# Το PSA στο εδώλιο:

## Το PSA οδηγεί τουλάχιστον σε αναίτια υπερ-θεραπεία

**Διονύσης Μητρόπουλος**

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Ιατρική Σχολή Πανεπιστημίου Αθηνών

## Σύγκρουση συμφερόντων:

Abbott, Astellas, Amgen, Ferring, GSK,
Eli Lilly, Sanofi-Aventis, Specifar

**Υπερ-διάγνωση:** η διάγνωση νόσου που αν μείνει χωρίς θεραπεία δεν θα προκαλέσει ιατρικά προβλήματα κατά την διάρκεια της ζωής ενός ασθενούς σε συνδυασμό με τις επιπτώσεις της πρώϊμης θεραπευτικής παρέμβασης σ' αυτές τις περιπτώσεις.

# Επιβλαβή αποτελέσματα της διαγνωστικής διαδικασίας

6.4.8 ***Antibiotics prior to biopsy***

Oral or intravenous antibiotics are state-of-the-art treatment. Optimal dosing and treatment time vary. Quinolones are the drugs of choice, with ciprofloxacin superior to ofloxacin (41) (LE: 1b), but in the last few years increased resistance to quinolones has been reported (42) associated with a rise in severe infectious complications after biopsy (43).

6.4.11 ***Complications***

Complications include macrohaematuria and haematospermia (Table 5) (46). Severe post-procedural infections were initially reported in < 1% of cases, but this rate has increased in the last few years as a consequence of the evolution of antibiotic resistance strains with more post-biopsy hospitalizations for infectious complications while the rate of non-infectious complications has remained stable (43) .

Low-dose aspirin is no longer an absolute contraindication (47) (LE: 1b).

**Table 5: Percentage given per biopsy session, irrespective of the number of cores***

| Complications | % of biopsies |
|---|---|
| Haematospermia | 37.4 |
| Haematuria > 1 day | 14.5 |
| Rectal bleeding < 2 days | 2.2 |
| Prostatitis | 1.0 |
| Fever > 38.5°C (101.3°F) | 0.8 |
| Epididymitis | 0.7 |
| Rectal bleeding > 2 days ± requiring surgical intervention | 0.7 |
| Urinary retention | 0.2 |
| Other complications requiring hospitalization | 0.3 |

* *Adapted from NCCN Guidelines Prostate Cancer Early Detection. V.s.2010 (42).*

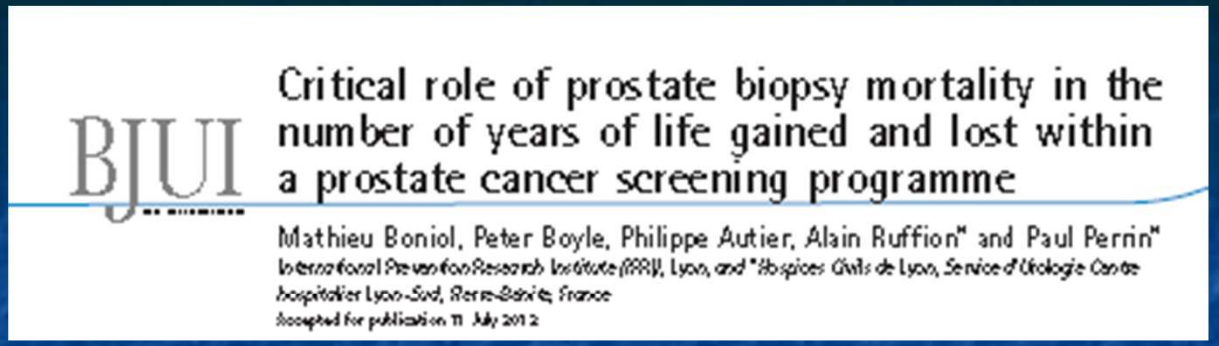
## TRUS-related harms

ERSPC study: Rate of over-diagnosis in the screening group 50%. No deaths were reported as a direct complication (such as septicemia or bleeding) from the biopsy procedure. Complication rates associated with TRUS-guided sextant biopsies from the Netherlands site indicated that the most common "minor" complications were hematospermia (50% of participants who underwent a biopsy) and hematuria for greater than 3 days (23%). The most common "major" complications were pain (7.5%) and fever (3.5%). Urinary retention occurred in 0.4% and hospitalizations due to urosepsis or prostatitis in 0.5%. Other harms associated with screening and diagnostic workup, such as pain and anxiety, and treatment-related harms, such as erectile dysfunction and urinary leakage, were not reported.

