Lo screening per il cancro della prostata

è utile? Quando? (e come?)

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IL TRATTAMENTO DEL CARCINOMA PROSTATICO:
ASPETTI CONTROVERSI – 20 giugno 2014 - Perugia

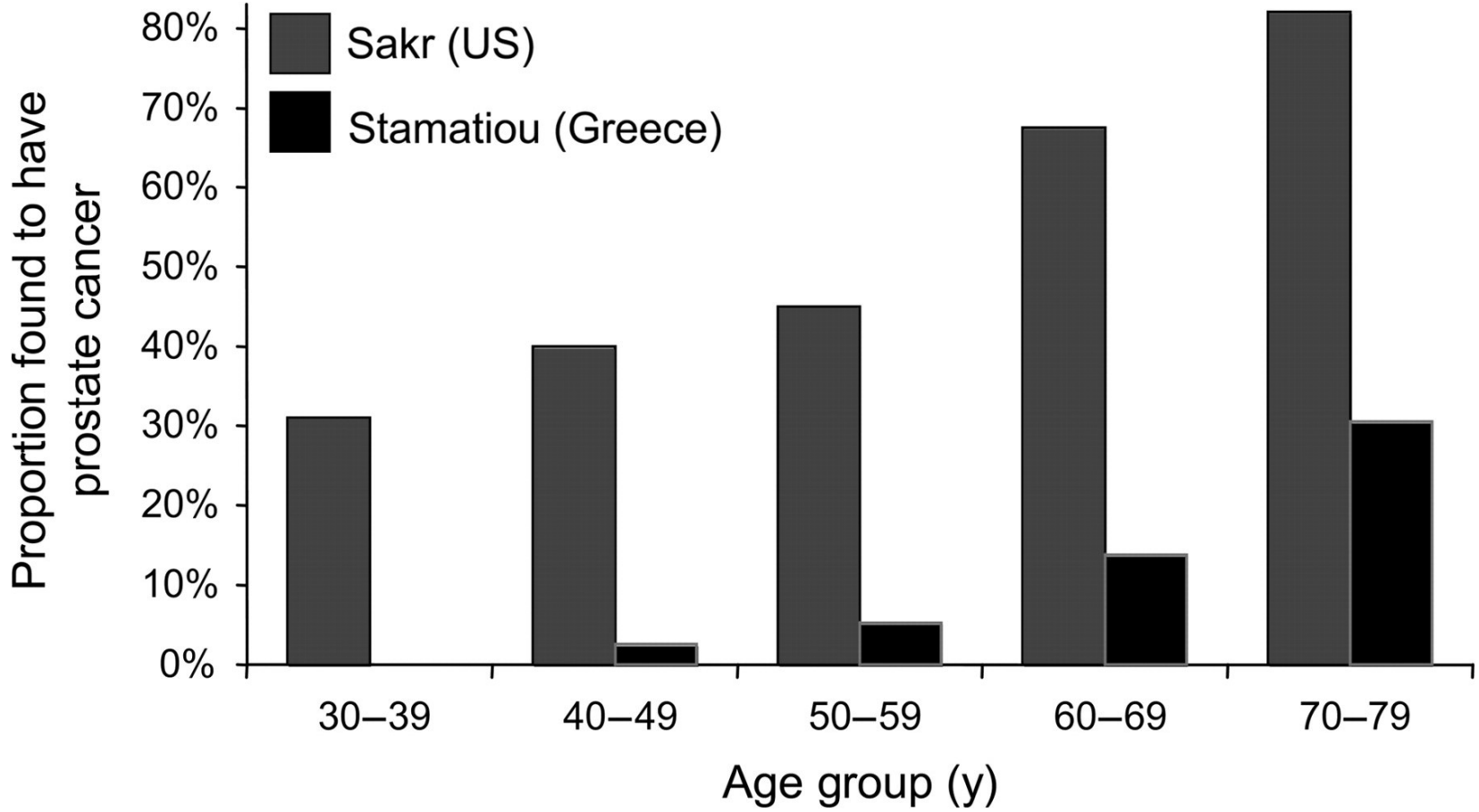
Era pre-PSA

- Molti anni orsono (anni ‘80): incidenza in aumento per **screening involontario** (diffusione resezione transuretrale retrograda per ipertrofia prostatica benigna)
- Ancora prima: **Studi autoptici** hanno evidenziato una elevata prevalenza di carcinoma prostatico occulto

Prevalence by age

- In 1935, two autopsy-based studies by A.R Rich and R.A. Moore identified a surprisingly high incidence of latent prostatic cancer in elderly men
- Later studies by other investigators indicate that latent prostate cancer may have an incidence as high as 70 to 80% in men in their 80s and 90s.
- These **extraordinary rates of latent cancer contrast with the 6 to 8% lifetime risk** that individual men have of developing clinically diagnosed prostate cancer.
- This striking discrepancy indicates that about 90% of latent prostatic cancers remain clinically silent for decades.

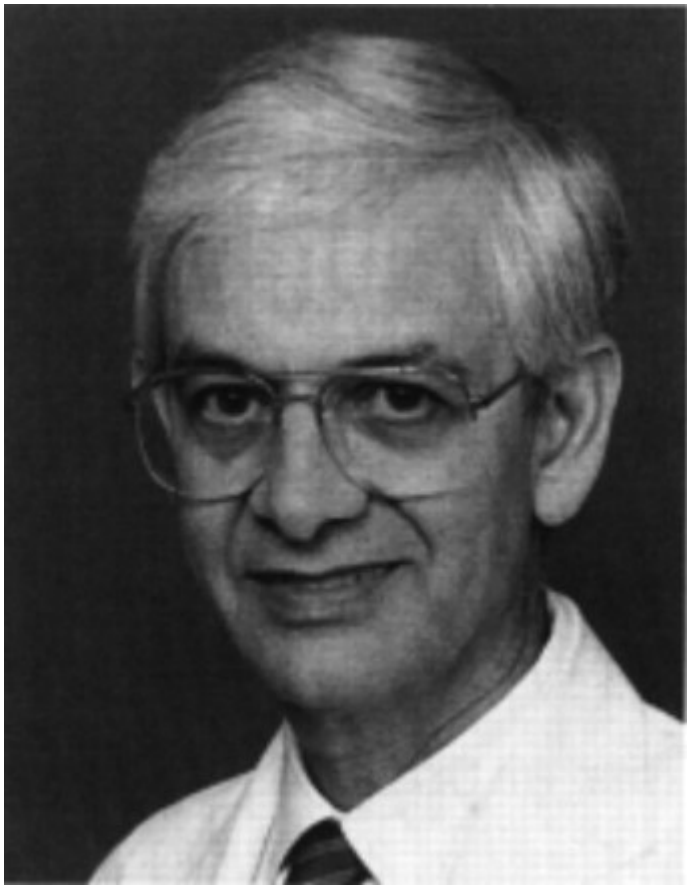
Prostate cancer reservoir in men dying from causes other than prostate cancer (and who were not known to have prostate cancer during life).



Welch H G , Black W C JNCI J Natl Cancer Inst 2010;102:605-613

SCREENING FOR PROSTATE CANCER ENTHUSIASM

WILLIAM J. CATALONA, M.D.

