged 70–79 years) [7]. Age was defined as the subject's age on the day of PSA assessment. All males according to age-referenced levels, had elevated PSA concentrations were invited to undergo further urological evaluation including DRE and ultrasound guided biopsies. Digital rectal and transrectal ultrasound examinations were performed by the same 4 urologists. With the help of 3-dimensional (3-D) ultrasound equipment ultrasonography was performed in three planes (sagittal, horizontal, coronal), and biopsies were made under ultrasound guidance with an automatic biopsy gun and a 18-gauge-needle (sextant biopsy).

Of the 21 078 volunteers 1618 (8%) were found to have elevated PSA levels. The age distribution is shown in Table 1. Overall, biopsies were obtained in 778 of 1618 men (48%) with elevated PSA levels. In 197 (25%) of them the biopsies were positive for prostatic carcinoma. The overall cancer detection rate was 1.2%. 70% of these lesions were missed on DRE and were detected only by PSA determination. Transrectal ultrasound was normal in 65% of the cancer patients. Of the 197 males presenting with cancer, 135 (69%) underwent radical prostatectomy. Of these 135 pathologically staged tumours, 130 (96%) were judged to be clinically important with regard to stage, grade and volume.

2.2. Comparison of different PSA cut-off points

This study was designed to investigate the usefulness of normal and age-referenced PSA cut-offs in our mass

Table 1
Age distribution, number of volunteers, number of biopsies and number of tumours

Age group (years)	No. of volunteers *n* (%)	No. of biopsies *n* (%)	No. positive for carcinoma *n* (%)
45–49	2054 (9.7)	28 (3.6)	3 (1.5)
50–59	9541 (45.3)	142 (18.3)	28 (14.2)
60–69	7601 (36.1)	401 (51.5)	109 (55.3)
70–75	1882 (8.9)	207 (26.6)	57 (28.9)
Totals	21 078 (100)	778 (100)	197 (100)

screening study for early detection of prostate cancer. Previously, most screening studies used a PSA concentration of 4.0 ng/ml as the upper limit of normal, while some reports suggested the use of age-specific PSA reference ranges [6].

In this mass screening project, we used the age-referenced PSA levels described above. Furthermore, all men aged between 50 and 75 years with PSA levels between 4 and 6.5 ng/ml, which were considered normal according to age-specific PSA reference ranges, were invited to undergo further urological evaluation as described above.

Of the 1618 men with elevated PSA levels, 66 presented with levels higher than 2.5 ng/ml but lower than 4.0 ng/ml. Age distribution, PSA levels, number of biopsies and number of cancers detected are shown in Table 2. The average age was 53.7 years and the average PSA level was 3.66 ng/ml. DRE findings were negative in all 66 subjects; all of them underwent biopsy. As a result, the biopsy rate increased to 100%. In 16 (24%) of these men the biopsies were positive for cancer. All 16 pathologically staged tumours (100%) were organ-confined, and none of the lesions were microscopically focal and well differentiated and hence possibly insignificant.

When the normal PSA cut-off of 4.0 ng/ml was used 1872 (9%) of the 21 078 volunteers had elevated PSA levels. 320 men with PSA concentrations higher than 4.0 ng/ml but lower than 6.5 ng/ml were further evaluated as described above. The average age was 72.5 years and the average PSA level was 6.12 ng/ml. Overall, 205/320 men (64%) underwent biopsy. In 23 (11%) of these men

Table 2
Age distribution, average value, number of biopsies and number of carcinomas in men with PSA levels between 2.5–4.0 ng/ml

Age group (years)	No. of volunteers *n* (%)	Average PSA (ng/ml)	No. of biopsies *n* (%)	No. positive for carcinoma *n* (%)
45–49	18 (27)	3.2	18 (27)	2 (13)
50–59	48 (73)	3.8	48 (73)	14 (88)
Total	66 (100)	3.66	66 (100)	16 (100)

the biopsies were positive for cancer. 7/23 (30%) had positive findings on rectal examination. All 23 males underwent radical prostatectomy. Overall, 8/23 pathologically staged tumours (35%) were organ-confined. Only 5 tumours were considered clinically significant with regard to stage, grade and volume.

These 205 biopsies represent 21% of the 983 biopsies performed in the study population. The 23 patients whose cancers would not have been detected, if age-specific reference ranges had been used, represent 0.1% of all participants in the study and 10% of all cancers detected. In the younger age groups (45–49 years and 50–59 years) the number of biopsies did not increase significantly. In this cohort, 66 biopsies (8%) were performed and 16 (24%) cancers were detected. All cancers detected were organ-confined and clinically significant (100%). In the group older than 59 years, by comparison, only 5 (2%) cancers were considered to be of clinical importance. Thus, only a small number of life-threatening cancers was missed in this age group as a result of using age-specific reference ranges. The detection rates of organ-confined cancers showed a significant age-related difference ($P = 0.00004$); in the younger group (PSA 2.5–4.0 ng/ml) 16/16 cancers and in the older group (PSA 4.0–6.5 ng/ml) 8/23 tumours were detected. The results obtained from 21 078 screening participants support the clinical usefulness of age-specific reference ranges for serum PSA.

2.3. PSA-based screening study in blood donors

Every year approximately 50 000 blood donors aged between 18 and 65 years are recruited by the regional Blood Bank at Innsbruck University Hospital. Donation of blood routinely involves a medical check-up which comprises various blood tests such as liver function tests, cholesterol, neopterin, human immunodeficiency virus (HIV) and other investigations. In 1991 PSA determination was also included and is now routinely performed in all male blood donors aged between 40 and 65 years. The study was launched on 2 January 1991 and carried out over a period of 3 years. PSA was measured with a commercially available immunoradiometric assay (Tandem-R-PSA, Hybritech Corp., San Diego, CA, USA).

The volunteers were divided into two age groups. Group 1 included men between 40 and 49 years, while Group 2 comprised males aged between 50 and 65 years. PSA serum levels were determined at our laboratory in a total of 2272 asymptomatic blood donors.

2.3.1. Age Group 1: 40–49 years

In this screening group volunteers presenting with serum PSA levels higher than 4 ng/ml were invited to undergo further urological evaluation. In patients with abnormal findings on DRE, ultrasound guided biopsies

Table 3
Pathological stage and grade of carcinoma in 6 patients (Group 1)

Staging				Grade (Gleason score)			
Organ-confined		Advanced		4	6	7	8
pT2a	pT2b	pT2c	pT3a	1	1	3	1
1	3	1	1				

were performed to sample regions with palpable abnormalities and/or hypoechoic areas.