PLCO study: The risk of having at least one false positive after four PSA tests was 12.9%. Almost 6% of men had at least one biopsy due to a false-positive result. Medical complications from the diagnostic procedures occurred in 68 of 10,000 evaluations after a positive result from screening. These complications were primarily infection, bleeding, clot formation, and urinary difficulties; relatively small in magnitude and unlikely to have a major impact on screening decision making if screening resulted in substantial mortality reduction.

## Worry and anxiety

Previous systematic reviews have found that worry and anxiety related to prostate cancer are increased among men and their partner due to screening *[Lin K, Lipsitz R, Miller T, Jahakieraman S. Benefits and harms of prostate-specific antigen screening for prostate cancer: an evidence update for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;149:192-9].*



BJUI

Critical role of prostate biopsy mortality in the number of years of life gained and lost within a prostate cancer screening programme

Mathieu Boniol, Peter Boyle, Philippe Autier, Alain Ruffion* and Paul Perrin*
International Prevention Research Institute (IPRI), Lyon, and *Hospices Civils de Lyon, Service d'Urologie Centre hospitalier Lyon-Sud, Pierre-Bénite, France
Accepted for publication 11 July 2012

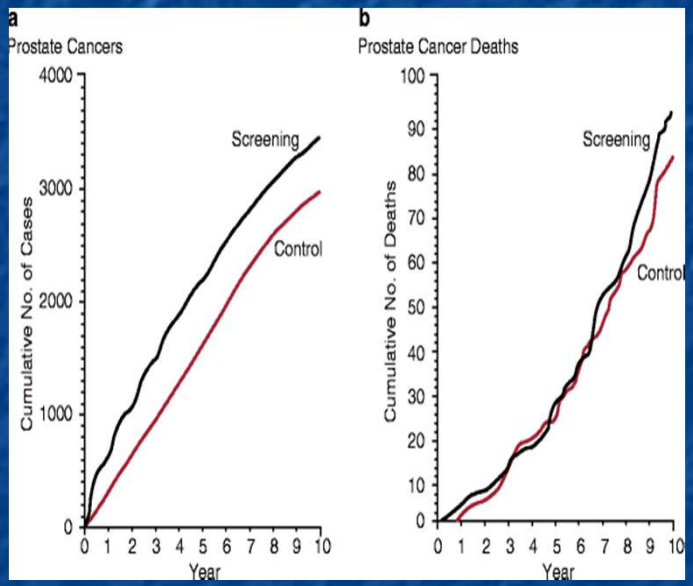
It should be kept in mind that the biopsy rate would also continue to increase in an ageing population, a population with an even higher risk associated with biopsy. The negative effects described in the present paper would then at least run in parallel and more likely increase, with a prolonged follow-up.

From the present evaluation under the best case scenario of the impact of prostate cancer screening, the implementation of PSA testing in the general population cannot be recommended as public health policy. Unless the mortality rate associated with prostate biopsy can be decreased, screening for prostate cancer with PSA should be discouraged.