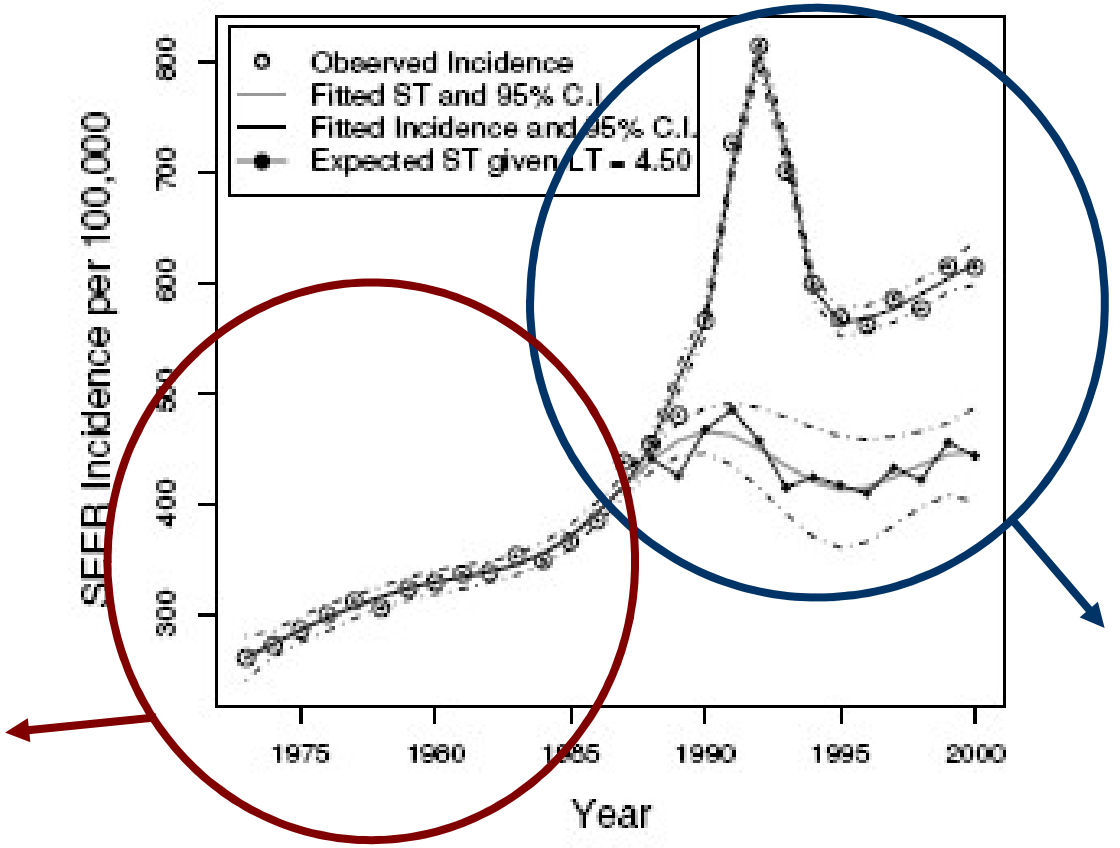


The American Cancer Society and the American Urological Association now **recommend annual prostate-specific antigen (PSA) testing** and rectal examinations **beginning at age 50** for early prostate cancer detection, and beginning at age 40 in high risk men. Upper age limits have not been set, but it is generally agreed that **routine screening is not desirable in men with a life expectancy of less than 10 years; therefore, the upper age limit should be between 70 and 75 years of age.**

Urology. 1993 Aug;42:113-5.

Negli US

Trattamento ipertrofia prostatica benigna



PSA

Telesca D, Etzioni R, Gulati R. **Estimating lead time and overdiagnosis associated with PSA screening from prostate cancer incidence trends**. Biometrics. 2008;64:10-9. Epub 2007 May 14.

Le nuove evidenze: trial ERSPC (e PLCO) 2009

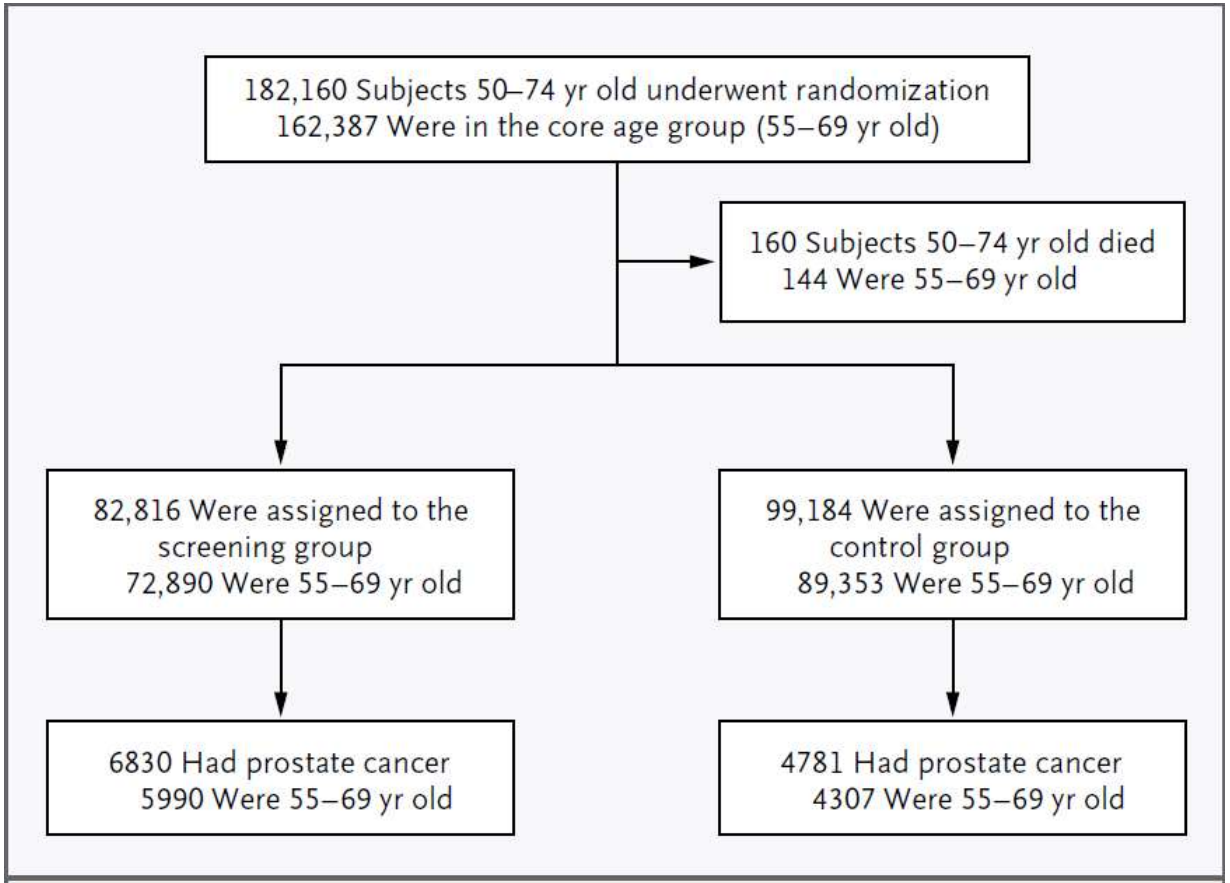
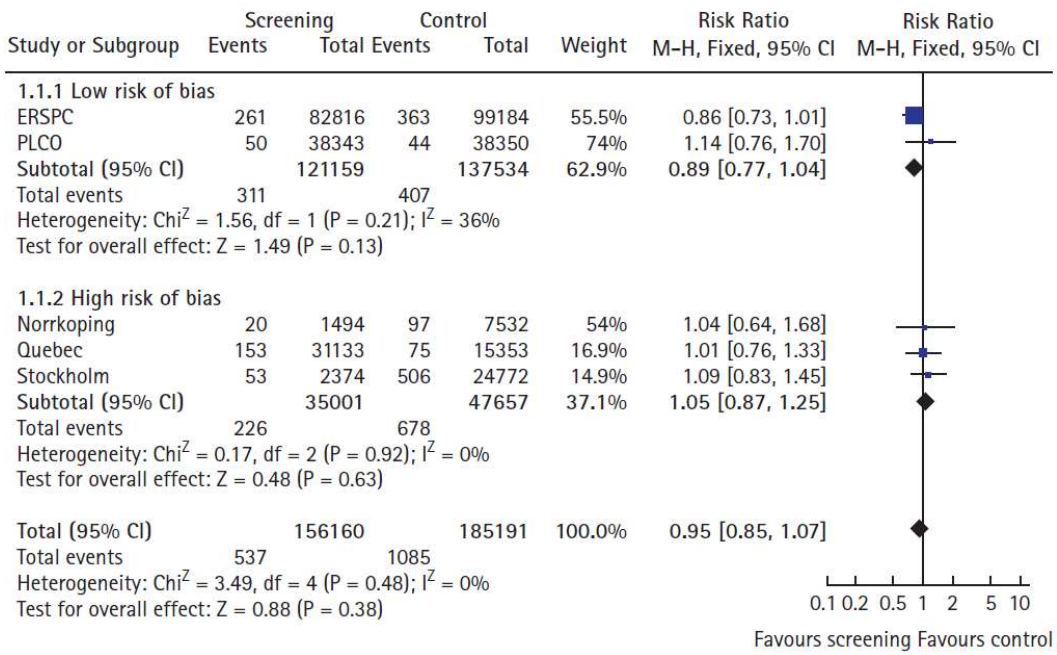


Figure 1. Enrollment and Outcomes, According to Age Group at Randomization.
The predefined core age group for this study included 162,243 men between the ages of 55 and 69 years.

FIG. 2. Prostate cancer-specific mortality (sub-group analysis risk of bias).