In view of their young age, patients in this group who had normal findings on DRE were not further evaluated. However, they were encouraged to return for annual PSA determination. 568 males showed a 20% increase in PSA; they underwent systematic sector biopsy under ultrasound guidance. 44 men (8%) presenting with serum PSA levels exceeding 4 ng/ml were further evaluated by DRE (compliance rate 100%). Only 2 males (5%) who had suspicious findings on DRE underwent biopsy, the results of which, however, were negative for carcinoma.

42 patients with PSA levels of greater than 4 ng/ml and normal findings on DRE were encouraged to return annually for PSA assessment. 12 of them showed a 20% increase in the concentration of PSA 1 year later. Among those biopsied, prostate cancers were detected in 4 males (33%). 2 patients who, despite suspicious DRE findings, had negative biopsies in the first year presented with an increase in PSA in the second year (4.1–6.2 and 4.8–5.8 respectively) and exhibited carcinoma when biopsied again.

Clinical staging in the 4 patients presenting with carcinoma revealed non-palpable clinical stage T1 cancer in 2; their Gleason scores ranged from 4 to 8 (mean: 5.2). Radical prostatectomy was performed in all 6 men. Table 3 provides information on the pathological stages. Five of the cancers detected were organ-confined. Only 1 patient had advanced disease with microscopically positive margins. None of the lesions were a possibly incident tumour.

2.3.2. Age Group 2: 50–65 years

In this age group PSA determination was performed in a total of 1704 males. Men with serum PSA levels exceeding 4 ng/ml were referred for transrectal ultrasonography and, depending on the findings, random or ultrasound guided biopsies of suspicious areas.

240 (14%) of the 1704 males were found to have serum PSA levels of greater than 4 ng/ml; only 9% of them had suspicious findings on DRE. Biopsy specimens were obtained from all males presenting with elevated PSA levels (compliance rate 100%). In 58 (24%) of them the biopsies were positive for prostatic carcinoma. The overall cancer detection rate was 3.4%. 42 (72%) of these lesions were missed on DRE and detected solely by PSA. When used to confirm suspicious findings on DRE or PSA assessment, transrectal ultrasonography yielded false-negative results in 48% of patients.

In all 58 patients whose biopsy specimen had yielded prostatic lesions, clinical staging revealed non-palpable or clinical stage T1 cancers (100%), with Gleason scores ranging from 4 to 9 (mean: 5.5).

All of these underwent radical prostatectomy. Table 4 shows the pathological stages. Overall, 50 of the 58 pathologically staged lesions (86%) were found to be organ-confined. Of the 8 patients presenting with advanced cancer 7 had microscopically positive margins, while only 1 showed invasion of the seminal vesicles; none of them had pelvic lymph node metastases. Only two tumours were microscopically focal and well-differentiated and hence possibly clinically insignificant.

By PSA-based screening a significantly higher percentage of organ-confined cancers could be detected (50/50; 100%) than by DRE (6/50; 12%). Of the organ-confined cancers 44 (88%) were missed by DRE and detected solely by PSA (Table 5). The higher the PSA level, the less likely was the chance of the lesion to be organ-confined.

2.4. Incidence and clinical significance of transitional zone cancer

Approximately 20% of prostate cancers originate from the transitional zone (TZ) [7]. Although transrectal ultrasound guided biopsies in men with elevated PSA levels and negative rectal examination findings have improved the diagnosis of peripheral zone cancer, the yield of carcinoma can be further improved by additional biopsies obtained from the TZ.

Table 4
Pathological stage and grade of carcinoma in 58 patients (Group 2)

Staging								Grade (Gleason score)					
Organ-confined				Advanced				4	5	6	7	8	9
pT1a	pT1b	pT2a	pT2b	pT2c	pT3a	pT3b	pT3c	2	5	24	21	5	1
1	1	22	18	8	3	4	1						

Table 5
Detection of organ-confined carcinoma ($n = 50$; Group 2)

Results category		Pathological stage				
Digital rectal examination	PSA (ng/ml)	pT1a	pT1b	pT2a	pT2b	pT2c
Negative	4.1–9.9	1	1	13	12	8
Negative	⩾10.0	0	0	2	2	5
Positive	4.1–9.9	0	0	1	1	2
Positive	⩾10.0 or more	0	0	2	0	2

PSA, prostate specific antigen.

To evaluate the incidence and clinical significance of TZ cancers, two TZ biopsies were added to the routinely performed sextant biopsies in males with elevated PSA levels and negative findings on rectal examination. The study included 340 volunteers with negative rectal examination findings and clearly visible prostatic zones on 3-D transrectal ultrasound, who were recruited from our PSA screening programme. Ultrasonography was performed in three planes (sagittal, horizontal, coronal).

The three sections of the prostate in the horizontal, sagittal and coronal planes are displayed simultaneously on the monitor of the system. Depending on the level of the horizontal section, the relative proportions of the transition and peripheral zones vary considerably. C- nially, the enlarged transitional zone dominates th horizontal plane, whilst the slightly hypoechoic periph- eral zone forms a narrow band of tissu dor and lateral to the transitional zone. Cau to th ver- umontanum only the peripheral zone see coronal plane, the enlarged tran ional e and the hypoechoic central zone, which displaced c sally and cranially, can be demonstr ed st clearly, d the regions of the apex of the prostate a the bladder neck can be visualised even tter. This plan allows for bet- ter assessment of the topog aphical relationships not only between the ostatic ones but also between the prostate and its surro ng struc es, thus facilitating precise deli ea n of e pro atic zones. The addi- tional in rmatio provid y the coronal plane per- mits id tificati of the different prostatic zones in any section.

The ultrasound images were evaluated for abnormalities in the transitional zone before biopsies were made as described above. Following systematic sextant biopsy, all patients underwent two additional biopsies of the TZ. These biopsies were obtained from both the right and the left portion of the TZ.