Υπάρχει όφελος από την εφαρμογή του screening;

# Καρκίνος του προστάτη: screening και θνησιμότητα

- The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial: 76,693 men at 10 US centres to receive either annual screening with PSA and DRE, or standard care as the control. After 7 years' follow-up:




| | Screening group | Control group | Rate ratio |
|---|---|---|---|
| Incidence per 10,000 person-years | 116 (2,820 cases) | 95 (2,322 cases) | 1.22 |
| Incidence of death per 10,000 person-years | 2.0 (50 deaths) | 1.7 (44 deaths) | 1.13 |

PCa mortality is very low and not significantly different between the two study groups (LE: 1b)

*Andriole GL, et al. N Engl J Med 2009;360(13):1310-9*

Contamination rate for PSA testing in the control arm: 40% (1st year), 52% (6th year). Biopsy compliance: 40-52%

# Καρκίνος του προστάτη: screening και θνησιμότητα

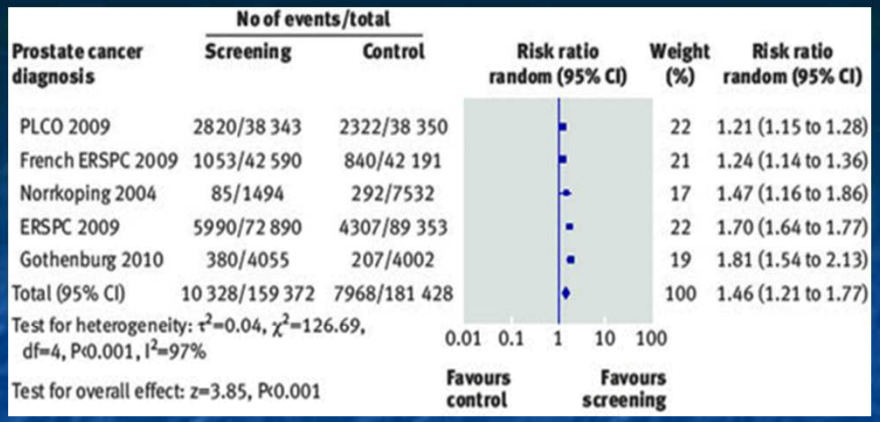
- The European Randomized Study of Screening for Prostate Cancer (ERSPC): 162,243 men from seven countries aged between 55 and 69 years randomly assigned to a group offered PSA screening at an average of once every 4 years or to an unscreened control group. During a median follow-up of 9 years:

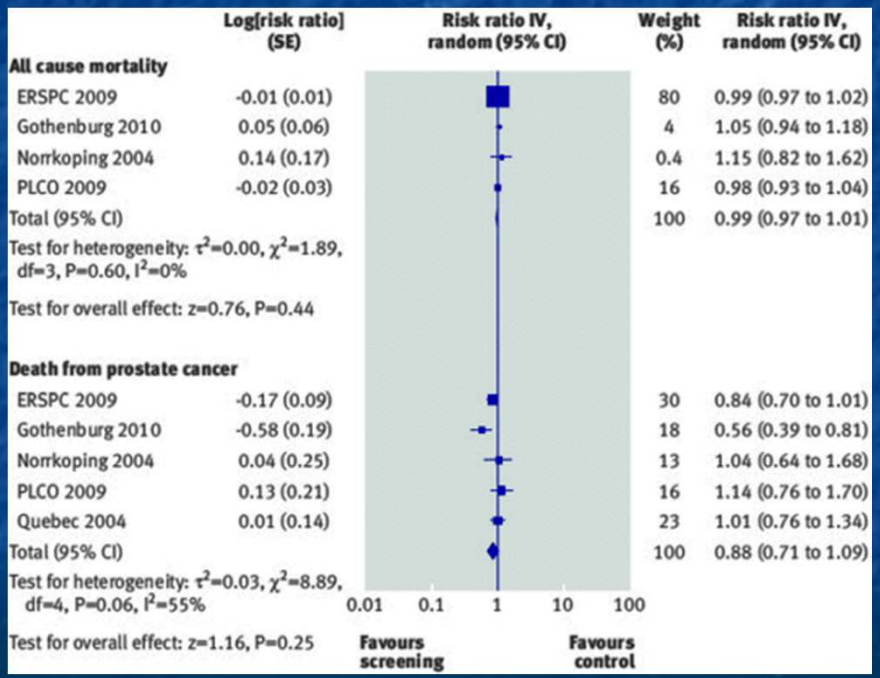
| | Screening group | Control group | Rate ratio |
|---|---|---|---|
| Cumulative Incidence | 8.2% | 4.8% | |
| Death from CaP | | | 0.80 |