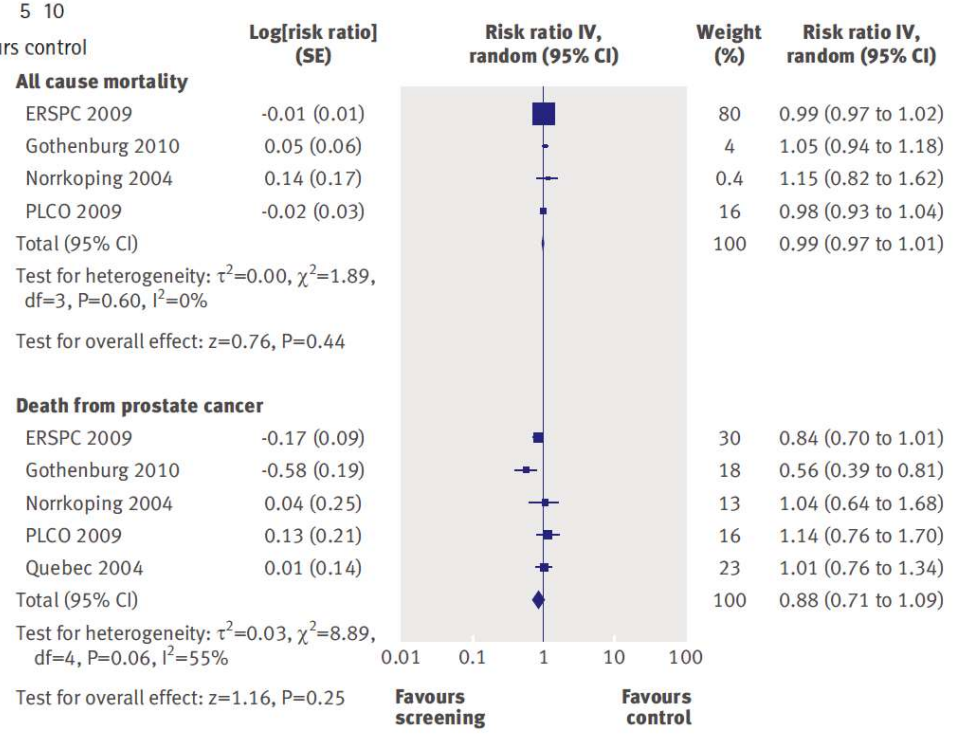


Study or Subgroup	Screening Events	Screening Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Low risk of bias						
ERSPC	261	82816	363	99184	55.5%	0.86 [0.73, 1.01]
PLCO	50	38343	44	38350	74%	1.14 [0.76, 1.70]
Subtotal (95% CI)		121159		137534	62.9%	0.89 [0.77, 1.04]
Total events	311		407			
Heterogeneity: Chi^2 = 1.56, df = 1 (P = 0.21); I^2 = 36%						
Test for overall effect: Z = 1.49 (P = 0.13)						
1.1.2 High risk of bias						
Norrkoping	20	1494	97	7532	54%	1.04 [0.64, 1.68]
Quebec	153	31133	75	15353	16.9%	1.01 [0.76, 1.33]
Stockholm	53	2374	506	24772	14.9%	1.09 [0.83, 1.45]
Subtotal (95% CI)		35001		47657	37.1%	1.05 [0.87, 1.25]
Total events	226		678			
Heterogeneity: Chi^2 = 0.17, df = 2 (P = 0.92); I^2 = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		156160		185191	100.0%	0.95 [0.85, 1.07]
Total events	537		1085			
Heterogeneity: Chi^2 = 3.49, df = 4 (P = 0.48); I^2 = 0%						
Test for overall effect: Z = 0.88 (P = 0.38)						

Tre meta-analisi dei trial pubblicate

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

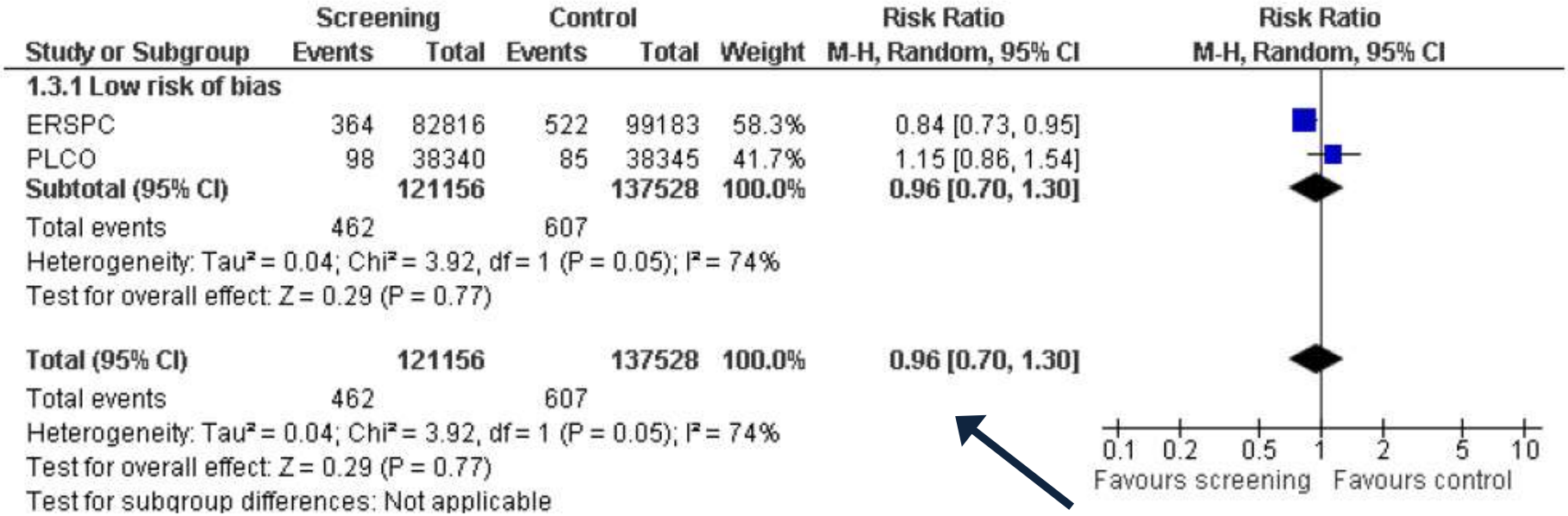
Ilic D et al. BJU Int. 2011;107:882-91.



	Log[risk ratio] (SE)	Risk ratio IV, random (95% CI)	Weight (%)	Risk ratio IV, random (95% CI)
All cause mortality				
ERSPC 2009	-0.01 (0.01)		80	0.99 (0.97 to 1.02)
Gothenburg 2010	0.05 (0.06)		4	1.05 (0.94 to 1.18)
Norrkoping 2004	0.14 (0.17)		0.4	1.15 (0.82 to 1.62)
PLCO 2009	-0.02 (0.03)		16	0.98 (0.93 to 1.04)
Total (95% CI)			100	0.99 (0.97 to 1.01)
Test for heterogeneity: τ^2=0.00, χ^2=1.89, df=3, P=0.60, I^2=0%				
Test for overall effect: z=0.76, P=0.44				
Death from prostate cancer				
ERSPC 2009	-0.17 (0.09)		30	0.84 (0.70 to 1.01)
Gothenburg 2010	-0.58 (0.19)		18	0.56 (0.39 to 0.81)
Norrkoping 2004	0.04 (0.25)		13	1.04 (0.64 to 1.68)
PLCO 2009	0.13 (0.21)		16	1.14 (0.76 to 1.70)
Quebec 2004	0.01 (0.14)		23	1.01 (0.76 to 1.34)
Total (95% CI)			100	0.88 (0.71 to 1.09)
Test for heterogeneity: τ^2=0.03, χ^2=8.89, df=4, P=0.06, I^2=55%				
Test for overall effect: z=1.16, P=0.25				

Fig 2 | Effects of screening on all cause mortality and death from prostate cancer

Figure 3. Forest plot of comparison: 1 Screening versus control, outcome: 1.3 Prostate cancer-specific mortality (sensitivity analysis overall risk of bias).



Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database Syst Rev. 2013;1:CD004720

ERSPC vs PLCO

I. Use of PSA testing prior to randomization (PLCO>50%)
II. Contamination (30% vs 55%)
III. Compliance with biopsy indication (83% vs 40%)

Schröder FH. ERSPC, PLCO studies and critique of cochrane review 2013. Recent Results Cancer Res. 2014;202:59-63.

