



# Nutzen und Schaden von PSA-Screening



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‘All screening programs do harm;  
some do good as well.’

Gray JAM. New concepts in screening. Br J Gen Pract 2004; 54:  
292-8.

## *Primum Non Nocere* and the Quality of Evidence: Rethinking the Ethics of Screening

Ewart RM. J Am Board Fam Pract 2000; 13: 188-96.

‘Because most of the harms of screening fall on the healthy and **because screening is initiated by physicians**, nonmaleficence takes precedence over beneficence. ... that these ethical implications require that screening programs be backed up by better evidence than is the usual case for investigative medicine.’

## Mögliche Ausgänge eines Screening-Tests

richtig positiv (rp)	falsch positiv (fp)
falsch negativ (fn)	richtig negativ (rn)

rp

Frühzeitige(re) Intervention/Therapie führt zu besseren  
Ergebnissen als späte(re) Intervention/Therapie

rn

Beruhigung

Aber: gar nicht nachgefragt!  
(‘because screening is initiated by physicians’)

Wozu jemand beruhigen, der gar nicht beunruhigt ist?

fp

Einschränkung der Lebensqualität

Ggf. unnötige Folgediagnostik mit ihren Risiken oder  
gar falsche Therapie mit ihrem Schadenspotenzial

## False-positive screening results in the European randomized study of screening for prostate cancer

Tuomas P. Kilpeläinen <sup>a,b,\*</sup>, Teuvo L.J. Tammela <sup>a</sup>, Monique Roobol <sup>c</sup>, Jonas Hugosson <sup>d</sup>, Stefano Ciatto <sup>e</sup>, Vera Nelen <sup>f</sup>, Sue Moss <sup>g</sup>, Liisa Määttänen <sup>h</sup>, Anssi Auvinen <sup>b</sup>

Our aggregate results from the ERSPC trial confirm that FP results are common in PC screening – one in six men have at least one FP result during the screening protocol. Three quarters of them have only one FP, but 25% have two or three.

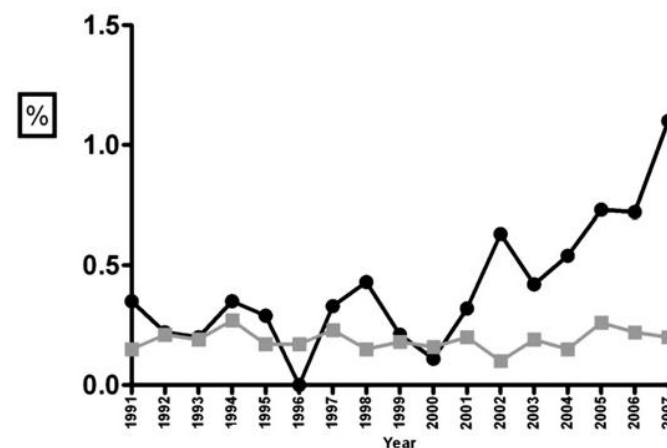
[Eur J Cancer 2011; doi:10.1016/j.ejca.2011.06.055](https://doi.org/10.1016/j.ejca.2011.06.055)

## Complications After Prostate Biopsy: Data From SEER-Medicare

Stacy Loeb,\* H. Ballentine Carter, Sonja I. Berndt, Winnie Ricker  
and Edward M. Schaeffer

‘... our results indicate that ... the rate of hospitalization within 30 days of prostate biopsy was more than double that in a control population. ..., the number needed to harm would be 24, ie **1 additional hospitalization within 30 days for each 24 prostate biopsies.**

### Hospitalisationen wegen Infektion



J Urol 2011; 186: 1830-4

## Increasing Hospital Admission Rates for Urological Complications After Transrectal Ultrasound Guided Prostate Biopsy

Robert K. Nam,<sup>\*,†</sup> Refik Saskin,<sup>†</sup> Yuna Lee,<sup>†</sup> Ying Liu,<sup>†</sup> Calvin Law,<sup>†</sup> Laurence H. Klotz,<sup>‡</sup> D. Andrew Loblaw,<sup>†</sup> John Trachtenberg,<sup>†</sup> Aleksandra Stanimirovic,<sup>†</sup> Andrew E. Simor,<sup>†</sup> Arun Seth,<sup>†</sup> David R. Urbach<sup>†</sup> and Steven A. Narod<sup>†</sup>

*From the Division of Urology (RKN, LHK, AS), Division of General Surgery (CL), Department of Microbiology and Division of Infectious Diseases (AES), Department of Radiation Oncology (DAL) and Division of Molecular and Cellular Biology (AS), Sunnybrook Research Institute; and Division of General Internal Medicine, St. Michael's Hospital (YL); Institute of Clinical Evaluative Sciences (RS, YL); Division of Urology (JT), Division of General Surgery (DRU), University Health Network; Department of Public Health Sciences (SAN); and Department of Health Policy Management and Evaluation (RKN, CL, DRU), University of Toronto, Toronto, Ontario, Canada*

**Conclusions:** The hospital admission rates for complications following transrectal ultrasound guided prostate biopsy have increased dramatically during the last 10 years primarily due to an increasing rate of infection related complications.