Absolute risk difference: 0.71 deaths per 1.000 men, meaning that 1.410 men would need to be screened and 48 additional cases would need to be treated to prevent one death from PCa

PSA-based screening reduced the rate of death from PCa by 20%, but was associated with a high risk of over-diagnosis (LE: 1b)

*Schröder FH, et al. N Engl J Med 2009;360(13):1320-8*




Το screening σχετίζεται με αυξημένη πιθανότητα (RR = 1.46, range = 1.21–1.84) διάγνωσης προστατικού καρκίνου και διπλασιασμού της διάγνωσης ασθενών σταδίου 1.

Όμως, το screening δεν είχε σημαντική επίδραση στη πιθανότητα θανάτου από προστατικό καρκίνο (RR = 0.88, 95% CI = 0.71–1.09; P=0.25) ή την συνολική θνησιμότητα (RR = 0.99, 95% CI = 0.97–1.01; P = 0.44).

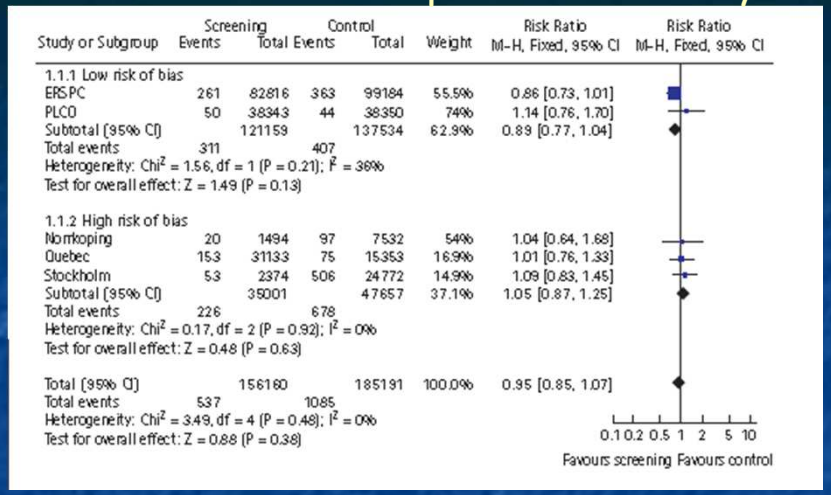
Όταν η θνησιμότητα αναλύθηκε σε διάφορες ομάδες ηλικιών ανά 5ετία στις ηλικίες 50-74 έτη, το screening είχε σαν αποτέλεσμα στατιστικά σημαντική ωφέλεια μόνο στην ομάδα ηλικιών 65–69.