The study group included 340 males. In 98 (29%) of them the biopsies were positive for prostate cancer. Of these 98 patients, 66 (67%) presented with peripheral cancers, which were detected by traditional sextant biopsies. 28 cancers (29%) origi ating m the TZ could only be detected by two ditional TZ iopsies; 5 males (5%) presented with lesio which were cated in the TZ and the PZ. Non of the p ients sh ed palp- able abnormalities o DRE. 18 n owed TZ abnormalities on u sound aging; i 4 of them the biopsies were po tive r cancer TZ abnormalities included hypo hoic are and lo ised asymmetry at the junctio the prostati sule with the anterior fibromus ar st ma. 18 patients with proven TZ can- cer had preoperativ erum PSA levels ranging between 2.5 nd 9.9 ng/ml (me : 5.6 ng/ml), whilst 10 patients p sented with levels higher than 10 ng/ml (mean: 12.2 /ml). Of 3 patients undergoing radical prosta- te omy; 28 p sented with cancers arising solely from the whil 5 had cancers originating from the PZ as well as the TZ. The pathological stages and grades as the PSA levels are shown in Tables 6 and 7. Of the prostatic carcinomas detected 96% (27/28 cases) had a malignant potential, while only one tumour (4%) was microscopically focal and well-differentiated and, therefore, possibly insignificant with regard to stage and grade. In the radical prostatectomy specimens, the mean Gleason grade (score) was 7.2 (range: 4–8) for TZ cancers and 7.4 (range: 7–9) for cancers originating from the TZ as well as the PZ. Overall, 71% of the pathologically-staged cancers (20/28) were found to be organ-confined. All 5 combined TZ and PZ cancers were advanced lesions showing invasion of the seminal vesicles in all men and, in addition, invasion of the pelvic lymph nodes in 1 patient. Altogether, 30% of the cancers detected were so-called TZ cancers, which corresponds to a 95% confidence interval (CI) of (20–40%).

These data support the assumption that a significant subset of prostatic carcinomas originate from the tran-

Table 6
Pathological findings and PSA levels of TZ carcinomas

Patients ($n = 28$)	Pathological stage	Gleason score	PSA = 2.5–9.9 ng/ml	PSA ⩾10 ng/ml
1	pT1b	5	1	0
9	pT2a	4.7	7	2
10	pT2b	5	8	2
4	pT3a	5.5	2	2
4	pT3b	7	0	4

PSA, prostate specific antigen; TZ, transitional zone.

Table 7
Pathological findings and PSA levels of carcinomas originating in the transition and peripheral zones

Patients ($n = 5$)	Pathological stage	Median Gleason score	PSA (ng/ml)
4	pT3c N0	7	8.5 (median)
1	pT3c N1	9	50

PSA, prostate specific antigen.

Table 8
Pathological stages of 49 radical prostatectomy specimens

Stage	No. of patients
pT1b	1
pT2a	5
pT2b	10
pT2c	17
pT3a	9
pT3b	4
pT3c	2
N+	1

sitional zone. These results further support the concept that cancers of transitional zone origin have a malignant potential.

2.5. Evaluation of the clinical utility of the free/total PSA ratio in distinguishing benign prostatic disease from prostate cancer in a screening population

2.5.1. Retrospective study

This study was conducted with 266 screening volunteers who were identified to have elevated serum PSA levels by means of a conventional PSA determination kit (Abott MEIA performed on an IMX equipment). Subsequently, their diagnosis was confirmed by biopsies. The serum samples of these 266 patients were stored at −80°C for further measurement. Free and total PSA levels were determined with the DELFIA PSA dual label free/total PSA kit (Wallac Oy, Turku, Finland). This kit uses two different labelled antibodies, one specific for free PSA, the other for complexed PSA, and allows for simultaneous equimolar measurement of free PSA and alpha-1-antichymotrypsin-complexed PSA. The assay was performed according to the recommendations of the manufacturer. A modular DELFIA System equipped with the MultiCalc software (Wallac) was used to determine the two labels europium (Eu) and samarium (Sm), and to calculate the amounts of free and complexed PSA.

The mean age of the 266 men enrolled in this study was 63 years ranging from 41 to 75 years. In 64 (24%) men the biopsies were positive for prostate cancer, while 202 men (76%) were histologically free of cancer. Only 8/64 patients (13%) with biopsy proven cancer had suspicious findings on DRE. In 56 patients (88%) clinical staging revealed non-palpable or clinical stage T1c cancer. Radical prostatectomy was performed in 48 patients. Table 8 demonstrates the pathological stages. Overall, 33/48 pathologically staged lesions were found to be organ-confined (69%). Of the 15 patients presenting with advanced cancer, 2 showed invasion of the seminal vesicles and 1 had pelvic lymph node metastases. The 64 cancer patients had a mean total PSA of 16.4 ng/ml (4.1–168.0 ng/ml), while the 202 patients who were histologically free of cancer had a mean total PSA of 7.5 ng/ml (2.6–28.2 ng/ml). The mean free/total PSA in the 64 patients with prostate cancer was 0.10. This differed significantly ($P=0.001$) from the mean free/total PSA of the 202 men with negative biopsy results, which was 0.1[illegible] (Fig. 1 and 2).

In order to clearly distinguish BPH patients from prostatic carcinoma patients, we chose a cut-off for the percentage of free/total (f/t) PSA that would include virtually all prostate cancer patients with elevated total PSA, regardless of their DRE findings. Receiver operating characteristic curve analysis showed that by using a f/t PSA of less than 18% as a biopsy criterion in men with elevated PSA levels, 37% of the negative biopsies could be eliminated while still detecting 94% of carcinomas. Fig. 3 shows ROC curves for total PSA and the f/t PSA ratio. The main difference between the two ROC curves is in the region indicated by arrows. Only four prostate cancers (6%) showed f/t PSA ratios of more than 18%. All 4 patients had suspicious findings on rectal examination. Per cent f/t PSA did not correlate with tumour stage (organ-confined disease versus extracapsular extension or lymph node involvement). In the group of men with elevated serum PSA levels of less than 10 ng/ml, a f/t PSA ratio of up to 0.18 as a criterion for biopsy would eliminate 42% of negative biopsies while still detecting 94% of carcinomas. By using this f/t PSA ratio (⩽0.18) as a criterion for biopsy in the group with total PSA levels lower than 20 ng/ml, 38% of

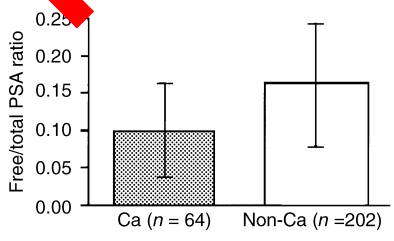

Fig. 1. Free/total prostate specific antigen (PSA) ratio in 64 patients with prostate carcinoma (Ca) and 202 patients with non-malignant disease (non-Ca).