J Urol 2010; **183**: 963-8

## COMPLICATION RATES AND RISK FACTORS OF 5802 TRANSRECTAL ULTRASOUND-GUIDED SEXTANT BIOPSIES OF THE PROSTATE WITHIN A POPULATION-BASED SCREENING PROGRAM

RENÉ RAAIJMAKERS, WIM J. KIRKELS, MONIQUE J. ROOBOL, MARK F. WILDHAGEN,  
AND FRITZ H. SCHRÖDER

**TABLE III.** *Review of recently published studies*

Investigator	Year	Men (n)	Biopsy Cores (n)	Enema	AB	Fever (%)	Adm (%)	HU (%)	HS (%)	RB (%)	RET (%)
Rietbergen <sup>6</sup>	1997	1687	6–7	No	Yes	4.2	0.4	23.6	45.4	1.7	0.4
Sieber <sup>15</sup>	1997	4439	6–8	No	Yes	NA	<0.1	NA	NA	NA	NA
Enlund <sup>16</sup>	1997	426	1–8	Yes	No	2.9	0.7	21	NA	21.7	0.2
Rodriguez <sup>8</sup>	1998	129	6–?	Yes	Yes	1.7	0.8	47.1	9.1	8.2	1.6
Deliveliotis <sup>3</sup>	1999	120	6	No*	Yes	6.6	1.6	10.0	29.1	33.3	4.6
Manseck <sup>20</sup>	2000	162	10	NA	Yes	0.6	0	17.9	19.8	4.9	0
Djavan <sup>18</sup>	2001	1015	8	NA	Yes	3.0	NA	15.9	9.8	2.1	2.6
Peyromaure <sup>7</sup>	2002	289	10	Yes	Yes	3.7	0	74.4	78.3 <sup>†</sup>	39.6	NA
Present	2002	5802	6–7	No	Yes	3.5	0.5	22.6	50.4	1.3	0.4

KEY: AB = antibiotics; Adm = admission at hospital; HU = hematuria; HS = hematospermia; RB = rectal bleeding; RET = urinary retention; NA = not available.

\* No enema but investigators cleaned anterior rectal wall with antiseptic.

<sup>†</sup> Percentage with HS of men who reported sexual intercourse.



Nur ein Teil der Patienten profitiert

Ggf. überflüssige Therapie mit ihrem Schadenspotenzial

Problem: Geschädigte Patienten in der Regel nicht  
identifizierbar

**Schadenspotenzial abstrakt**

## 'Results

In the screening group, 82% of men accepted at least one offer of screening. During a median follow-up of 9 years, the cumulative incidence of prostate cancer was 8.2% in the screening group and 4.8% in the control group. The rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.80 (95% confidence interval [CI], 0.65 to 0.98; adjusted  $P = 0.04$ ). **The absolute risk difference was 0.71 death per 1000 men. This means that 1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer.**

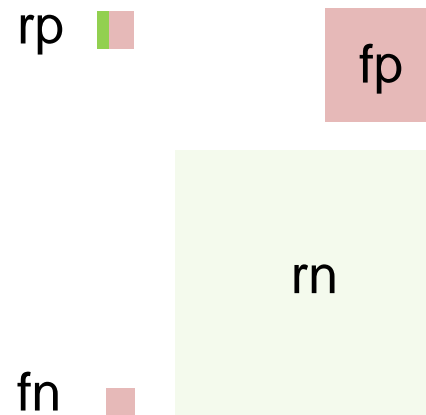
## Conclusions

PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with **a high risk of overdiagnosis.**'

N Engl J Med 2009; **360**: 1320-8

fn

Falsche „Beruhigung“



- Möglicher Nutzen
- Möglicher Schaden



UK Screening Portal

Home UK N

## The Screening programme

13 There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.

## The Treatment

10 There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

## The Test

5 There should be a simple, safe, precise and validated screening test

## Chou R et al. Screening for Prostate Cancer. A Review of the Evidence for the U.S. Preventive Services Task Force.

Ann Intern Med 2011; doi:10.1059/0003-4819-155-11-201112060-00375

<b>Death</b>		
ERSI		1.01)
Goth		0.81)
Norm		o 1.68)
PLCC		o 1.70)
Quel		o 1.34)
<b>Total (95% CI)</b>	<b>100</b>	<b>0.88 (0.71 to 1.09)</b>

Test for heterogeneity:  $\tau^2=0.03$ ,  $\chi^2=8.89$ ,  
df=4, P=0.06,  $I^2=55\%$



Test for overall effect: z=1.16, P=0.25

**‘Prostate-specific antigen–based screening results in small or no reduction in prostate cancer–specific mortality ...’**

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

‘It is interesting to note that the review notes that none of the studies reviewed reported the adverse effects associated with screening for Prostate Cancer. As physicians we must do no harm but I question how researches can morally and ethically conduct studies without reviewing this outcome? Labelling more and more patients with "early stage" or "localised" Prostate Cancer merely creates worry for them, anxiety for us and costs for the Health service. The quality of the research also highlights that once again we are not practicing evidence based medicine.’