Prostate-Cancer Mortality at 11 Years of Follow-up Fritz H. Schröder et al. NEJM 2012

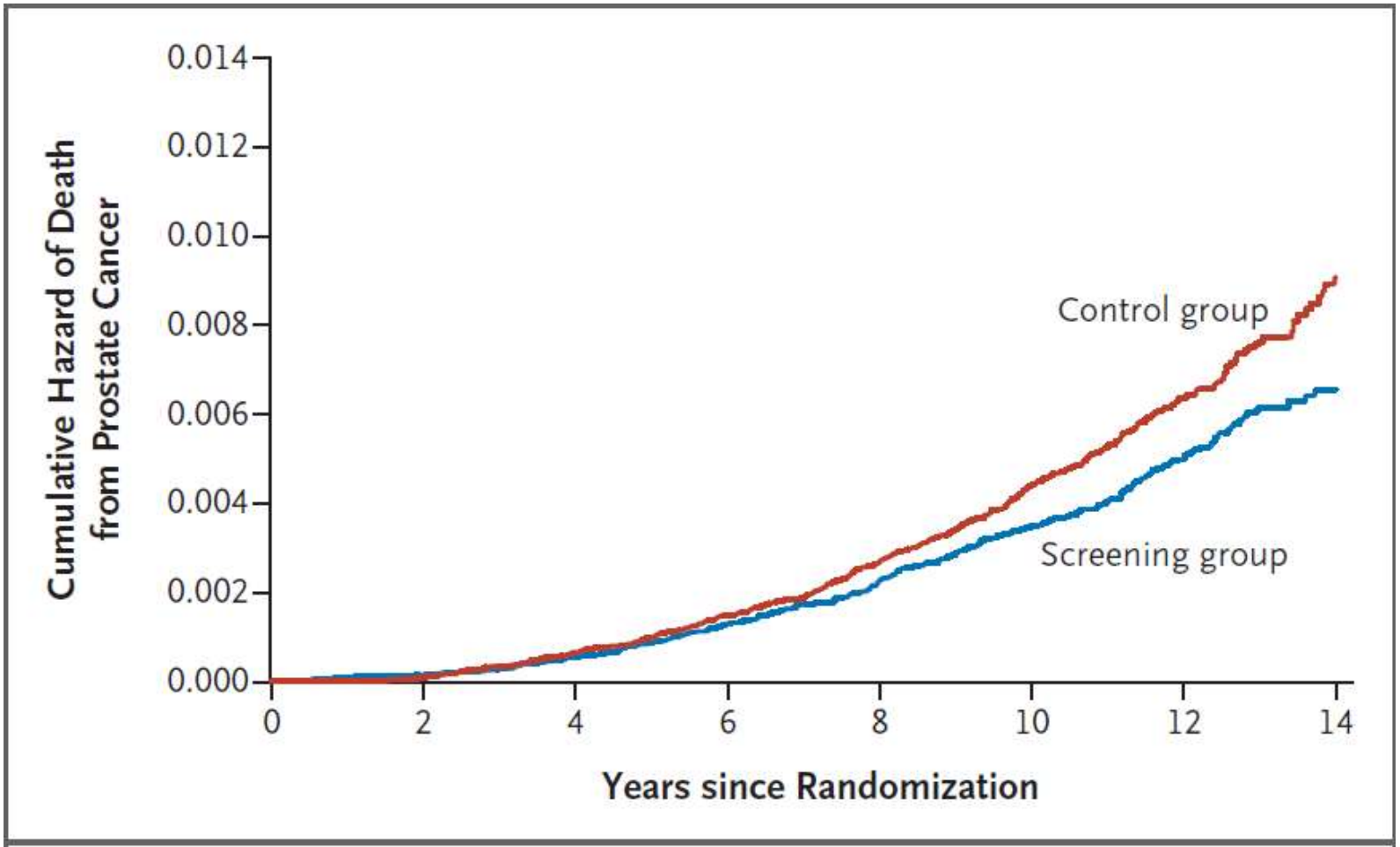


Figure 2. Cumulative Hazard of Death from Prostate Cancer among Men 55 to 69 Years of Age.

Conclusions Fritz H. Schröder et al. NEJM 2012

- the **relative reduction in the risk of death from prostate cancer in the screening group was 21%** (rate ratio, 0.79; 95% confidence interval [CI], 0.68 to 0.91; P = 0.001)
- **To prevent one death** from prostate cancer **at 11 years** of follow-up, **1055 men would need to be invited for screening and 37 cancers would need to be detected.**
- Analyses after 2 additional years of follow-up consolidated our previous finding that PSA-based screening **significantly reduced mortality from prostate cancer but did not affect all-cause mortality**
- **More information** on the balance of benefits and adverse effects, as well as the cost-effectiveness, of prostate-cancer screening is needed **before general recommendations** can be made

I risultati del trial europeo:

- Si riferiscono alla sola classe d'età 55-69 anni
- Evidenziano che le curve di mortalità iniziano a divergere solo dopo 7-8 anni
- Non evidenziano riduzione della mortalità nell'anziano: "However, there was no indication of a mortality reduction for men 70 years of age or older…"

Appendix ERSPC 11 years

	Rate ratio (95% CI)		Rate difference per1000 person years (95% CI
All causes			
Core age group	0.99	(0.97-1.01) p=0.50	
All ages	1.00	(0.98-1.02) p= 0.85	
Prostate c			
<=54	0.65	(0.23 - 1.83)	-0.05 (-0.17 – + 0.07)
55-59	0.81	(0.62 – 1.05)	-0.05 (-0.12 – +0.02)
60-64	0.92	(0.71 - 1.18)	-0.05 (-0.18 – +0.07)
65-69	0.67	(0.53 - 0.86)	-0.33 (-0.52 – +0.15)
70+	1.18	(0.81 - 1.72)	0.20 (-0.26-0.66)
Core age group	0.79	(0.68-0.91) p=0.001	-0.10 (-0.17 – -0.04)
All ages	0.83	(0.72-0.94) p=0.005	-0.08 (-0.14 – -0.02)

“Conclusioni (1)

➔ Anche se vi sono prove convincenti che la diagnosi precoce con PSA riduca la mortalità del Ca Prostata **non ci sono ,al momento attuale, giustificazioni per screening di popolazione** per il livello elevato di sovradiagnosi e sovratrattamento che ne deriverebbe

➔ A livello individuale il soggetto che vuole sottoporsi a diagnosi preventiva **dovrebbe essere informato** dei **benefici** ma anche dei **danni** che ne possono derivare”

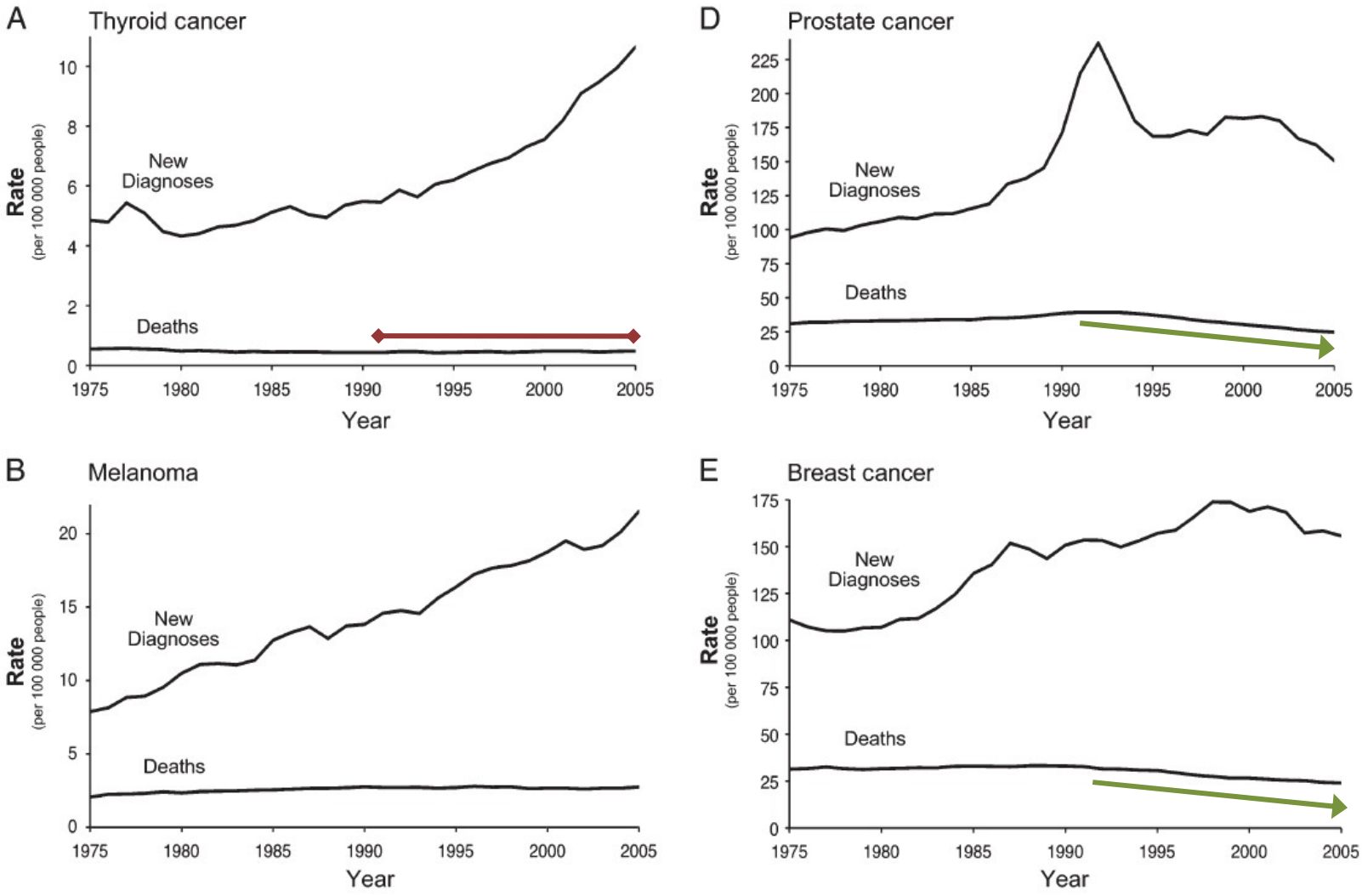
*Cortesia Dr. **Marco Zappa** – presentazione al congresso nazionale di urologia – Venezia ottobre 2012*