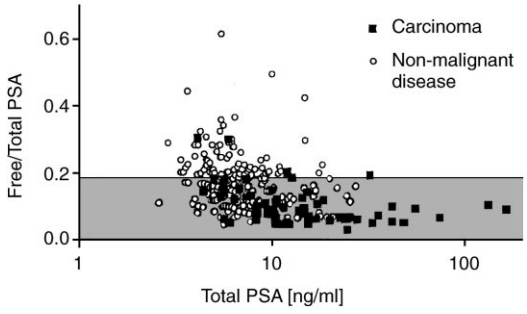

Fig. 2. Semilogarithmic plot of free/total prostate specific antigen (PSA) ratio versus total PSA in men with prostate carcinoma and in men with non-malignant disease. The cut off for free/total PSA ratio (0.18) is indicated.

negative biopsies could be avoided while still detecting 98% of prostate cancers. The diagnostic specificity of our f/t PSA ratio measurements was evaluated by comparing them with those obtained by conventional measurement of serum PSA concentration. Age-referenced cutoffs for total serum PSA yielded a specificity of 25% and a sensitivity of 93%. When calculating specificity at a sensitivity level of 93% from a plot of f/t PSA ratios against total PSA concentrations a significant increase in specificity (from 25–37%) was observed at a cut-off level of 0.18 for the f/t PSA ratio.

2.5.2. Prospective study I

The results of our retrospective study encouraged us to incorporate assessment of free PSA into our current screening study. Between March 1995 and May 1996 total serum PSA levels were determined in 1426 prostate cancer screening volunteers aged between 45 and 75 years. The study protocol was described previously [8]. All males who, according to age-specific reference ranges, had elevated total PSA levels (2.5–10.0 ng/ml) were entered into the study. Age was defined as the subject's age on the day of PSA assessment. A total of 158 men met the aforementioned selection criteria and were included in the current analysis. Measurement of free PSA was done immediately after obtaining the results of total PSA assessment.

The cut-off points for the f/t PSA ratio were determined on the basis of the data obtained in the retrospective study and other studies on the assessment of free PSA concentrations in males with elevated total PSA levels undergoing evaluation for prostate cancer. The f/t PSA ratio cut-off point chosen for this study group was 22%. All screening volunteers were further evaluated by DRE, transrectal ultrasonography and biopsy as described above.

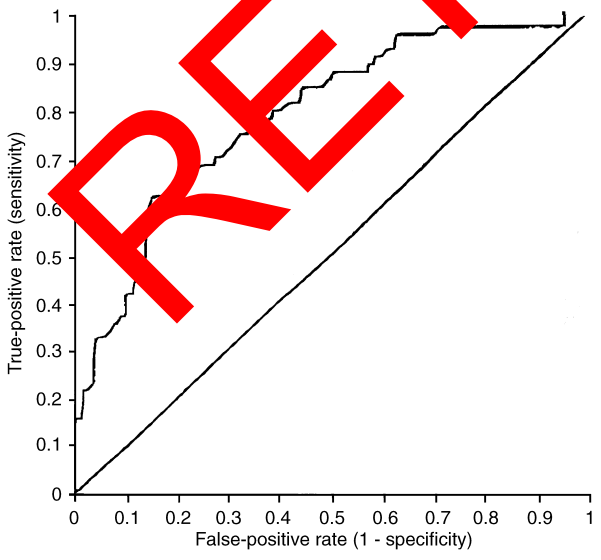

Fig. 3. Receiver operating characteristic curve for free/total prostate specific antigen for men with elevated PSA levels.

106 of the men studied showed PSA levels between 2.5 and 10.0 ng/ml. Biopsy specimens were obtained from all of them; 37 (35%) biopsies were positive for prostate cancer, while 69 (65%) were histologically free of cancer. 6/37 cancer patients (16%) had suspicious findings on DRE [9,10]. The majority of the 37 patients (62%) had Gleason scores 5 or 6, 31% had Gleason scores 7 or 8 and 7% had a Gleason score of 4. The 37 cancer patients had a mean total PSA of 7.2 ng/ml (2.5–10.0 ng/ml), while the 69 patients with no evidence of disease had a mean total PSA of 5.4 ng/ml (2.5–10.0 ng/ml). The mean f/t PSA in the 37 cancer patients was 0.10, which differed significantly from the mean f/t PSA of the males without cancer (0.2). In order to determine whether assessment of the f/t PSA ratio in men with serum PSA levels of 2.5–10.0 ng/ml would help distinguish prostate cancer patients from patients with benign disease, a cut-off for the percentage of f/t PSA that would include virtually all prostate cancer patients was chosen.

Table 9 shows the percentages of cancers missed with different cut-offs for per cent free PSA. The f/t PSA ratio ⩽0.18 used in our retrospective study corresponded to a 25% loss of prostate cancers.

By using a f/t PSA ratio of up to 0.22 as an indication for biopsy, 30% of negative biopsies could be eliminated while still detecting 98% of cancers independent of the findings on DRE.

2.5.3. Prospective study II (using halved age-referenced ranges)

The two studies presented above address the usefulness of the f/t PSA ratio in the range of 2.5 to 10.0 ng/ml. Both studies have shown that per cent free PSA significantly improves specificity with a minimal decrease in sensitivity [11,12]. In the two studies the standard age-referenced ranges were used in combination with per cent free PSA, therefore, we were unable to detect cancers in subjects whose total PSA levels were within the normal range. In the literature 38–48% of patients with clinically significant organ-confined cancers are reported to have normal PSA levels [13,14]. In

Table 9
Different free/total PSA cut-off values

Cut-off value %	Total PSA (ng/ml)	Biopsy saving %	PCA loss %
18	⩽10	44	25
	>10	46	25
20	⩽10	36	10
	>10	31	9
22	⩽10	30	2
	>10	29	1

PSA, prostate specific antigen; PCA, prostate cancer.

Table 10
Bisected age specific reference ranges

Age (years)	Range (ng/ml)
40–49	0–1.25
50–59	0–1.75
60–69	0–2.25
70–79	0–3.25

addition, at least 30% of all prostate cancers detected are locally advanced with PSA levels between 4 and 10 ng/ml. Hence, reducing the upper limit of normal for PSA may improve detection of organ-confined prostate cancer. Our objective was to evaluate the clinical utility of the f/t PSA ratio in distinguishing benign prostatic disease from prostate cancer in screening volunteers with low total PSA levels.

The f/t PSA ratio was measured in 465 screening volunteers who had total serum PSA levels between 1.25 and 6.49 ng/ml according to our modified age-referenced ranges which had been reduced by 50%. Table 10 summarises the halved age-referenced PSA levels. Our aim was to enhance detection of cancer (sensitivity) within the range of 1.25–6.49 ng/ml, although this is associated with an increase in the number of biopsies. Various f/t PSA ratio cut-off points were analysed and finally a cut-off point of 18% was chosen.

120/465 volunteers (25.8%) presented with per cent free PSA levels of less than 18% and normal DRE findings; for this reason, they were further evaluated by ultrasound guided prostatic biopsies.

Of the 120 men, 27 (23%) were found to have cancer, while 2 showed isolated high grade prostatic intraepithelial neoplasia. The mean total PSA level was 2.66 ng/ml for prostate cancer patients, and 2.55 ng/ml for males with no evidence of disease. The mean per cent free PSA was 10.4% for prostate cancer patients, and 15.3% for men with benign disease. Table 11 summarises the values for total and per cent free PSA in the study group.