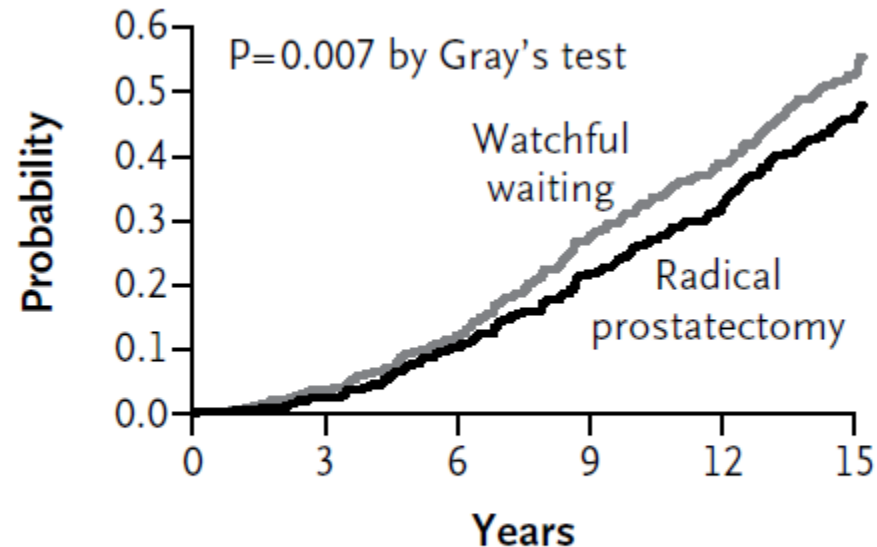
Samuel DG. Rapid Response to Djulbegovic et al. 2010.

Evidenzbasis für die Behandlung des lokal begrenzten Prostatakarzinoms (RCTs zum Vergleich verschiedener Strategien):

Bill-Axelson 2011 (SPCG-4)	Skand.	RP vs. WW	1989-1999	695 (698)	OS: RP > WW PCS: RP > WW
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**Weltweit 700 Patienten**

## A Death from Any Cause, Total Cohort

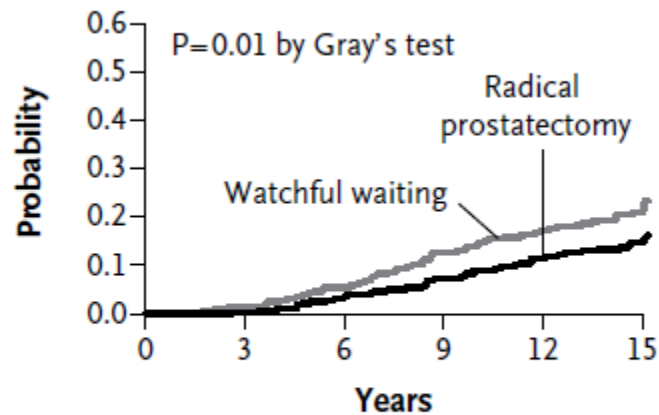


### No. at Risk

Radical prostatectomy	347	339	311	271	214	109
Watchful waiting	348	334	306	251	192	96

Bill-Axelsson et al. N Engl J Med 2011; 364: 1708-17

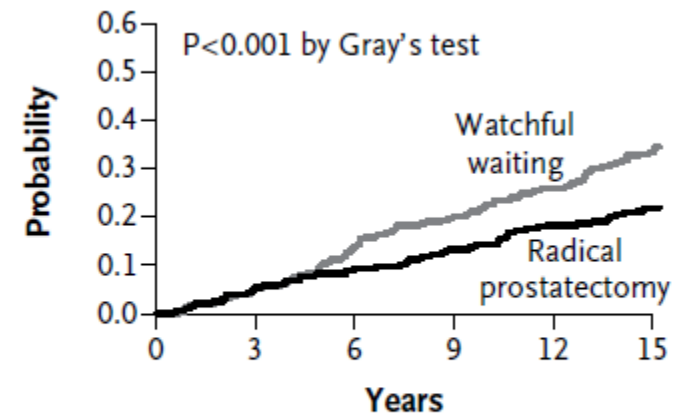
## B Death from Prostate Cancer, Total Cohort



### No. at Risk

Radical prostatectomy	347	339	311	271	214	109
Watchful waiting	348	334	306	251	192	96

## C Metastases, Total Cohort

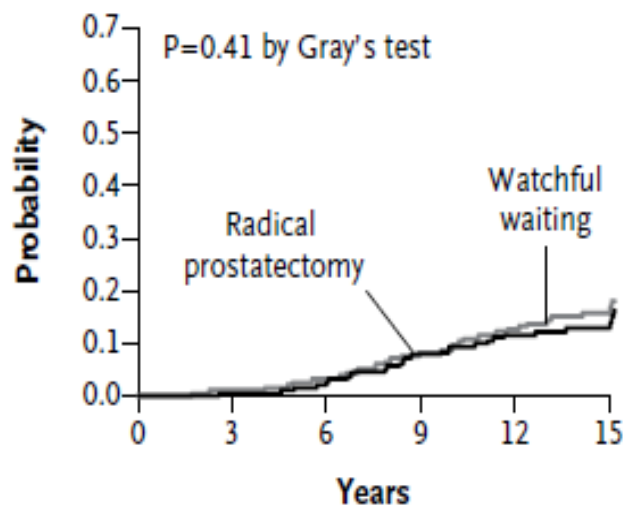


### No. at Risk

Radical prostatectomy	347	323	291	252	194	99
Watchful waiting	348	322	281	229	173	78