Il danno

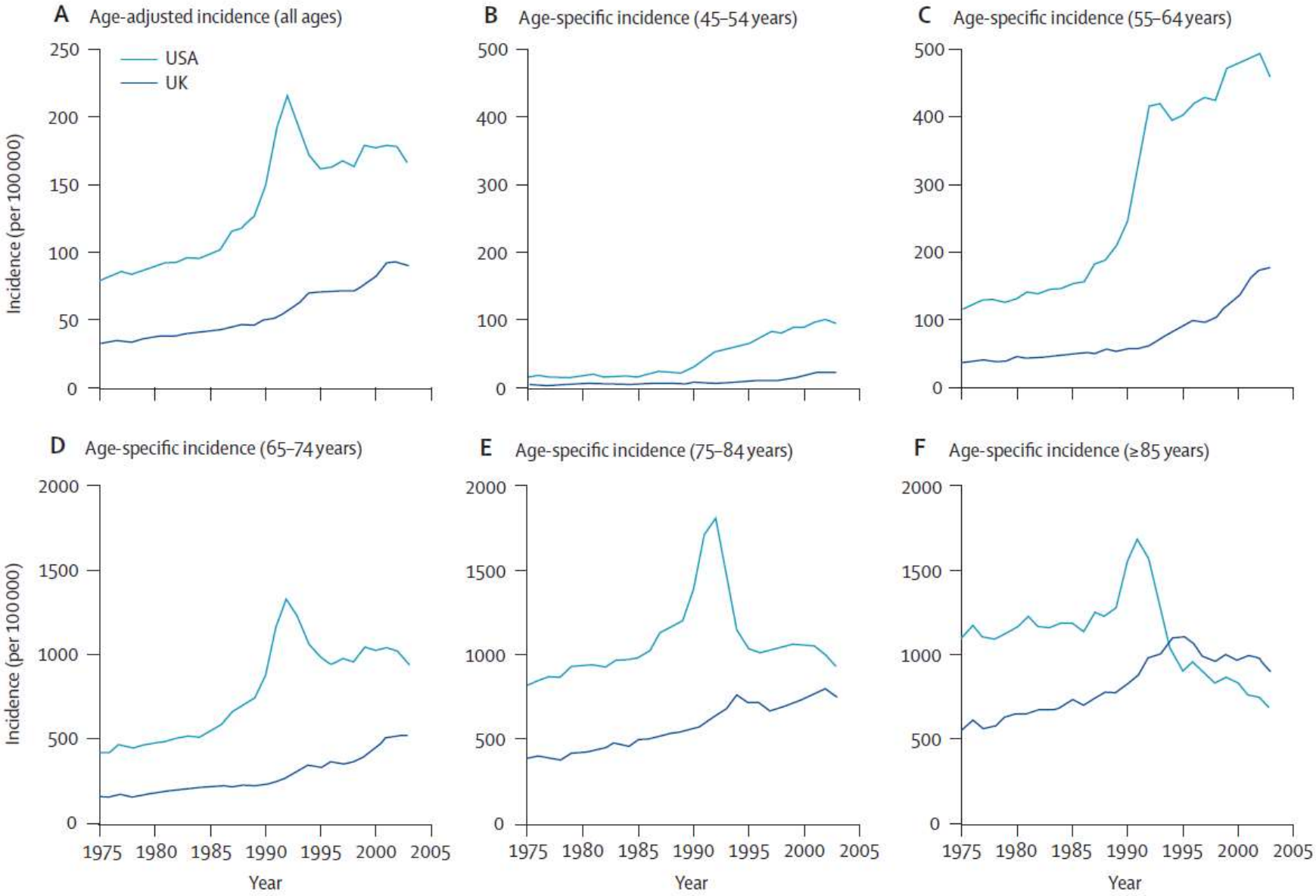
- The rate of **overdiagnosis** of prostate cancer (defined as the diagnosis in men who would not have clinical symptoms during their lifetime):
- Results of the **ERSPC demonstrated a 63% higher** prostate cancer **incidence** in the screened group compared with the control group during 11-year follow-up
- Has been estimated to be **as high as 50%** in the screening group Draisma G, et al.J Natl Cancer Inst 2003

Overdiagnosis in Cancer

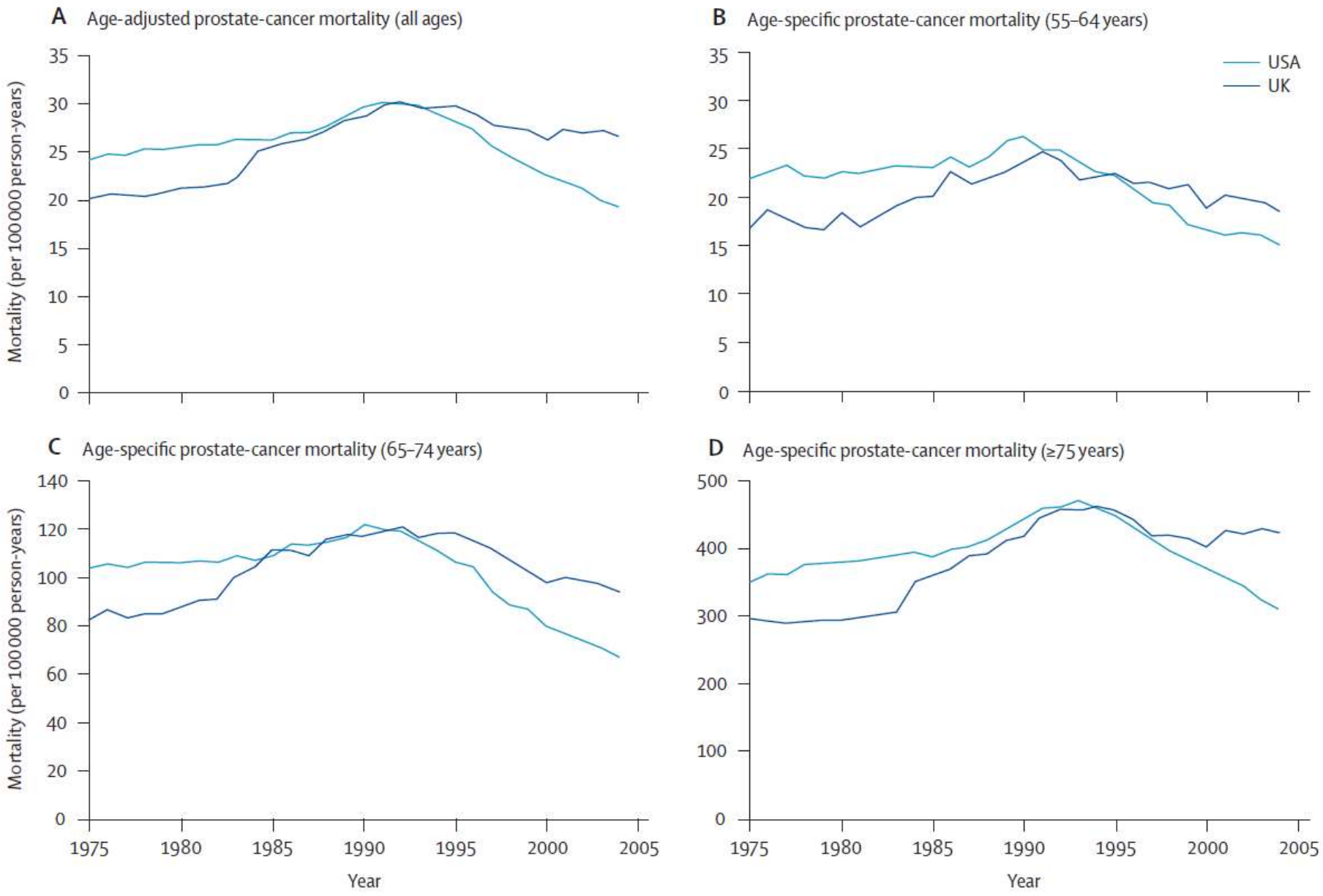
H. Gilbert Welch, William C. Black, JNCI 2010



Confronto tra US (frequente PSA screening) e UK (screening infrequente) *Collin SM et al. Lancet Oncol 2008*