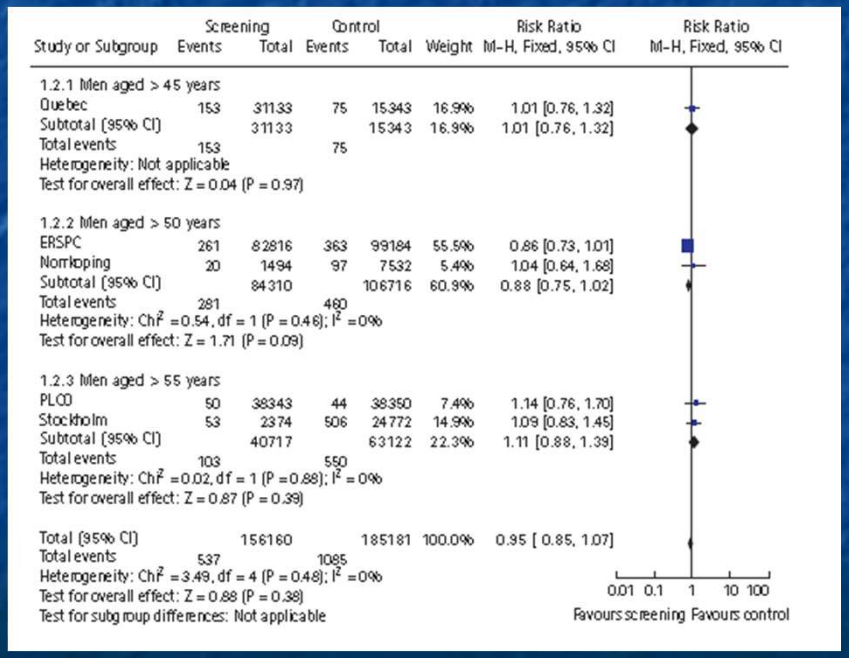
Η κάθε αιτίας θνησιμότητα δεν μειώθηκε σημαντικά σε κάποια ομάδα ηλικιών. Επίσης, τα αποτελέσματα δεν ήταν σημαντικά στις μελέτες στις οποίες πραγματοποιείτο δακτυλική εξέταση.

Οι μελετητές κατέληξαν ότι "οι υπάρχουσες αποδείξεις από τις τυχαιοποιημένες μελέτες δεν μπορούν να υποστηρίξουν την σε ρουτίνα χρήση του screening για τον προστατικό καρκίνο με PSA με ή χωρίς ΔΕΠ"

*Djulbegovic M, et al. BMJ. 2010;341:c4543*

# Prostate cancer-specific mortality




- Harms of screening included high rates of false-positive results for the PSA test, over-diagnosis and adverse events associated with transrectal ultrasonography guided biopsies such as infection, bleeding and pain.

## CONCLUSIONS

- Prostate cancer screening did not significantly decrease all-cause or prostate cancer-specific mortality in a combined meta-analysis of five RCTs.
- Any benefits from prostate cancer screening may take >10 years to accrue; therefore, men who have a life expectancy of <10–15 years should be informed that screening for prostate cancer is not beneficial and has harms.

*Ilic D, et al. Cochrane Database Syst Rev. 2010 (8).*
*Ilic D, et al. BJU Int. 2011;107(6):882-91*

# Επιβλαβή αποτελέσματα της υπερ-διάγνωσης

Η υπερ-διάγνωση αποτελεί μείζον πρόβλημα στους άνδρες που υποβάλλονται σε έλεγχο με PSA.
Μεταξύ άλλων, οι «υπερ-διαγιγνωσκόμενοι» ασθενείς υφίστανται ψυχολογικές βλάβες και ονοματίζονται "καρκινοπαθείς", κάτι που μπορεί να έχει και αρνητικές οικονομικές επιπτώσεις.

*Brawley OW, Ankers DP, Thompson IM. Screening for prostate cancer. CA Cancer J Clin. 2009;59: 264-73.*

# Επιβλαβή αποτελέσματα των θεραπειών

All therapies for localized prostate cancer can cause important harms

*Wilt TJ, et al. Ann Intern Med. 2008;148:435-48*

Death due to surgery occurs in approximately 0.5% of men and is high as 5% in older men or those with serious comorbidities

*Brawley OW, et al. CA Cancer J Clin. 2009;59: 264-73*
*Wilt TJ, et al. Med Care. 1999;37:1046-56*

Cardiovascular complications occur in 1-7% of Medicare eligible men

*Wilt TJ, et al. Med Care. 1999;37:1046-56.*
*Lu-Yao GL, et al. JAMA. 1993;269: 2633-6*

SPCG-4 study: η ριζική προστατεκτομή αυξάνει την πιθανότητα σεξουαλικής δυσλειτουργίας σε σχέση με τη προσεκτική παρακολούθηση (1.2–18.0 for specific domains), την πιθανότητα ακράτειας (18% έναντι 2%) και την ανησυχία (29% έναντι 9%).
Η προσεκτική παρακολούθηση σχετίσθηκε με χειρότερη λειτουργία του εντέρου.

