National Societies usually recommend screening for Prostate Cancer (PC) with Serum Prostate Specific Antigen (PSA) and digital rectal examination annually beginning at age 50. In high risk population including men with a family history of PC or African population screening should start at age of 45 years. PSA has been widely used to detect PC despite the fact that PSA is not specific for PC. Over the years serum PSA level of greater than 4,0ng/ml was considered the threshold to perform prostate biopsy, searching for PC. In 2005 the Prostate Cancer Prevention Trial (PCPT) demonstrated that the cut-off of 4,0ng/ml for PSA is not anymore adapted due to the fact that this survey found in 15% of men with PSA < or = 4,0ng/ml a prostate cancer on sextant biopsies.

Today the value of PSA and the cut-off for Prostate biopsy is questioned suggesting that PSA level higher than 2,6ng/ml must be the case to propose Prostate Biopsy. Catalona confirms that approximately 25% to 30% of men with PSA 2,6 to 4,0ng/ml have prostate cancer. Schröder and Gosselaar assert that screening for PC at low PSA levels (<4,0ng/ml) risks to detect clinically insignificant cancers which are no threat to man.

So far in the year 2006 screening for PC demonstrates accumulating evidences of efficacy but persistent uncertainty. The major question for an urologist at work when facing a young men searching early diagnosis of PC is: at which level of PSA do we have to perform rectal biopsy?

Key words: prostate cancer, screening

I – SCREENING FOR PC IS A MAJOR ISSUE

Prostate cancer is a large public health problem. It is currently the most common neoplasm and the second leading cause of cancer death in Western men. The prevalence of PC is higher in older men. The expectancy of life at birth is increasing all the time reaching 79 years in French men and life expectancy increases with aging, such that by the time a man is 70 years old, he is supposed to live an additional 15 years and 12 years when he reaches 75 years. According to these data, PC can be threatening for a men around 60 years of age even at a low stage.

The rationale for active screening is convincing, but estimated life-time risk of developing prostate cancer for a 50 years old man is around 40% based on autopsy and the life-time risk that he will have a clinically detected PC is only 10% and the risk to die from the disease 3%. The wide discrepancy between the high prevalence of histological changes evoking PC and the much lower prevalence of clinical disease is due to the fact that clinically insignificant PC are common because of their low aggressivity. In these patients, comorbiditities as cardiovascular of neurologic diseases are more likely causes of death than PC (intercurrent disease). Schröder and al considering "he favorable characteristics of tumors detectable at very low PSA levels seems to justify the conclusion that an unknown but sizeable proportion of the cancers found at biopsy are clinically insignificant."

How can we get out of this dilemma?

II – SCREENING IN DIFFERENT COUNTRIES

There is a major difference in between early diagnosis for PC and screening. Screening is an active policy of survey on community men participating in a prostate cancer screening study. Early diagnosis is the situation encountered by Urologist when facing a patient who want to known if his prostate is safe.

To reach the best management for early diagnosis needs to know the results of well designed screening study.

1. The European Randomized Study of Screening for Prostate Cancer evaluates the predictive value of a PSA increase to PSA 3,0ng/ml or greater in a 4-year period in
men who present with low PSA value (less than 3,0ng/ml) at first screen in Rotterdam – Netherlands (F8).

Among a group of 42376 men randomized for screening or control, 5771 men with a low PSA (<3,0ng/ml) did not undergo biopsy at the entry in the study and were controlled after 4 years with PSA 3,0ng/ml or greater. PSA progression higher than 3,0ng/ml occurred in 0,9%, 9,3% and 48,6% of men who presented initially with PSA values less than 1,1 to 1,9 and 2 to 2,9ng/ml. PSA progression to the arbitrary cut-off of 3,0ng/ml and the diagnosis of PC with a 4-year interval depends strongly on PSA values at the entry in the study. When the men had PSA less than 2,0ng/ml, PSA progression to 3,0 ng/ml is rare (4,8% of men) (Table 1).