All 15 patients who underwent radical prostatectomy had organ-confined disease. Table 12 provides information on the pathological stages and grades.

In conjunction with halved total PSA ranges per cent-free PSA proved a useful tool for detecting clinically significant and pathologically organ-confined prostate cancers in screening volunteers with negative rectal examination findings.

2.6. Improvement of early detection of prostate cancer by using PSA TZ density and per cent free PSA in addition to total PSA levels

As BPH almost exclusively results from hyperplasia of the transitional zone, the PSA production in the peripheral zone can be assumed to remain relatively constant as the gland enlarges [14]. Therefore, it can be reasoned that in BPH changes in PSA levels are attributable to the TZ of the prostate.

In the following study the diagnostic benefit from PSA transitional zone density (PSA TZ density = total PSA/TZ volume) alone and in combination with per cent free PSA for the detection of early prostate cancer was evaluated.

Between August 1995 and May 1996, 308 consecutive screening volunteers with elevated total PSA levels ranging from 2.5–10.0 ng/ml were evaluated. All patients underwent DRE, transrectal ultrasound and transrectal ultrasound guided biopsy of the prostate. Prior to these investigations, serum was obtained and total as well as free PSA levels were assessed with the DELFIA PSA dual label f/t PSA kit (Wallac Oy Turku, Finland) in one laboratory. Transrectal ultrasonography using 3-D ultrasound equipment with a 10 MHz endorectal transducer was performed in three planes. The volume of the entire prostate as well as the volume of the transitional zone were calculated for a prolate ellipsoid.

PSA transitional zone density (PSA TZ density) was defined as follows:

PSA TZ density = total PSA (ng/ml)/TZ volume (cc).

The results for total PSA, per cent free PSA and PSA TZ density were subjected to statistical analysis. The Mann–Whitney U test was used to investigate whether there are significant differences between the groups. We evaluated the reciprocal relationship between sensitivity and specificity by plotting true-positive (sensitivity) against false-positive (1 minus specificity) results in

Table 11
Mean total and per cent free PSA

All patients (PSA range, 1.25–6.49 ng/ml)			
	Benign disease ($n=91$)	Prostate carcinoma ($n=27$)	PIN ($n=2$)
Total PSA (ng/ml)			
Mean	2.45	2.66	2.55
Per cent free PSA			
Mean	15.3	10.4	12.2

PSA, prostate specific antigen; PIN, prostatic intraepithelial neoplasia.

Table 12
Pathological stage and grade in 15 radical prostatectomy specimens ($n=15$)

No. of tumours	Pathological stage	Gleason score
2	pT2a	3–5
3	pT2b	4–7
10	pT2c	5–8

Table 13
Mean values for total PSA, per cent-free PSA, and PSA TZ density[a]

	BPH	PCA	Prostatitis
t-PSA (ng/ml)	6.6 (2.5–10.0)	6.0 (3.1–10.0)	8.0 (2.5–9.7)
f-PSA (per cent)	22 (4.7–43.2)	11.3 (4.1–19.1)	9.1 (4.6–20.2)
PSA TZ density (ng/ml/cc)	0.35 (0.06–1.93)	0.56 (0.23–1.20)	0.50 (0.33–2.90)

[a] PSA, prostate specific antigen; TZ, transitional zone; BPH, benign prostatic hyperplasia; PCA, prostate carcinoma; t-PSA, total prostate specific antigen; f-PSA, free prostate specific antigen.

receiver operating characteristic curves. To check the validity of our findings the individual diagnostic tests were compared by means of the Youden Index.

Of the 308 screening volunteers undergoing transrectal biopsy 228 (74%) had biopsy proven benign prostatic hyperplasia (BHP), 22 (7%) had prostatitis with no evidence of hyperplastic tissue and 58 (19%) had biopsy proven prostate cancer.

The mean total PSA levels were 6.6 ng/ml (range: 2.5–10.0) in the BPH group, 8.0 ng/ml (range: 2.5–9.7) in the group with chronic inflammatory disease, and 6.0 ng/ml (range: 3.01–10.0) in the cancer group. Mean per cent-free PSA levels in the BPH, prostatitis and prostate cancer groups were 22.0% (range: 4.7–43.2%), 9.1% (range: 4.6–20.2%) and 11.3% (range: 4.1–19.1%), respectively. The differences between the BPH and prostate cancer groups and between the BPH and prostatitis groups were statistically significant whereas the difference between the prostate cancer and prostatitis groups did not reach statistical significance.

The mean values for PSA TZ density were 0.35 ng/ml/cc (range: 0.06–1.93) in the BPH group, 0.50 ng/ml/cc (range: 0.33–2.90) in the prostatitis group, and 0.56 ng/ml/cc (range: 0.23–1.20) in the cancer group. The differences between the BPH and PCa groups, between the BPH and prostatitis groups, and between the PCa and prostatitis groups were statistically significant. The values for t-PSA, f-PSA and PSA TZ density are shown in Table 13.

ROC curve analyses (Fig. 4) show that by using per cent-free PSA <20% as a biopsy criterion in men with elevated PSA, 45.5% of negative biopsies could be eliminated while still detecting 100% of prostate cancers.

ROC curve analyses (Fig. 5) for PSA TZ density show that by using a PSA TZ density of more than 0.22 ng/ml/cc as a biopsy criterion 24.4% of negative biopsies could be avoided without missing a single cancer. When combining these two diagnostic tests with the biopsy criteria mentioned above 54.2% of negative biopsies could be eliminated.

In this study per cent-free PSA proved to be a better predictor of prostate cancer than PSA TZ density, since it had the largest area under its receiver operating characteristic curve. In order to check the validity of our findings the individual diagnostic tests were compared by means of the Youden Index. (Table 14). This statistical test confirmed that per cent free PSA is a better predictor of prostate cancer than PSA-TZ density alone. However, the combination of per cent-free PSA and PSA TZ density is superior to free PSA alone.

In conclusion, our study demonstrated that, in addition to total and free PSA, PSA TZ density is an important diagnostic tool for calculating the probability of a patient developing prostate cancer. However, further prospective studies will be required to confirm the reproducibility and usefulness of PSA TZ density in PSA-based screening.