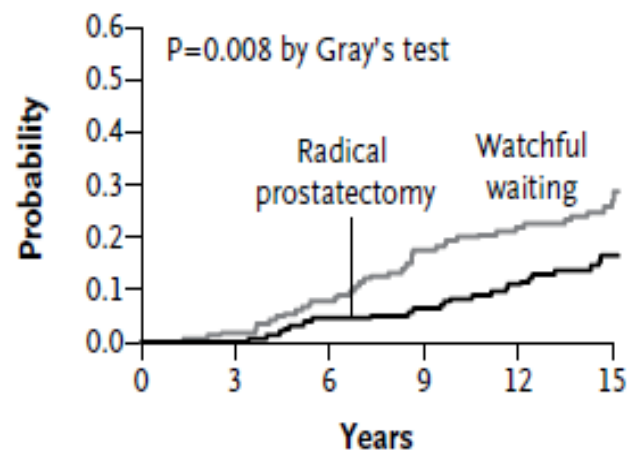
Bill-Axelson et al. N Engl J Med 2011; 364: 1708-17

## E Death from Prostate Cancer, Men ≥65 Yr of Age



No. at Risk		0	3	6	9	12	15
Radical prostatectomy	190	185	166	135	99	42	
Watchful waiting	182	177	162	133	101	42	

## H Death from Prostate Cancer, Men <65 Yr of Age



No. at Risk		0	3	6	9	12	15
Radical prostatectomy	157	154	145	136	115	67	
Watchful waiting	166	157	144	118	91	54	

Bill-Axelsson et al. N Engl J Med 2011; 364: 1708-17

## Limitations

It is unclear whether these results would apply to today's Western male populations, who, unlike the men in the SPCG-4 trial, are diagnosed with prostate cancer mainly by prostate-specific antigen screening.

*From the Editors*

*Zu Bill-Axelsson et al. J Natl Cancer Inst 2008; 100: 1144-54*

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*From the Editors*

Characteristic	All ages	
	Radical prostatectomy (n = 347)	Watchful waiting (n = 348)
Method of detection, No. (%)		
Opportunistic screening‡	18 (5.2)	18 (5.2)
Coincidental§	87 (25.1)	91 (26.1)
TURP	40 (11.5)	56 (16.1)
Symptoms	152 (43.8)	138 (39.7)
Other	49 (14.1)	44 (12.6)
Unknown	1 (0.3)	1 (0.3)

Bill-Axelsson et al. J Natl Cancer Inst 2008; 100: 1144-54

# Aber ... ?

End Point	Cumulative Incidence		Absolute Risk Reduction with Radical Prostatectomy
	Radical Prostatectomy*	Watchful Waiting†	percentage points (95% CI)
	% (95% CI)		
<div style="border: 1px solid black; padding: 5px; width: fit-content;">                     PSA &lt; 10 ng/ml und Gleason &lt; 7 oder WHO-Grad 1                 </div>			
<b>Death from any cause</b>			
All	46.1 (40.8 to 52.0)	52.7 (47.4 to 58.6)	6.6 (-1.3 to 14.5)
Low-risk cancer	31.4 (23.9 to 41.3)	44.6 (36.6 to 54.4)	<b>13.2</b> (0.9 to 25.5)
<b>Death from prostate cancer</b>			
All	14.6 (11.2 to 19.1)	20.7 (16.7 to 25.6)	6.1 (0.2 to 12.0)
Low-risk cancer	6.8 (3.5 to 13.5)	11.0 (6.8 to 17.8)	<b>4.2</b> (-2.9 to 11.2)

Bill-Axelsson et al. N Engl J Med 2011; 364: 1708-17

# Aber ... ?

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<b>Death from any cause</b>			
All	46.1 (40.8 to 52.0)	52.7 (47.4 to 58.6)	6.6 (-1.3 to 14.5)
Low-risk cancer	31.4 (23.9 to 41.3)	44.6 (36.6 to 54.4)	13.2 (0.9 to 25.5)
<b>Age &lt;65 yr and low-risk cancer</b>	<b>16.9 (9.5 to 30.1)</b>	<b>36.2 (26.1 to 50.2)</b>	<b>19.3 (4.0 to 34.7)</b>
<b>Death from prostate cancer</b>			
All	14.6 (11.2 to 19.1)	20.7 (16.7 to 25.6)	6.1 (0.2 to 12.0)
Low-risk cancer	6.8 (3.5 to 13.5)	11.0 (6.8 to 17.8)	4.2 (-2.9 to 11.2)
<b>Age &lt;65 yr and low-risk cancer</b>	<b>7.1 (2.7 to 18.6)</b>	<b>11.6 (6.0 to 22.4)</b>	<b>4.5 (-5.7 to 14.8)</b>