2. The American Cancer Society and the National comprehensive Cancer Network9 recruited for screening 10174 men, 45 to 59 years old with a PSA less than 2,6ng/ml and benign DRE. All men underwent annual DRE and PSA testing in a screening study between 1991 and 2001. Of the 10174 men, 232 (2,3%) were subsequently diagnosed with PC. All patients had clinically localized disease but 13% were considered possibly harmless tumors by their low volume (Epstein criteria tumor volume less than 0,5ml and no Gleason pattern 4 or 5) and 2% were considered possibly rapidly progressive (Table 2). Mostly patient have been treated by Radical Prostatectomy (87%) and radiation therapy (10%). After 10 years follow-up, 2,3% of the men only were found to have PC but one might anticipate that during the next 10 years of follow-up a substantial number of men considered as free of cancer to day, will suffer of PC. It is evident that such on annual screening prolonged 20 years will cumulatively result in over detection and probably over treatment6.

3. A population based case-control study was conducted in Toronto Canada10 comparing data from 236 patients with metastatic prostate cancer and 462 controls. In this study screening of asymptomatic men with PSA was associated with a significantly reduced risk (35%) of metastatic prostate cancer. Among asymptomatic men, frequency of PSA testing was significantly lower in men with metastatic PC.

**DISCUSSION**

Introduction of PSA screening for detecting early stage prostate cancer resulted in a dramatic change in the evolution of the disease. 75% of the diagnosed prostate cancer in the years 1980-1990 were locally advanced or metastatic. Since 1995, and the extensive use of PSA in France, 75% of Prostate Cancer diagnosed are now localized and considered as curable. Decreasing the threshold of PSA to perform Prostate Biopsy, we are now facing an increasing risk to detect insignificant Prostate Cancer. In the PSA era the value of PSA to determine the need of Prostate biopsy has been questioned due to evidence from 2 sources.

1. Men with normal PSA can have PC. This was clearly shown by the PCPT,1 where on the end of study biopsy almost 15% of men with PSA less than 4ng/ml had PC. Therefore PSA cut-off to search for PC becomes unclear.

2. The American Cancer Society and the National comprehensive Cancer Network9 recruited for screening 10174 men, 45 to 59 years old with a PSA less than 2,6ng/ml and benign DRE. All men underwent annual DRE and PSA testing in a screening study between 1991 and 2001. Of the 10174 men, 232 (2,3%) were subsequently diagnosed with PC. All patients had clinically localized disease but 13% were considered possibly harmless tumors by their low volume (Epstein criteria tumor volume less than 0,5ml and no Gleason pattern 4 or 5) and 2% were considered possibly rapidly progressive (Table 2). Mostly patient have been treated by Radical Prostatectomy (87%) and radiation therapy (10%). After 10 years follow-up, 2,3% of the men only were found to have PC but one might anticipate that during the next 10 years of follow-up a substantial number of men considered as free of cancer to day, will suffer of PC. It is evident that such on annual screening prolonged 20 years will cumulatively result in over detection and probably over treatment6.

**TABLE 1**

<table>
<thead>
<tr>
<th>Initial PSA</th>
<th>Less than 1,0</th>
<th>1,0-1,9</th>
<th>2,0-2,9</th>
<th>Over all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>2622</td>
<td>2268</td>
<td>881</td>
<td>5771</td>
</tr>
<tr>
<td>Prostate Ca</td>
<td>4</td>
<td>43</td>
<td>105</td>
<td>152</td>
</tr>
</tbody>
</table>

2. A recent study from Stamey11 found that PSA was only weakly associated with PC volumes in men treated with Radical Prostatectomy. The author proclaimed that "the PSA era in the United States is over for Prostate Cancer".

This is not true and Partin and al12 demonstrates in 2371 consecutive patients operated by Retropubic Prostatectomy (RP) for PC that men with higher PSA were more likely to have higher clinical stages, higher grade cancers in the biopsy and greater positive margins, seminal vesicle invasion and lymphnode metastasis in the final RP specimen. The 5-year PSA free survival rates after RP in men with PSA less than 10, 10 to 20, and 20 or greater ng/ml were 94%, 77% and 53%. In men with PSA less than 10ng/ml, for each 2-point increase in initial PSA the risk of biochemical progression after RP approximately doubled.

**What about PSA density?**

PSA is a protease produced as well by benign and malignant prostate epithelium. PSA is prostate specific, just not cancer specific. Gram per gram of prostate tissue, prostate cancer results in 10-fold greater increases in serum PSA relative to benign hyperplasia. However, to day median tumor volume in the prostate gland is small (1 t 2cc) and the cancer contribution to the PSA level is small.