Mortalità

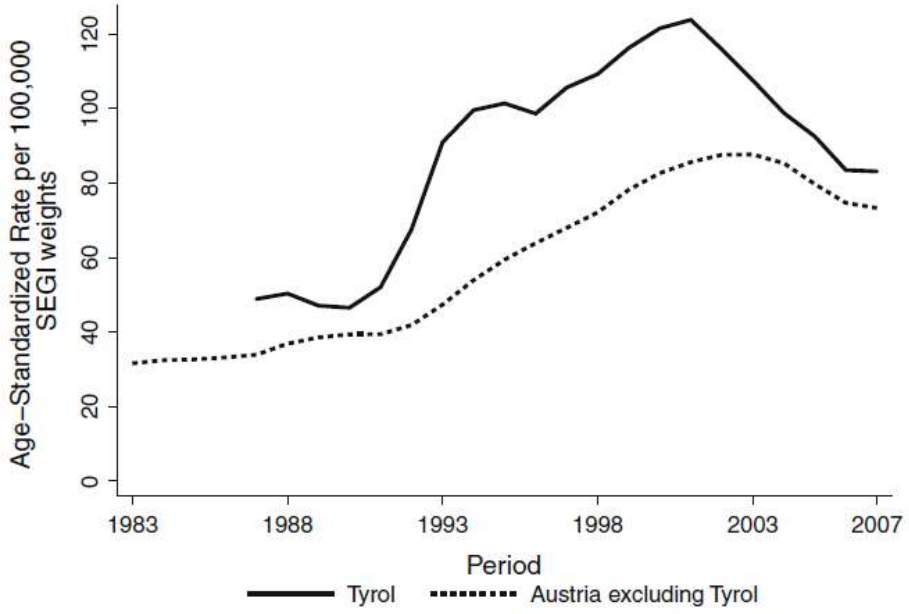

A Age-adjusted prostate-cancer mortality (all ages)
B Age-specific prostate-cancer mortality (55–64 years)
C Age-specific prostate-cancer mortality (65–74 years)
D Age-specific prostate-cancer mortality (≥75 years)
USA
UK
Mortality (per 100 000 person-years)
Year
0
5
10
15
20
25
30
35
40
60
80
100
120
140
200
300
400
500
1975
1980
1985
1990
1995
2000
2005

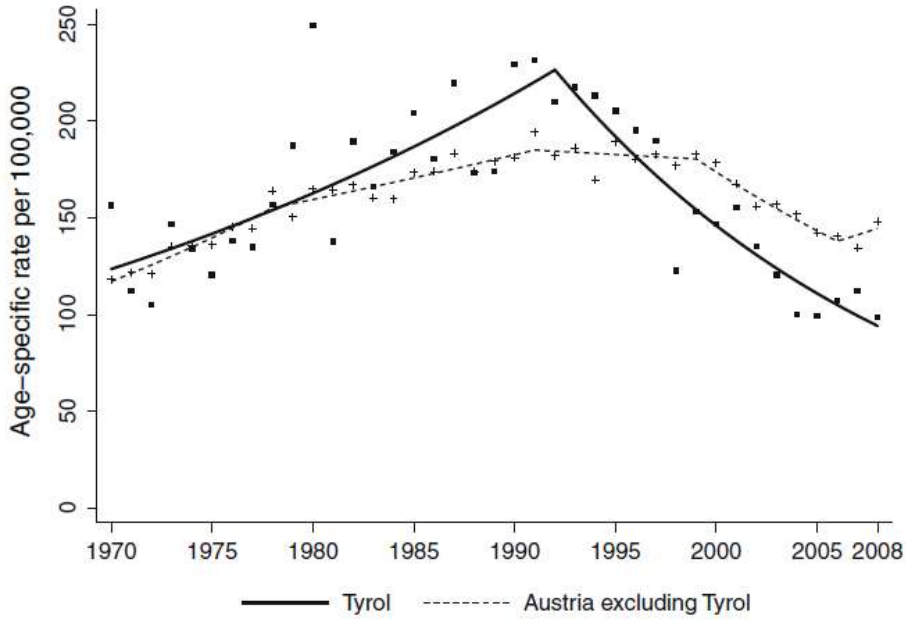
Tirolo – regione con offerta gratuita del PSA

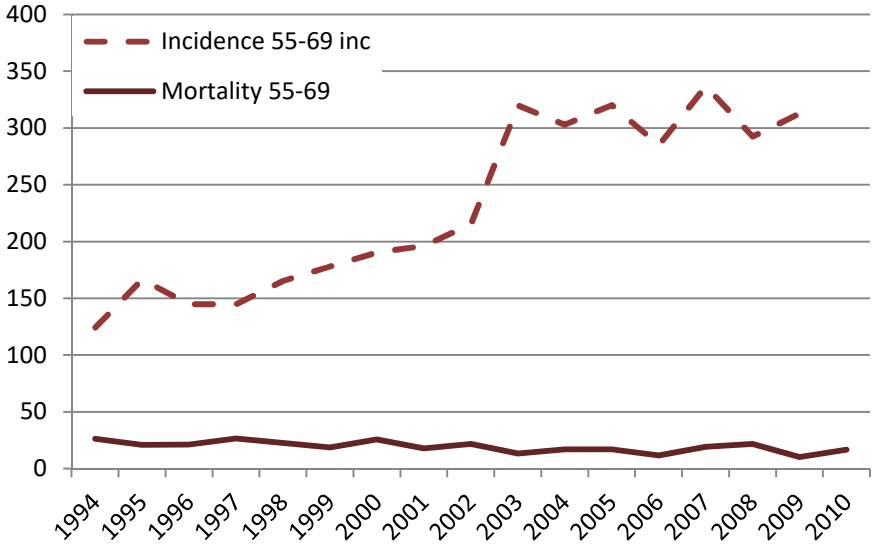
Year	No. men with PSA screening	Male population, *n*	Testing rate, %	Cumulative testing rate, %
1993	9 474	*86 067*	11.0	11.0
1994	14 147	*88 342*	16.0	23.3
1995	20 309	*90 153*	22.5	34.6
1996	23 839	*91 497*	26.1	44.1
1997	26 796	*92 607*	28.9	51.0
1998	30 228	*93 719*	32.3	56.8
1999	36 366	*95 000*	38.3	63.3
2000	41 860	*96 692*	43.3	70.1
2001	44 400	*98 638*	45.0	75.1
2002	50 370	*100 740*	50.0	80.2
2003	51 658	*102 904*	50.2	84.0
2004	52 503	*105 216*	49.9	86.1
2005	46 591	*107 600*	43.3	86.6

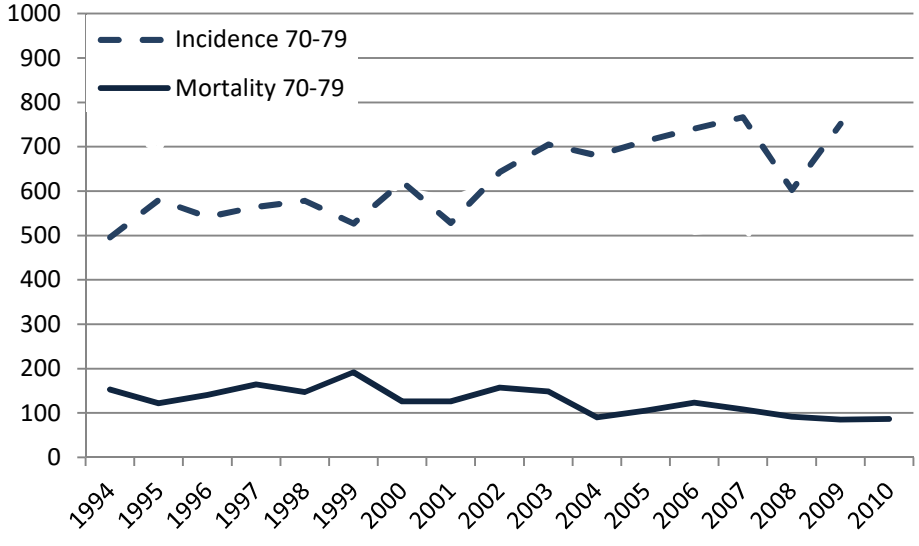
TABLE 1
Annual uptake rates of PSA testing in Tyrol in men aged 45–74 years

Oberaigner W et al. Prostate-specific antigen testing in Tyrol, Austria: prostate cancer mortality reduction was supported by an update with mortality data up to 2008. Int J Public Health. 2012