*Steineck G, et al. N Engl J Med. 2002;347:790-6*

BMJ. 2013 Feb 6;346:f696. doi: 10.1136/bmj.f696.

**Long term harms after treatment for prostate cancer.**

[No authors listed]

Συγκριτική μελέτη της ποιότητας ζωής και της ικανοποίησης σε ασθενείς που υπεβλήθησαν σε χειρουργική επέμβαση, βραχυθεραπεία και ακτινοθεραπεία:

- Οι σημαντικές παρενέργειες ήταν σπάνιες
- Ολες οι θεραπευτικές παρεμβάσεις επηρρέασαν την σεξουαλική ζωή
- Η ριζική προστατεκτομή σχετίζεται με ακράτεια ούρων, αλλά παράλληλα βελτίωσε τα αποφρακτικά και ερεθιστικά LUTS
- Η βραχυθεραπεία και η εξωτερική ακτινοθεραπεία σχετίζεται με μείωση της σχετιζόμενης με την λειτουργία του εντέρου ποιότητας ζωής.
- Γενικά, οι ασθενείς υποτιμούν την επίδραση των επιπτώσεων των διαταραχών της σεξουαλικής ζωής, της ούρησης και της λειτουργίας του εντέρου στη ποιότητα ζωής γιατί επέλεξαν την όποια θεραπεία και πίστευαν ότι ήταν αναγκαία και αποτελεσματική.

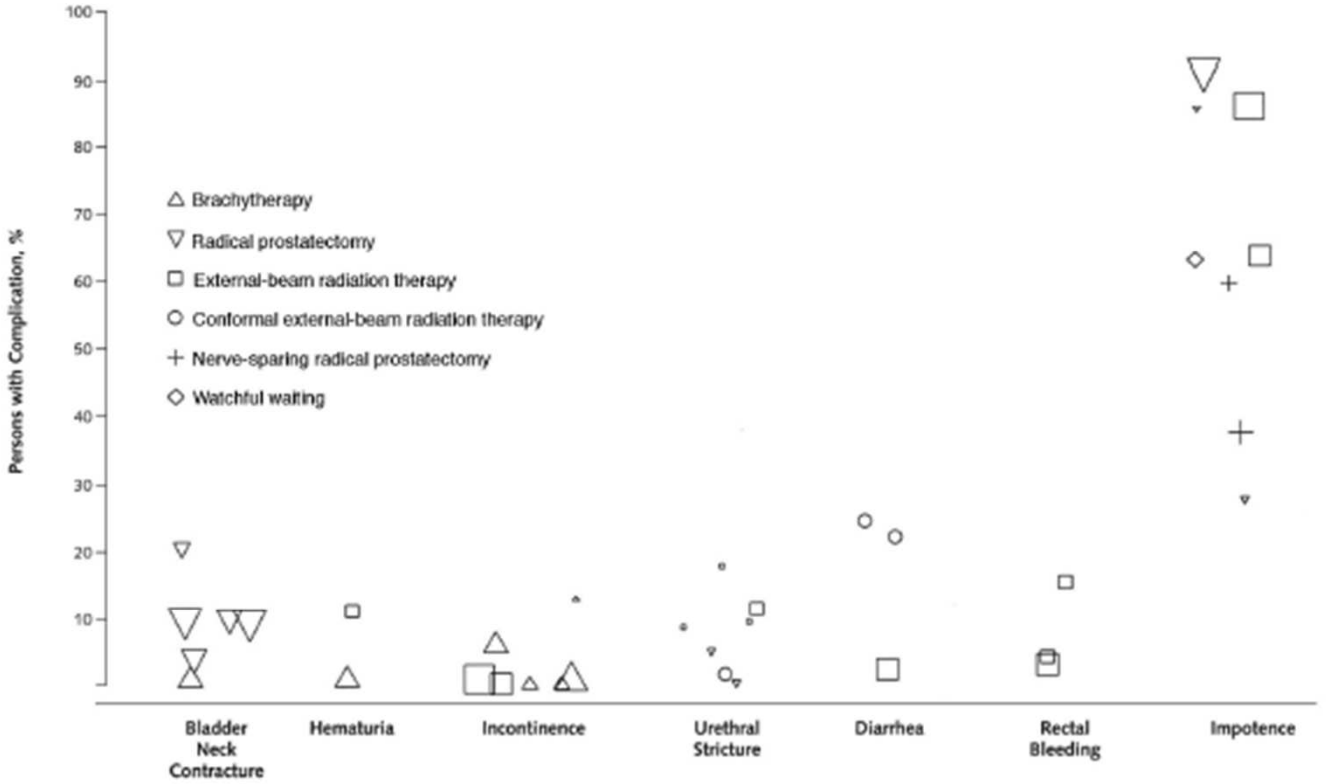
*Sanda MG, et al. Engl J Med. 2008;358:1250-61*