2.7. PSA-based screening and incidental prostate cancer

PSA-based screening dramatically improves early detection of non-palpable prostate cancer. In the discussion about the usefulness of screening programmes concerns have been raised about whether these programmes would also lead to the detection of very small and well-differentiated prostate cancers requiring no therapy. The majority of well-differentiated A1 tumours are known to be clinically insignificant and, therefore, do not require further therapy, whereas patients

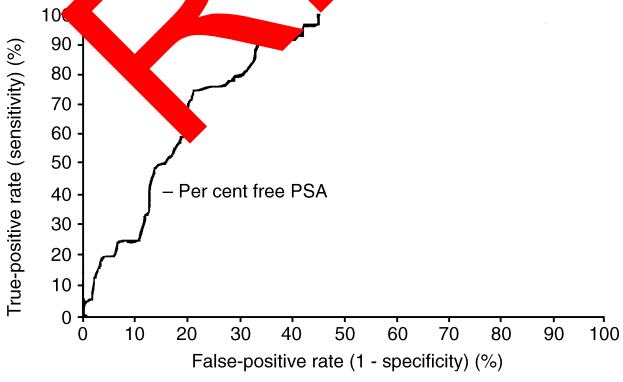

Fig. 4. Receiver operating characteristic curves analysis for per cent free prostate specific antigen (PSA).

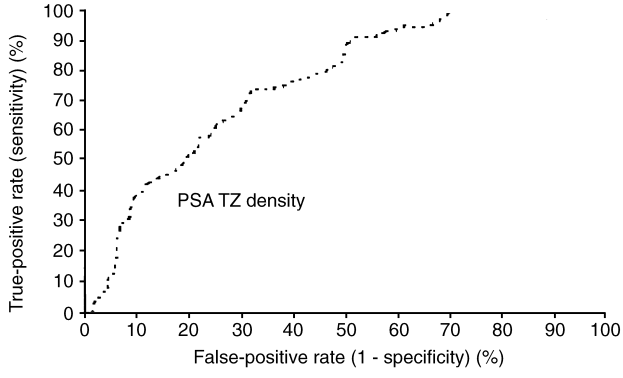

Fig. 5. Receiver operating characteristic curves analysis for prostate specific antigen (PSA) transitional zone (TZ) density.

Table 14
Youden index for percent free PSA, PSA TZ density and the combination of per cent free PSA and PSA TZ density[a]

	J	T	*P* value
Per cent f-PSA <20 ng/ml	0.560		
PSA TZ density >0.22	0.300	6.085	0.000
Per cent f-PSA <20 ng/ml and PSA TZ density >0.22	0.668	−2.496	0.013

[a] PSA, prostate specific antigen; TZ, transitional zone; J, Youden index; T, f-PSA free prostate specific antigen.

presenting with dedifferentiated A1 grade III and A2 prostate cancers definitively need treatment.

In order to find out whether PSA-based screening has an impact on the incidence of incidental prostate cancer, 1543 patients undergoing transurethral resection of the prostate (TURP) in our department over the past 6 years for suspected BPH were evaluated in a retrospective study. All patients older than 75 years were excluded as they did not participate in the screening programme, and two different groups were distinguished. Group 1 comprising 868 patients aged 58 to 75 years who were operated upon between 1990 and 1992 represented the pre-PSA era. Group 2 consisting of 675 consecutive patients aged 56 to 75 years who underwent TURP in the years 1993–1995 represented the PSA screening era. The men in group two either had PSA levels in the normal range (according to age-specific reference ranges) or underwent TURP after transrectal ultrasound guided biopsy of the prostate.

The mean age of the patients in group I [illegible] years compared with 69.7 years in group II. In the latter group, the mean PSA level for patients with stage A prostate cancer was 4.7 ng/ml. There was a significant difference in PSA levels between A1 and A2 cancer patients. Patients with A1 cancer had a mean PSA of 4.7 ng/ml, whereas patients with A1 grade III or A2 cancer had a mean PSA of 7.7 ng/ml.

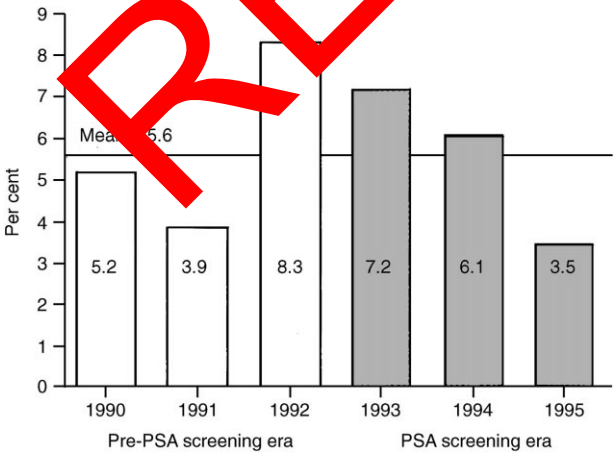

Fig. 6. Incidence of T1a,b prostate carcinoma.

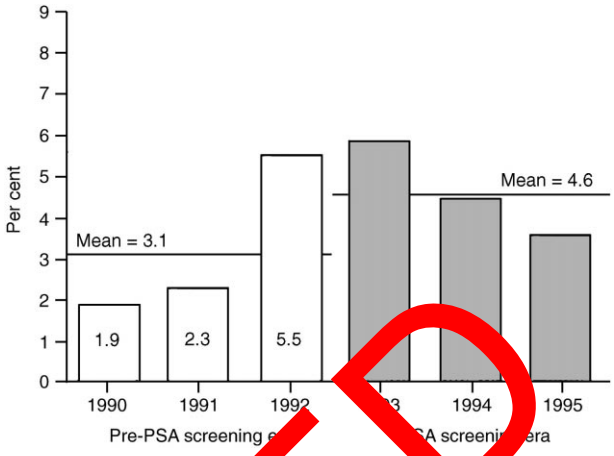

Fig. 7. Incidence of [illegible] Grade [illegible] 2 prost[illegible]rcinoma.

The incidence of stage A tumours in the years before the introduction of PSA-based screening (group I) was 5.2, 3.9 and 8.3% respectively (mean: 5.6%; Fig. 6). The incidence of A1 (T1a Grade 1 and 2) cancers in this group was 1.9, 2.3 and 5.5%, respectively (mean: 3.1%; Fig. 7). The incidence of A1 grade III and A2 cancer (T1a and T1b grade 3) was 3.2, 1.6 and 1.98% with an average of 2.3% (Fig. 8).

In the years after establishing PSA-based screening (group II) the incidence of stage A tumours was 7.2, 6.1 and 3.5%, respectively (Fig. 6). Again the mean was 5.6%, however, the incidence of A1 and A2 tumours was completely different. We found an incidence of A1 prostate cancer of 7.2, 6.1 and 4.6%, respectively (mean: 4.6% Fig. 7). The incidence of A1 grade III and A2 cancer was 1.4, 1.6 and 0%, respectively (mean: 1.03%; Fig. 8).