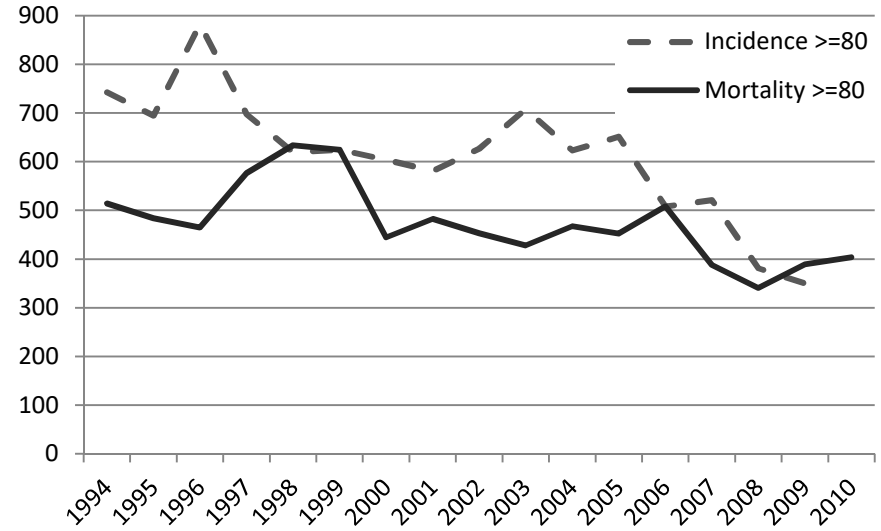




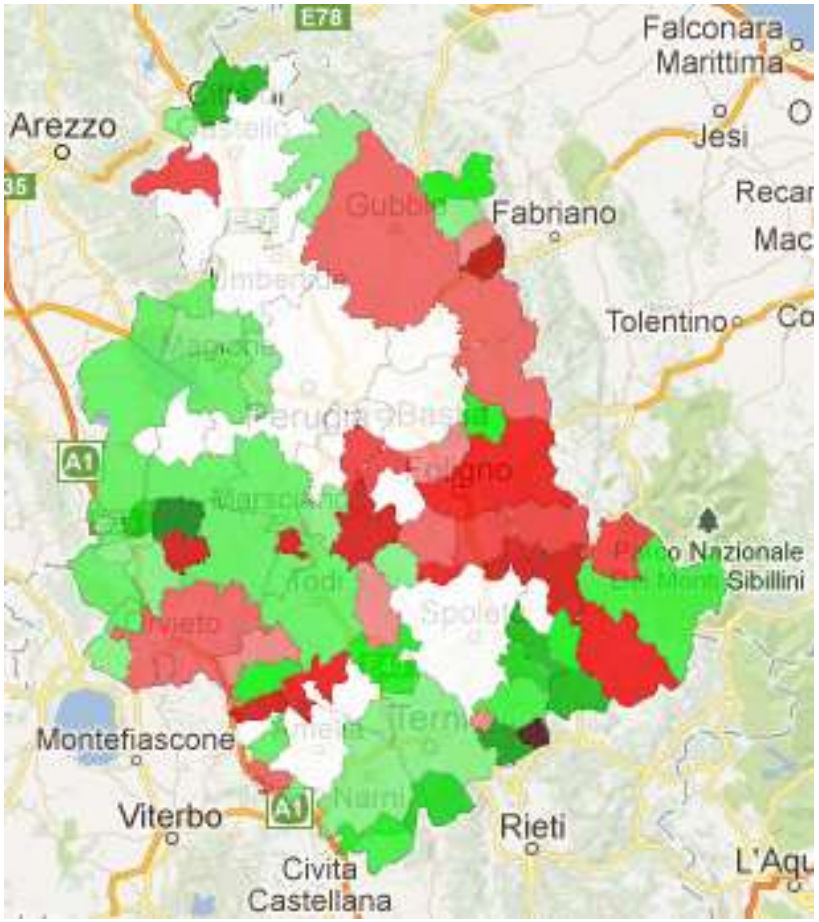




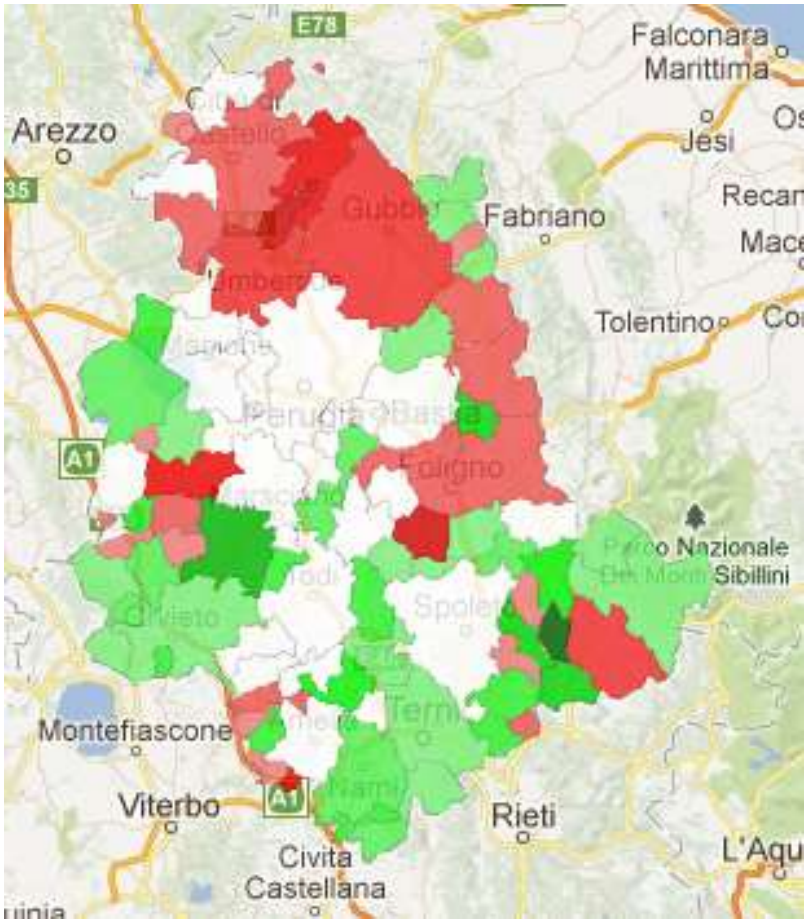
Incidenza e mortalità per classe d'età – Umbria 1994-2010