Annals of Internal Medicine | Review

# Systematic Review: Comparative Effectiveness and Harms of Treatments for Clinically Localized Prostate Cancer

Timothy J. Wilt, MD, MPH; Roderick MacDonald, MS; Indulis Rutks, BA; Tatyana A. Shamliyan, MD, MS; Brent C. Taylor, PhD; and Robert L. Kane, MD

*Figure 2.* Complications of brachytherapy, radical prostatectomy, external-beam radiation therapy, conformal external-beam radiation therapy, nerve-sparing radical prostatectomy, and watchful waiting from nonrandomized studies.




The symbol size is proportional to the number of patients: <50, 50–150, 150–300, or >300.

Ann Intern Med. 2008;148:435-448.

BJU Int. 2012 Oct;110 Suppl 1:3-7. doi: 10.1111/j.1464-410X.2012.011428.x.

# Landmarks in prostate cancer screening.

Schröder FH.

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## Abstract

• Prostate-specific antigen (PSA) has been widely applied to diagnosis and follow-up of prostate cancer, which led to research on its potential role in the early detection of the disease and its use in screening. • The value of PSA screening in reducing disease mortality is controversial and several studies have been conducted to determine the actual benefits. One of the early studies, the Tyrol Screening Study conducted in 1993, showed that during 2004 to 2008 there was a significant reduction in prostate cancer mortality in men aged >60 years compared with the mortality rate during 1989 to 1993. • Two studies that showed no benefit of screening in terms of prostate cancer death were conducted in Sweden in 1987 and 1988. • The Prostate, Lung, Colorectal, and Ovarian Screening Study conducted in the USA during 1993 to 2001 and involving 76,693 men showed no benefit of screening at 10 years but the trial can be criticised due to excessive contamination of the unscreened group. • In contrast, the European Randomized Study of Screening for Prostate Cancer (ERSPC), the largest randomised study with 162,388 participants study, showed that at a median follow-up of 9 years a prostate cancer mortality reduction of 20% resulted (P= 0.04). In an analysis limited to four ERSPC centres with a follow-up of 12.0 years, screening resulted in an overall reduction of metastatic disease of 31%. • The arguments against PSA screening include the risks associated with screening tests themselves, e.g. biopsy-related haematuria, urosepsis, and over diagnosis and overtreatment of prostate cancer. The overall evidence points in favour of PSA screening and steps can be taken to avoid overtreatment by offering patients active surveillance.

# Psychological aspects of active surveillance

Roderick C.N. van den Bergh[a,b], Ida J. Korfage[c], and Chris H. Bangma[a]

Curr Opin Urol 2012, 22:237–242

Το άγχος γιά τυχόν πρόοδο της νόσου σε μη θεραπεύσιμο στάδιο αποτελεί την κύρια αιτία απόρριψης της λύσης του active surveillance