**What about PSA velocity?**

PSA velocity and specially PSA doubling Time (DT) prior to diagnosis appears useful to suggest Prostate Biopsy. Despite the low level of PSA, in the range of 1,1 to 2,0ng/ml, if the DT is less than 2 years the need for Prostate biopsy is evident. A DT of less than 2 years appears to identify patients at high risk for local progression despite otherwise favorable factor.

There has been recent investigation into lowering the PSA prompt for biopsy, especially in men younger than 60 years using 2,6ng/ml as cut-off. Catalona13 suggest that also in men older than 60 years, the 2,6ng cut-off must be considered, in men who would be candidates for definitive treatment.

The choice of a PSA prompt for prostate biopsy is controversial because there are men with low PSA (below 4,0ng/ml) who harbor PC that is or will become life threatening as well as cancers that would have gone undetected during life in the absence of screening.

It is time to put less power on an absolute PSA threshold and explore other pathways as PSA velocity to discrimin-
CONCLUSION
Lowering PSA cut-off for prostate biopsy increases the risk of detecting clinically unimportant Prostate Cancer. Since the PCPT we have to admit that biopsy detected PC, including high grade cancers is not rare among men with a PSA level of 4,0ng/ml. The EAU guidelines suggest that “the exact cut-off level of what is considered to be normal PSA value has not yet been determined but values 2,5 – 3ng/ml are often used for younger men (grade C recommendation). A PSA treshold of 3,0ng/ml has now to be considered for prostate biopsy. This is a good balance between an acceptable rate of detection and the need to avoid clinically insignificant cancer. Among men with baseline PSA of 1,0 to 1,99ng/ml the risk to convert to PSA greater than 4ng/ml in the next 5 years is rare (4 – 9%) and must benefit to slow down the control of PSA every 2 to 3 years.

REZIME
Nacionalna udruženja često predlažu skrining za karcinom prostate (CP) koristeći nivo PSA u serumu i digitalni rektalni pregled jednom godišnje kod muškaraca počev od 50. godine života. U visoko rizičnoj populaciji uključujući muškarce sa porođenim opterećenjima, kao i kod afričke populacije, ovaj skrining se može primeniti od 45. godine života. Vrednost PSA može biti široko korišćena za otkrivanje CP uprkos činjenici da je PSA nespecifican za CP. Godinama je nivo PSA već od 4ng/ml odlučivao da se donese odluka za biopsiju prostate, tražeći karcinom. U 2005. godini studija za prevenciju karcinoma prostate (PCPT) pokazala je da granica od 4,0 ng/ml za PSA nije još prilagođena očekivanoj činjenici da ova anketa nalazi u 15% muškaraca sa nivoom PSA od 4,0ng/ml karcinom prostate na sekstantan př biopsiji. Danas, vrednost PSA ograničena za biopsiju prostate, postavljena je sugestivnići da nivo PSA preko 2,6ng/ml može biti slučaj u kome se predlaže biopsija prostate. Catalona potvrđuje da aproksimativno 25-30% muškaraca sa nivoom PSA od 2,6-4,0 ng/ml imaju CP. Schroder i Gaselaar tvrde da je skrining za CP kod malih nivoa PSA (4.0/ml) rizik da se otkriju klinički ne signifikantni karcinomi. Tako daleko u 2006. godini skrining za CP pokazuje gomilanje dokaza uspešnosti ali i postojanje nesigurnosti i kolebljivosti. Glavno pitanje za urologe u poslu kojim se bave tj. ranom otkrivanju CP je: koji nivo serumskog PSA određuje granicu kada ćemo morati da radimo transrektalnu biopsiju prostate?

Ključne reči: karcinom prostate, skrining

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<p>| TABLE 2 |</p>
<table>
<thead>
<tr>
<th>Screened men aged 45-59 years</th>
<th>PSA &gt;2,6ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men who complied with DRC and PSA screening protocol</td>
<td>N=10174(87%)</td>
</tr>
<tr>
<td>Men recommended to undergo biopsy</td>
<td>N=571(6%)</td>
</tr>
<tr>
<td>Men who underwent biopsy</td>
<td>N=429(75%)</td>
</tr>
<tr>
<td>Cancer N=232(54%)</td>
<td>No Cancer N=197(46%)</td>
</tr>
<tr>
<td>N=11636; RL Grubg and WJ Catalona J Urol 2005</td>
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</tr>
</tbody>
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