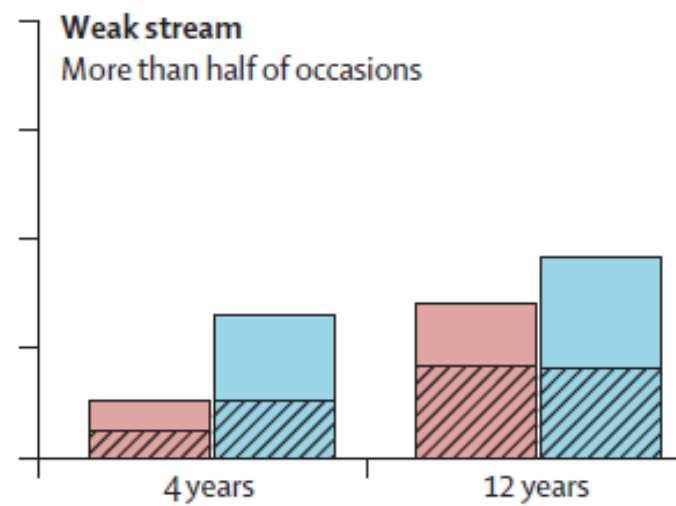
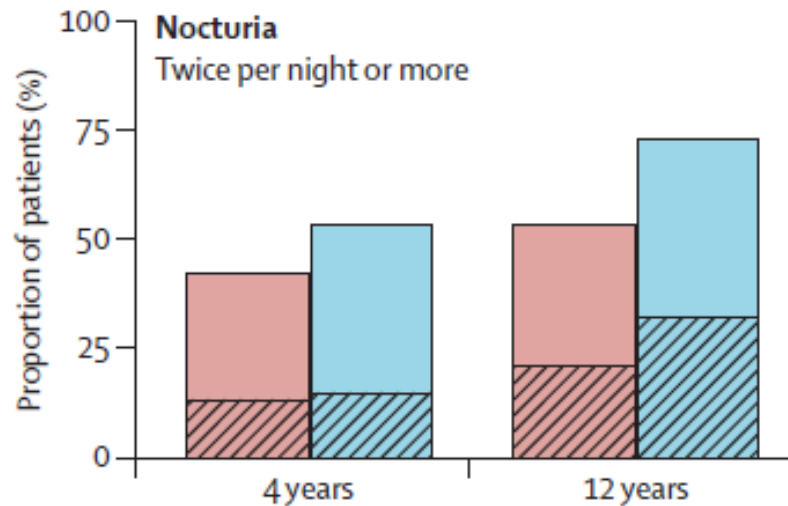
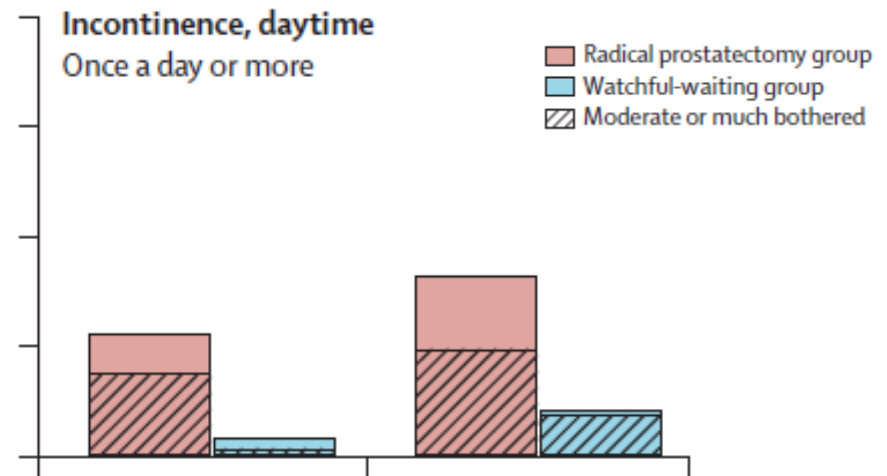
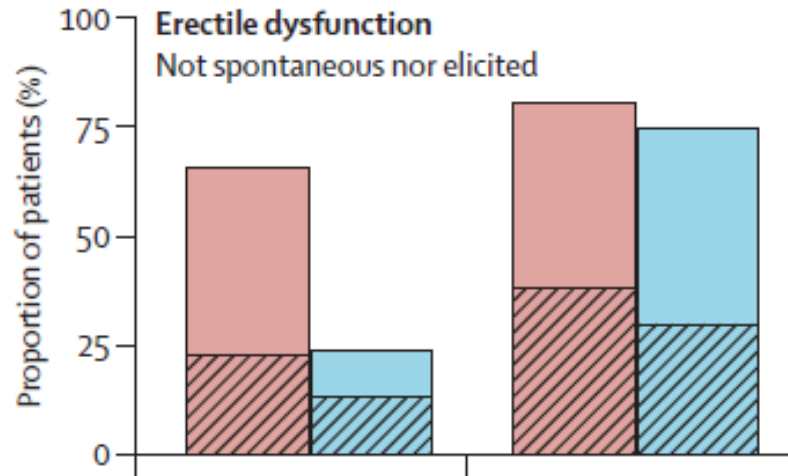
Bill-Axelsson et al. N Engl J Med 2011; 364: 1708-17