These data demonstrate that PSA-based screening for prostate cancer leads to a decrease in the incidence of dedifferentiated A1 grade III and A2 tumours, while there is no impact on the incidence of clinically insignificant A1 grades I and II prostate cancers.

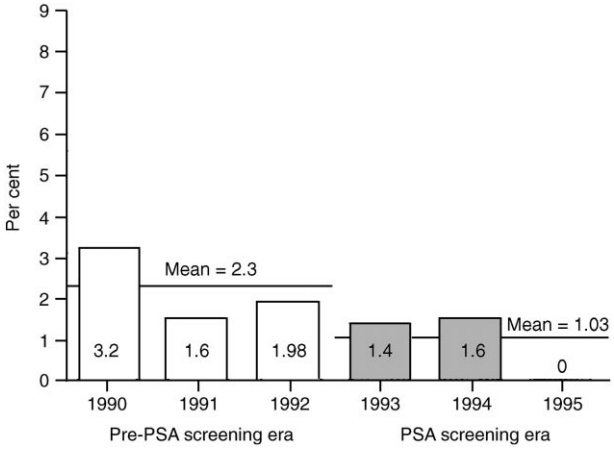

Fig. 8. Incidence of T1a Grade 3 and T1b prostate carcinoma.

2.8. Stage migration in 5-year PSA-based screening programme

Radical prostatectomy as a treatment for prostate cancer is potentially curative provided the tumour is still confined to the prostate at diagnosis [15,16]. The following study was designed to evaluate changes in PSA levels and pathohistological stages in radical prostatectomy specimens over a period of 5 years in a PSA based mass screening programme.

Between September 1993 and October 1997 the mean ages, mean total PSA levels and rates of organ and non-organ-confined tumours were evaluated in 595 patients undergoing biopsy and radical retropubic prostatectomy. Furthermore, the mean Gleason scores at biopsy were compared with those of the specimens obtained at radical prostatectomy. For statistical analysis the Mann–Whitney U-test was used to investigate whether there are significant differences for total PSA and pathological stage between the different years.

The results of this evaluation show a statistically significant decrease in total PSA levels from a mean value of 14.9 ng/ml in 1993 to 8.6 ng/ml in 1997. In addition, the rate of organ-confined prostate cancers increased from 28.7% in 1993 to 65.7% in 1997, whereas a reciprocal decrease from 71.2% (1993) to 34.2% (1997) was observed for the rate of non-organ-confined tumours (Table 15).

These data indicate that between 1993 when PSA-based screening was introduced at our department and 1997, a significant decrease in preoperative total PSA levels, a significant migration to lower stage, an increase in the number of organ-confined potentially curable prostate cancers were observed. Long-term follow-up will show whether these trends will also have a positive impact on prostate cancer mortality rates.

2.9. The probability of having prostate cancer given the patient's age, serum PSA value and DRE findings: results from the Tyrol Screening Project

Traditionally, the decision to perform a prostate biopsy has been based upon whether the total serum PSA level is normal and abnormal (specific cut-off point) and the DRE findings [5,6]. In the setting of a benign DRE, a 60-year old man with a PSA level of 4.1 ng/ml would be encouraged to undergo a biopsy, whereas the same man with a PSA concentration of 3.9 ng/ml might be discouraged from having the procedure. Yet, in reality, there is little to no difference between the two PSA values. What might be more appropriate is informing the patient of the actual probability or risk of having prostate cancer and letting him, together with his physician, decide about proceeding ahead with a transrectal, ultrasound guided prostate biopsy.

Using multivariate logistic regression analysis and data from the 2054 men (mean age 64 years, most of whom were part of the Tyrol Screening Project in Innsbruck, Austria (screening volunteers, 45–75 years of age) between September 1993 and October 1997, patient age, serum PSA level and DRE findings were identified as the three critical variables for determining the probability of having prostate cancer.

For men 40–80 years of age, the percentage of probability of having prostate cancer (with 95% confidence intervals) as a function of serum PSA and DRE findings are shown in Table 16.

By using this approach, the decision to proceed with a prostate biopsy is based upon the risk of having prostate cancer rather than a single cut-off point. For 1 patient a 22% risk warrants a biopsy; for another man it simply means a 78% chance of not having cancer, and watchful waiting is acceptable. Now, for the first time, the patient and the physician can make an informed decision as to whether a prostate biopsy is appropriate for that specific individual.

2.10. Correlation between preoperative predictors obtained at PSA-based screening and pathological features in radical prostatectomy specimens

Measurement of per cent-free PSA, PSA density and PSA TZ density in addition to total PSA is known to improve the specificity of PSA-based prostate cancer screening. However the value of total PSA in the preoperative staging of prostate cancer is controversial.

Table 15
Change in total PSA, Gleason score and rate of organ-confined tumours in a 5-year PSA-screening programme

			Histological examination of biopsy specimen	Radical prostatectomy specimen		
Year	Age (range)	Mean PSA (ng/ml)	Mean Gleason score	Organ-confined *n* (%)	Mean Gleason score (range)	*n*
1993	63.7 (51.6–76.1)	14.9 (2.5–100)	4.9 (3–10)	23 (28.7)	5.0 (2–10)	80
1994	62.9 (49.4–74.3)	14.2 (0.4–55.0)	4.8 (3–10)	42 (27.6)	5.1 (2–9)	152
1995	62.5 (45.2–74.1)	12.7 (4.0–60.0)	4.6 (2–8)	37 (25.1)	5.2 (2–9)	147
1996	64.2 (46.5–74.7)	9.7 (1.3–30.0)	5.3 (2–8)	57 (55.8)	5.8 (2–9)	102
1997	64.9 (47.0–77.0)	8.6 (1.2–35.9)	5.5 (2–8)	75 (65.7)	5.8 (2–9)	114
						Σ = 595

Table 16
The probability (%) of having prostate cancer according to age, PSA and digital rectal examination (DRE) findings

PSA range (ng/ml)	Age range (years)							
	40–50		51–60		61–70		71–80	
	DRE−	DRE+	DRE−	DRE+	DRE−	DRE+	DRE−	DRE +
0.0–2.5	9	37	12	39	15	42	20	44
2.6–4.0	9	41	12	42	16	44	20	47
4.1–6.0	10	41	14	44	17	47	22	48
6.1–10.0	11	33	15	48	19	50	25	52
10.1–20.0	13	55	19	54	25	58	31	60
>20.0	22	82	45	74	43	81	59	84

Although studies by Stamey and colleagues [17] suggest it to be useful as a preoperative staging marker other studies have not found it sufficiently reliable for predicting the final pathological stage on an individual basis [18]. In the following retrospective study the ability of total PSA, per cent-free PSA, PSA density and PSA TZ density to predict pathological features in radical prostatectomy specimens was evaluated.