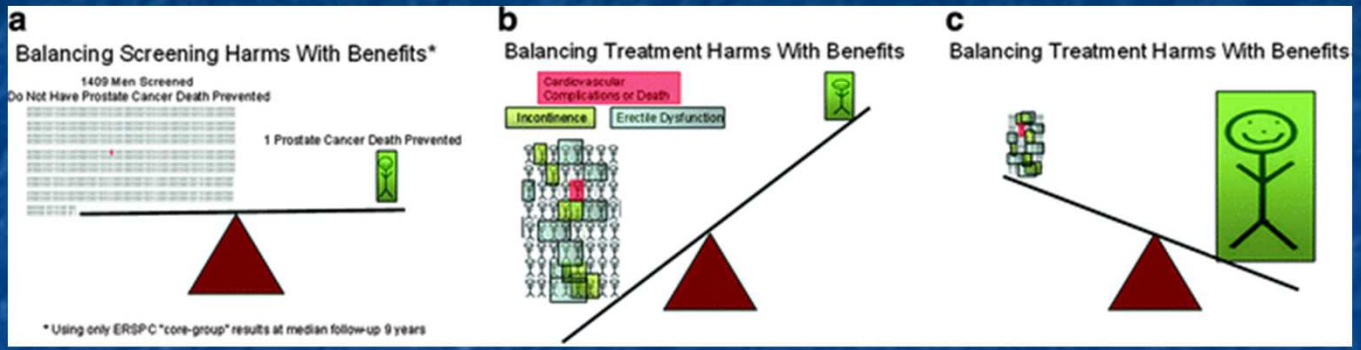
*Xu J et al. J Natl Med Assoc 2011; 103:68-478*
*Steringe SK et al. World J Urol 2008; 26:469-474*

Μετά την επιλογή της λύσης του active surveillance οι περισσότεροι ασθενείς είναι ικανοποιημένοι με την επιλογή τους και λίγοι φοβούνται τυχόν πρόοδο της νόσου.
Ο ψυχολογικός παράγοντας αποτελεί αιτία εγκατάλειψης αυτής της επιλογής

*Latini DM et al. J Urol 2007; 178:826-831*

Observations on the QoL effects and psychological aspects of this strategy are still scarce and short term, but may prove to be crucial factors in choosing and undergoing active surveillance for patients and physicians.


# *Deciding about screening*




Balancing screening and treatment benefits and harms: assessing screening net benefit requires evaluating and weighting benefits and harms of screening and treatment. Using only ERSPC core group results, 1,409 men would be screened without benefit and 1 man would have prostate cancer death prevented by screening at a median follow-up of 9 years. Harms are of small-to-moderate severity and include anxiety from false-positive screening results, pain, bleeding, and infection from prostate biopsies and diagnosis of cancers that would not cause health problems (over-diagnosis). Among men with ERSPC screen detected prostate cancer, 48 would require treatment to prevent 1 prostate cancer death. Adverse effects of treatment include cardiovascular complications, erectile dysfunction, and incontinence. The balance of benefits and harms depends on an individual weighting of adverse effects that are frequent, occur early, often persist, and are of moderate severity vs. preventing an infrequent prostate cancer death that would not occur for many years but is of large health importance. When using results from all randomized screening trials or from any individual screening trial according to all-men randomized, there is no reduction in overall or prostate cancer-specific mortality

# Συστάσεις γιά προσυμπτωματικό έλεγχο του καρκίνου του προστάτη

Οι περισσότερες, αν όχι όλες οι μεγαλύτερες ουρολογικές εταιρείες συστήνουν ότι προς το παρόν το mass screening γιά τον προστατικό καρκίνο δεν ενδείκνυται.
Αντ' αυτού, η πρώιμη διάγνωση (opportunistic screening) θα πρέπει να προτείνεται σε καλά ενημερωμένους άνδρες.

United States Preventive Services Task Force (USPSTF):

- for men younger than age 75 years, the balance of benefits and harms could not be determined
- For men aged 75 years and older or for those whose life expectancy is 10 years or less, recommended against routine screening (D recommendation) because there was moderate certainty that the harms of screening for prostate cancer outweighed the benefits.

# *ὠφελέειν, ἢ μὴ βλάπτειν*