**Table 3. Nonfatal Surgical Complications within 1 Year after Surgery among Men in the Radical-Prostatectomy Group.\***

<b>Complication</b>	<b>No. of Events</b>	<b>1-Year Cumulative Incidence (95% CI)</b>
Urinary leakage	93	32.2 (27.2–38.1)
Urinary obstruction	6	2.1 (0.9–4.6)
Impotence	168	58.1 (52.7–64.1)
Pulmonary embolism	4	1.4 (0.5–3.7)
Deep-vein thrombosis	3	1.0 (0.3–3.2)
Myocardial infarction	0	NA

Bill-Axelson et al. N Engl J Med 2011; 364: 1708-17

# SPCG-4: Schaden



Johansson et al. Lancet Oncol 2011; 12: 891-9

Chou R et al. Screening for Prostate Cancer. A Review of the Evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2011; doi:10.1059/0003-4819-155-11-201112060-00375

‘In the cohort studies, the median rate of **urinary incontinence** with watchful waiting was 6% (range, 3% to 10%), with prostatectomy associated with **a median increase in absolute risk of 18 percentage points** (range, 8 to 40 percentage points).

In the cohort studies, the median rate of **erectile dysfunction** with watchful waiting was 52% (range, 26% to 68%), with prostatectomy associated with **a median increase in absolute risk of 26 percentage points** (range, 21 to 29 percentage points).’

The cumulative incidence of side effects of surgery reflects a situation in which, historically, the need for radical excision of the tumor dictated extensive surgery more often than is the case today. Furthermore, the surgical techniques were not as well developed, and the number of surgeries performed was far from today's levels.

Bill-Axelsson et al. N Engl J Med 2011; 364: 1708-17

Wilt T et al. Systematic Review: Comparative Effectiveness and Harms of Treatments for Clinically Localized Prostate Cancer. Ann Intern Med 2008; 148: 435-48

‘Primary androgen deprivation, cryotherapy, brachytherapy, intensity-modulated radiation therapy, proton-beam radiation therapy, and laparoscopic and robotic-assisted radical prostatectomy have not been evaluated in randomized trials, despite their widespread use.’

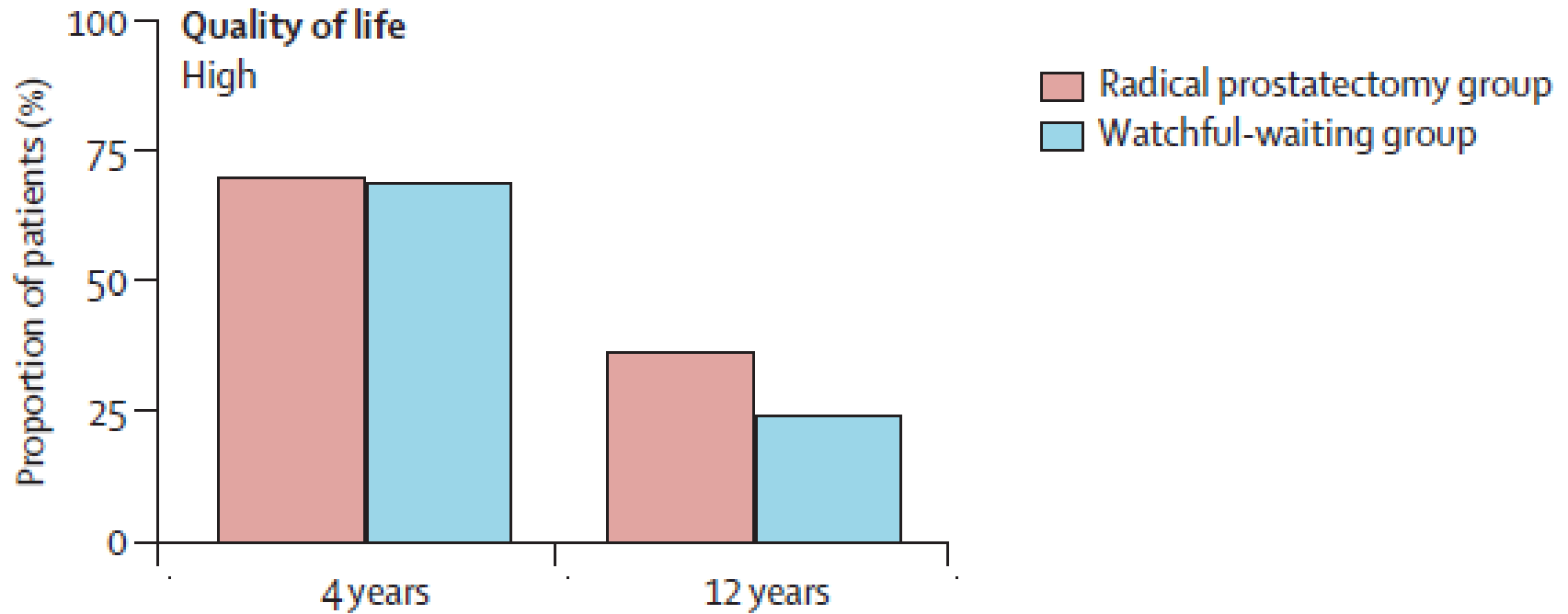
Chou R et al. Screening for Prostate Cancer. A Review of the Evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2011; doi:10.1059/0003-4819-155-11-201112060-00375