The levels of total PSA, per cent-free PSA, PSA density and PSA TZ density determined prior to the diagnosis of prostate cancer were correlated with the pathological features of 102 prostate cancer specimens obtained at radical prostatectomy. The entire organs were examined histologically. The results obtained were subjected to statistical analysis. We evaluated the correlation between preoperative predictors and pathological features in computing Pearson correlation coefficients. Independent predictors have been identified by means of stepwise logistic regression. The logistic model included only those predictors significantly identified within the univariant analysis. All P values of less than 0.05 were considered as significant, all stated P values are two-sided.

High total PSA, PSA density and PSA TZ density levels correlated significantly with high Gleason scores, capsular penetration, high percentage of cancer in the prostatectomy specimen and a high cancer volume. Free PSA was found to correlate well with a higher Gleason score, greater percentage of cancer and cancer volume but not with capsular penetration.

The four predictors were evaluated by means of logistic regression, which showed that only per cent-free PSA and total PSA were significant predictors of Gleason scores $\geqslant 7$ and cancer volumes $\geqslant 0.5$ cc. With clinically insignificant cancers per cent-free PSA and the Gleason score obtained at biopsy were the only significant predictors.

In men whose prostate cancers are detected at PSA-based screening, high total PSA levels in combination with low per cent-free PSA serum levels are suggestive of a potentially more aggressive type of cancer. This information may help both patients and clinicians in selecting the most appropriate therapeutic approach.

2.11. Correlation of total PSA with pathological stage and tumour volume in patients undergoing radical prostatectomy following PSA screening with low PSA cut-off levels

Recent studies [19,20] have shown that low cut-off values for total PSA in PSA-based screening may enhance the number of organ-confined prostate cancers detected at radical prostatectomy. In the following study the data of a subgroup of males from our screening programme with PSA levels below 3.99 ng/ml who underwent radical prostatectomy were evaluated.

Serial whole mount sections from 95 patients with PSA levels below 3.99 ng/ml who underwent radical prostatectomy were analysed with regard to pathohistological stage, surgical margin status, Gleason grade and tumour volume. For statistical analysis the Mann–Whitney U test was used.

5 men (group I) had PSA levels below or equal to 1.25 ng/ml, 27 (group II) between 1.26 and 1.99 ng/ml, 30

Table 17
Correlation of total PSA with per cent-free PSA, age, tumour volume, Gleason score, pathological stage and surgical margin status

PSA	% Free PSA	Age	Mean tumour volume (g) (range)	Gleason score	Pathological stage	Surgical margin status
Group I ($n=5$) 0.0–1.25	14.7 (7.9–20.7)	61 (49–73)	0.80 (0.37–0.98)	5.6 (4–7)	Organ-confined	Negative
Group II ($n=27$) 1.26–1.99	14.1 (4.9–19.1)	57 (50–75)	0.43 (0.22–1.13)	5.9 (3–8)	Organ-confined	Negative
Group III ($n=30$) (2.0–2.99)	15.1 (6.2–24.9)	61 (47–75)	0.92 (0.44–3.11)	5.6 (4–8)	Organ-confined	Negative
Group IV ($n=33$) (3.0–3.99)	12.9 (5.6–21.3)	61 (48–75)	0.79 (0.36–1.85)	5.4 (4–7)	Organ-confined	Negative

Table 18
Mean values for total PSA, per cent-free PSA, Gleason score, tumour volume, pathohistological stage and surgical margin status in males aged 40–49 and 50–59 years

	Group I (aged 40–49)	Group II (aged 50–59)
n	19	45
Mean total PSA (ng/ml) range	17 (0.9–2.4)	1.9 (1.1–2.4)
Mean free PSA (%) (range)	12.6 (6.2–19.1)	14.2 (4.3–21.9)
Mean Gleason score (range)	5.5 (4–7)	5.3 (4–7)
Mean tumour volume (g) (range)	0.26 (0.13–0.49)	0.78 (0.17–0.59)
Pathological stage	Organ-confined	-confined
Surgical margin status	Negative	Negat

(group III) between 2.0 and 2.99 ng/ml and 33 (group IV) between 3.0 and 3.99 ng/ml. The mean tumour volume (g) in group I, II, III and IV was 0.80 g, 0.43 g, 0.92 g and 0.79 g respectively. The results for per cent-free PSA, age, tumour volume, Gleason score as well as pathological stage and surgical margin status are shown in Table 17. With the exception of the tumour volume in group II, none of the parameters in the different groups showed a statistically significant difference.

The results of this evaluation indicate that the radical prostatectomy specimens in patients with low total PSA values who were diagnosed with prostate cancer exhibit low tumour volumes and low Gleason grades; however, all of these cancers were clinically significant. Furthermore, all patients had organ-confined prostate cancers with negative surgical margins.

2.12. PSA-based screening with very low PSA values: correlation between age and clinical pathological features in the 40–59 year age group

Recent data indicate that older men are more likely to have extensive disease compared with younger men with the same PSA levels [21]. To determine whether age has an impact on the extension of prostate cancer the data of a subgroup of males aged between 40 and 59 years from our PSA screening program who presented with PSA levels below 2.5 ng/ml were evaluated.

64 males undergoing radical retropubic prostatectomy for prostate cancer detected by PSA-based screening were evaluated in terms of pathohistological stage, surgical margin status, Gleason grade and tumour volume (g). The results obtained were subjected to statistical analysis to investigate whether there are statistically significant differences between the two groups.

Of the 64 patients evaluated, 19 were between 40 and 49 (group I) and 45 between 50 and 59 years of age (group II). The mean values in group I for total PSA was 1.7 ng/ml, for per cent-free PSA 12.6%, for Gleason score 5.5 and for the tumour volume 0.26 g. In group II the mean values for total PSA, per cent-free PSA, Gleason score and tumour volume were 1.9 ng/ml, 14.2%, 5.3 and 0.78 g respectively. In both groups all patients had organ-confined prostate cancer and all had a negative surgical margin status (Table 18).

The difference in tumour volumes between the two groups was statistically significant ($P \leqslant 0.001$). All other parameters (total PSA, per cent-free PSA and Gleason score) were statistically non significant. 2 patients in each group had clinically insignificant prostate cancers according to the definition by Epstein.

These data suggest that older men are more likely to have larger tumour volumes compared with younger men with the same PSA levels. Furthermore, the data suggest that in PSA-based screening low cut-off values may increase the detection rate of organ-confined tumours with negative surgical margins that are potentially curable.

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