‘We found little evidence with which to evaluate newer techniques for prostatectomy (including nerve-sparing approaches that use laparoscopy, either robotic-assisted or free-hand) compared with watchful waiting, **but found no pattern suggesting that more recent studies reported different risk estimates than older studies.**’

Chou R et al. Screening for Prostate Cancer. A Review of the Evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2011; doi:10.1059/0003-4819-155-11-201112060-00375

‘We found little evidence with which to evaluate newer techniques for prostatectomy (including nerve-sparing approaches that use laparoscopy, either robotic-assisted or free-hand) compared with watchful waiting, but found no pattern suggesting that more recent studies reported different risk estimates than older studies.’

‘Prostatectomy was also associated with perioperative (30-day) mortality (about 0.5%) and cardiovascular events (0.6% to 3%), ...’



Johansson et al. Lancet Oncol 2011; 12: 891-9

Korfage IJ et al. Patients' perceptions of the side-effects of prostate cancer treatment – A qualitative interview study. Soc Sci Med 2006; 63: 911-9

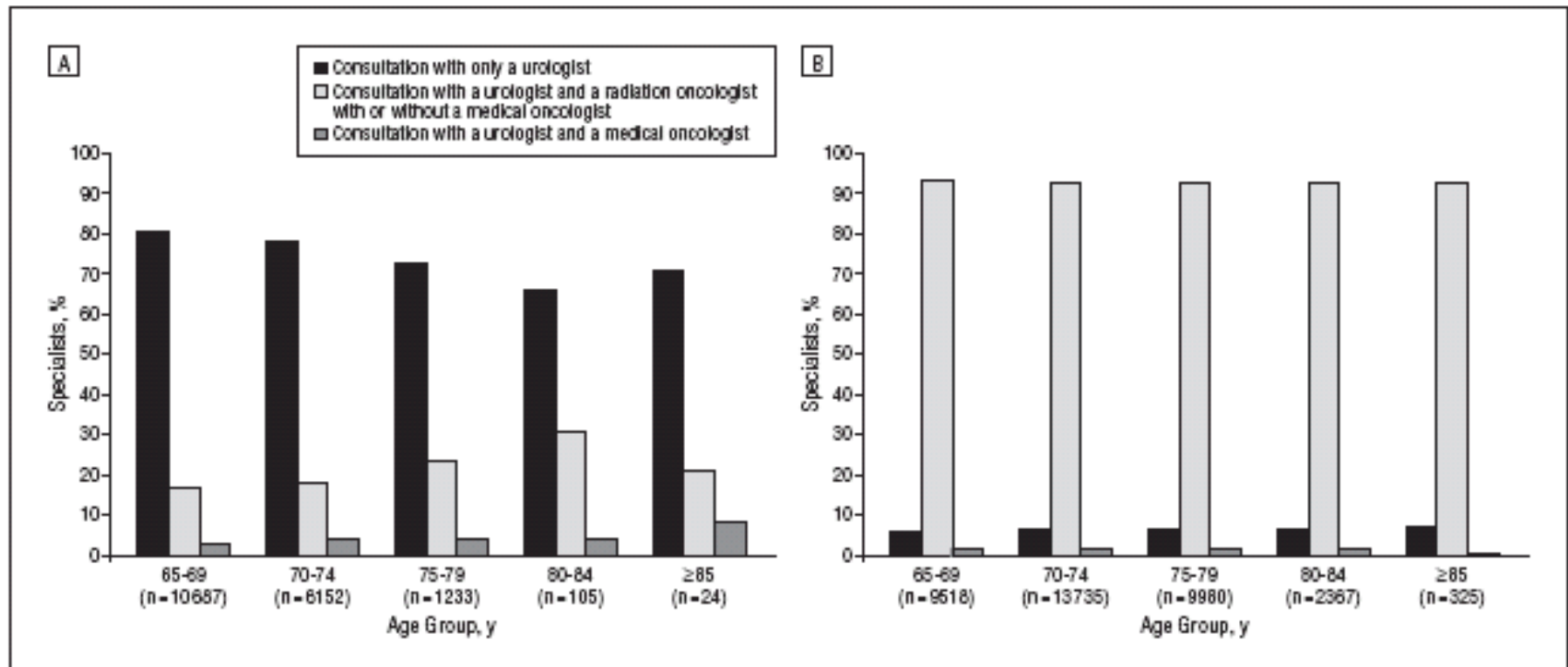
'Many patients accepted the side effects as inevitable consequences of having been treated for prostate cancer, a condition they perceived as life threatening. We conclude that generic QoL measures cannot reveal the impact of sexual, urinary and bowel dysfunctions on patients because such dysfunctions are not perceived as health problems. By presenting these findings we want to draw attention to issues that complicate QoL assessments in general and in prostate cancer patients in particular.'

Wilt T et al. Systematic Review: Comparative Effectiveness and Harms of Treatments for Clinically Localized Prostate Cancer. Ann Intern Med 2008; 148: 435-48

‘Assessment of the comparative effectiveness and harms of localized prostate cancer treatments is difficult because of limitations in the evidence.’

## Physician Visits Prior to Treatment for Clinically Localized Prostate Cancer

Lang et al. Arch Intern Med 2010; 170: 440-50



**Figure 2.** Specialists who were consulted prior to definitive treatment for 18 201 men who had a radical prostatectomy (A) and 35 925 men who had radiation therapy (B). Missing physician specialty codes on claims for radiotherapy accounted for the 7% of patients who received radiotherapy but for whom a visit with a radiation oncologist could not be identified.

## Physician Visits Prior to Treatment for Clinically Localized Prostate Cancer

Lang et al. Arch Intern Med 2010; 170: 440-50

**Table 5. Primary Treatment for Medicare Beneficiaries Diagnosed as Having Clinically Localized Prostate Cancer, According to Primary Care Physician Visit, Patient Age, and Patient Comorbidity Index<sup>a</sup>**

Physician Visited	Primary Treatment, % of Patients			
	Radical Prostatectomy	Radiation Therapy	Primary Androgen Deprivation Therapy	Expectant Management
PCP Visit (n=14 599)				
Age/Comorbidity Index score				
65-69 y (n=2257)				
0 (n=1717)	28.6	6.9	6.8	57.7
1 (n=342)	18.4	6.4	8.2	67.0
≥2 (n=198)	9.1	4.6	13.6	72.7
No PCP Visit (n=70 489)				
Age/Comorbidity Index score				
65-69 y (n=2257)				
0 (n=18 624)	48.4	40.3	4.7	6.6
1 (n=2539)	35.6	51.4	7.5	5.5
≥2 (n=923)	22.2	59.6	11.4	6.8

<b>Studie</b>	<b>Land</b>	<b>Arme</b>	<b>Rekrut.</b>	<b>Plan</b>	<b>Random.</b>
PIVOT	USA	RP vs. WW	1994-2002	1050	731
ProtecT Pilot	UK	RP vs. PST vs. AS	1999-2001	?	114
ProtecT	UK	RP vs. PST vs. AS	2001-2009	?	(700)
START	USA, Kanada, UK	RP, PST, BT vs. AS	2007-?	2130	?
SABRE	Kanada, UK	RP vs. BT	2008-2012	400	?

RP = Radikale Prostatektomie

PST = Perkutane Strahlentherapie

BT = Brachytherapie

WW = Watchful Waiting

AS = Active Surveillance

Studie	Land	Arme	Rekrut.	Plan	Random.
PIVOT	USA	RP vs. WW	1994-2002	1050	731
ProtecT Pilot	UK	RP vs. PST vs. AS	1999-2001	?	114
ProtecT	UK	RP vs. PST vs. AS	2001-2009	?	(700)
START	USA, Kanada, UK	RP, PST, BT vs. AS	2007-?	2130	?
SABRE	Kanada, UK	RP vs. BT	2008-2012	400	?
<b>PREFERE</b>	<b>D</b>	<b>RP vs. PST vs. BT vs. AS</b>	<b>? 2012-?</b>	<b>7000</b>	<b>?</b>

RP = Radikale Prostatektomie

PST = Perkutane Strahlentherapie

BT = Brachytherapie

WW = Watchful Waiting

AS = Active Surveillance

Ärzte Zeitung vom 15.09.2011

# ÄRZTE & ZEITUNG

**Seite:** 10  
**Ressort:** Medizin  
**Gattung:** Tageszeitung

**Jahrgang:** 2011  
**Nummer:** 164  
**Auflage:** 58.380 (gedruckt) 10.481 (verkauft)  
57.933 (verbreitet)

## Studie zu Prostata-Ca - und alle machen mit

Welche von vier Therapieoptionen bei lokal begrenztem Prostatakrebs ist die optimale? Antworten auf diese Frage soll eine Studie geben, an der viele Stellen im Gesundheitswesen beteiligt sind: Fachgesellschaften, GKV-Spitzenverband, IQWiG und G-BA.

‘Das Akronym **PREFERE** steht für "PREFEREnce based randomized evaluation of treatment modalities in low or early intermediate risk prostate cancer" und bedeutet, dass sowohl die Präferenzen der Patienten gewahrt werden als auch die Randomisierung auf die Therapiemöglichkeiten erfolgt.’

Die muss womöglich jeder selbst für sich treffen

‘I never dreamed that my discovery four decades ago would lead to such a profit-driven **public health disaster**. The medical community must confront reality and stop the inappropriate use of P.S.A. screening. Doing so would save billions of dollars and rescue millions of men from unnecessary, debilitating treatments.’

Richard J Ablin, Entdecker des PSA

20.03.2010, New York Times, The great prostate mistake

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**Danke!**