1994-2000

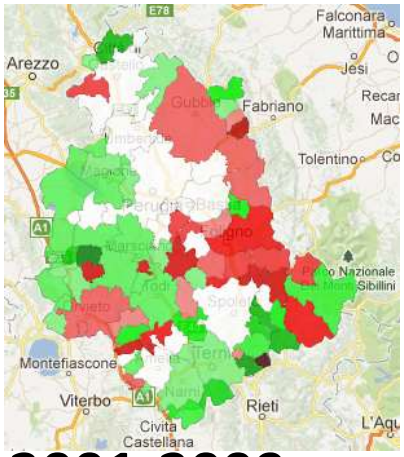


2001-2009

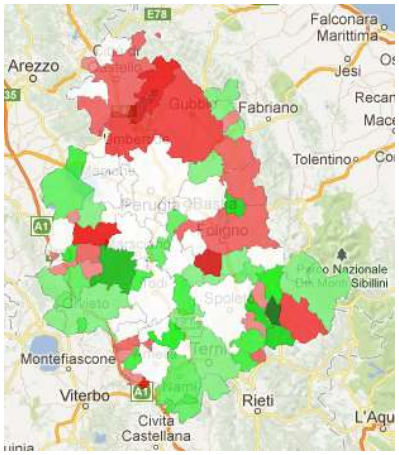


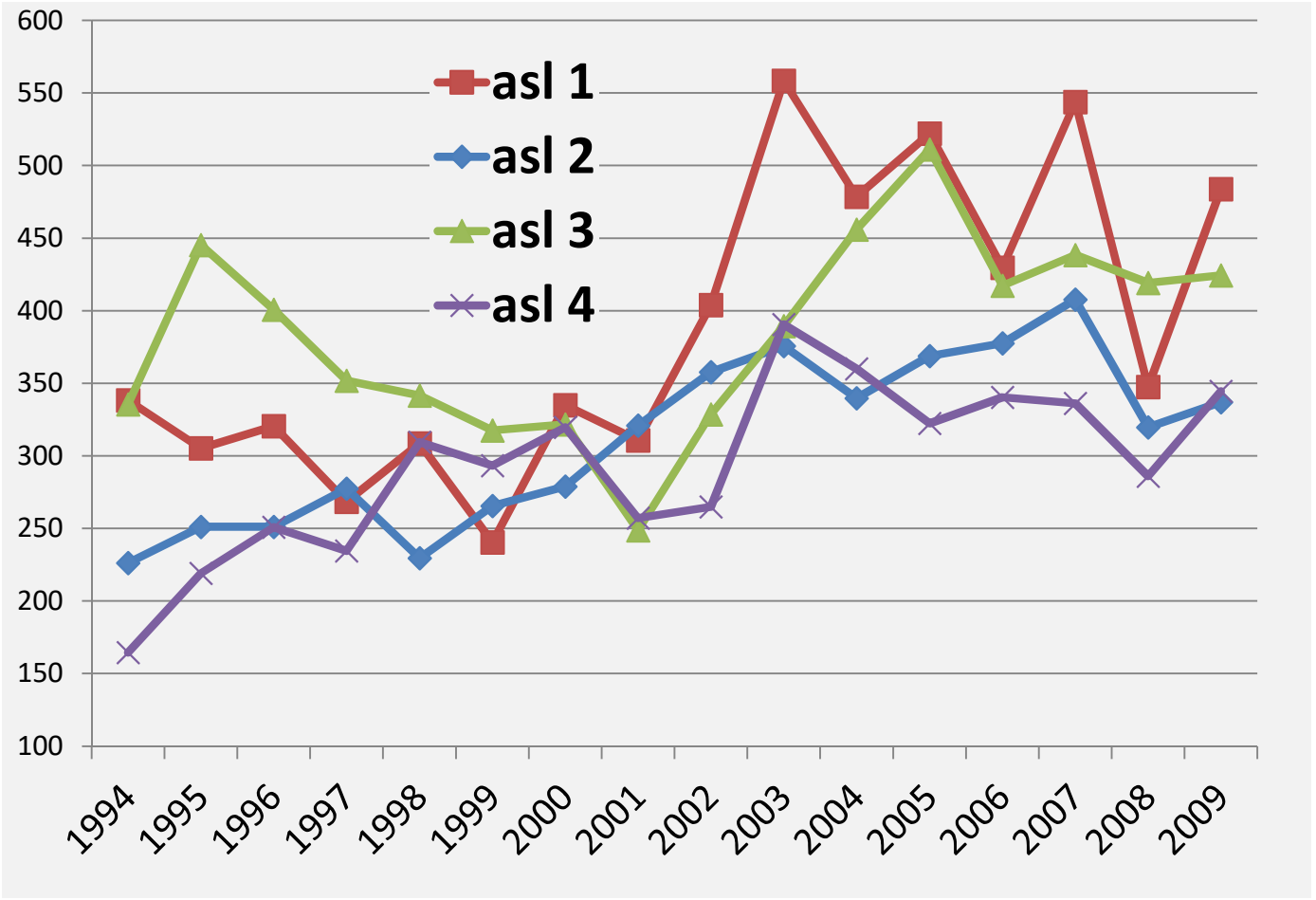
Incidenza per area geografica e periodo

1994-2000



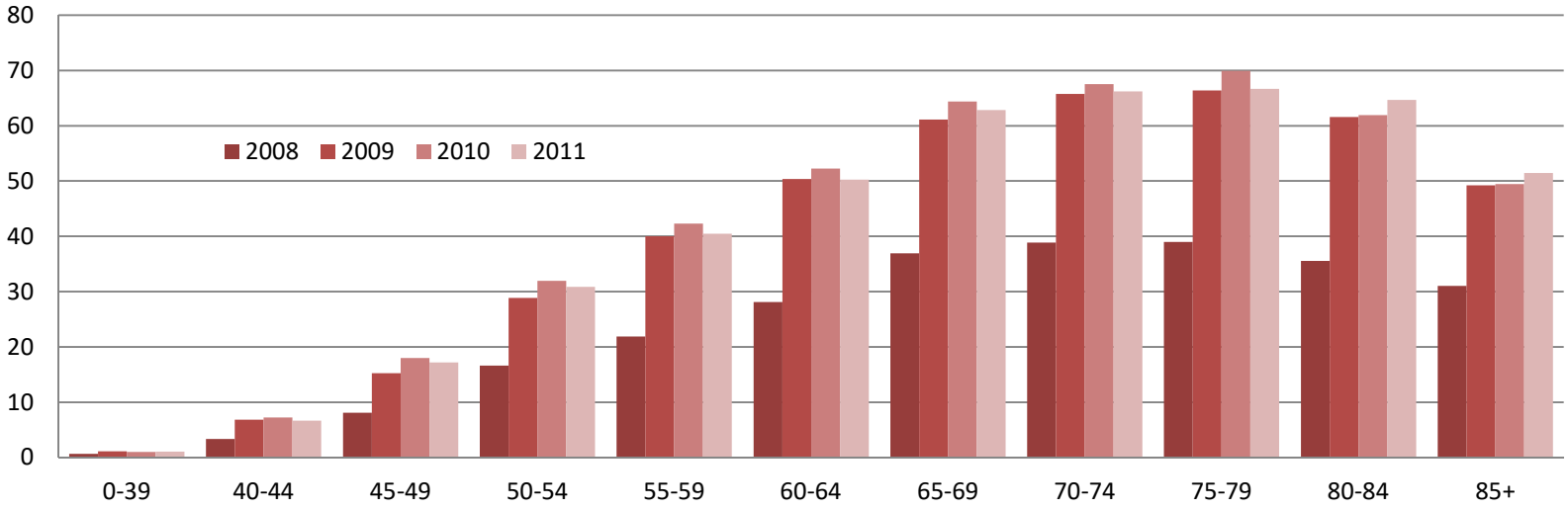
2001-2009



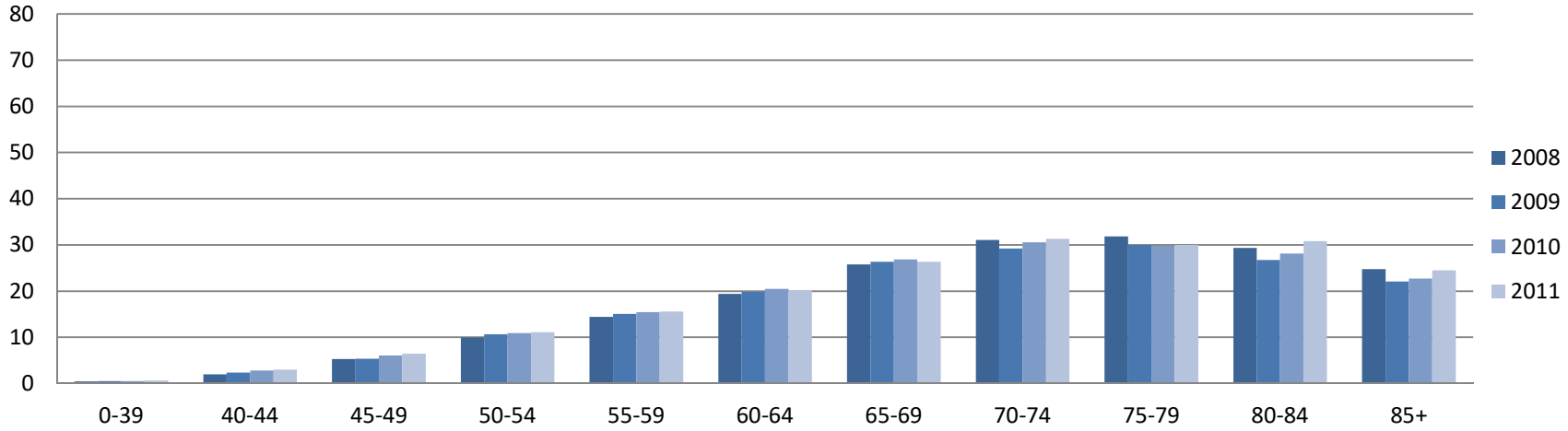


Trend di incidenza per asl

ASL 1 (% popolazione con almeno 1 PSA eseguito)



ASL 2 (% popolazione con almeno 1 PSA eseguito)



Diffusione test PSA

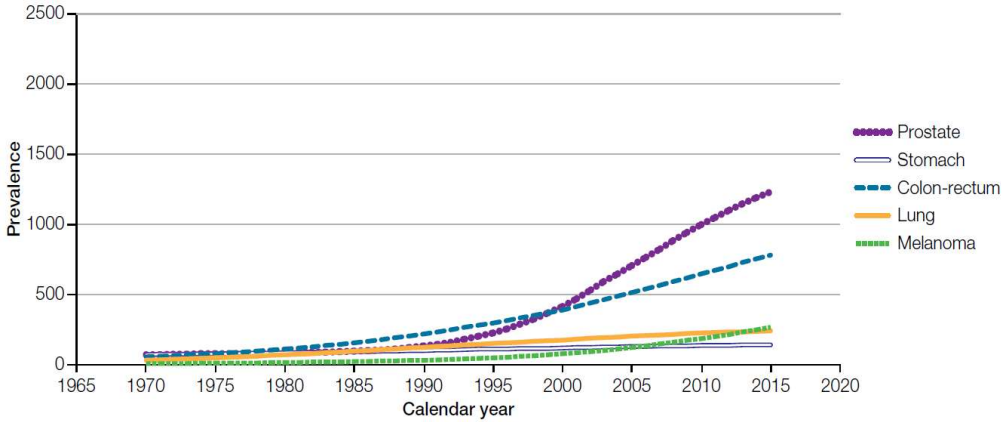
Opportunistic prostate-specific antigen screening in Italy: 6 years of monitoring from the Italian general practice database. *D'Ambrosio GG. Eur J Cancer Prev. 2010*

- Exposure to PSA screening (at least on PSA test in the considered period) of males aged over 50 years raised from 31.4% (confidence interval 95% 31.08-31.70%) during 2002 to 46.4% (confidence interval 95% 46.19-46.68%) during 2008.
- The highest yearly exposure to PSA screening (55%) and the highest frequency of repeat testing was observed in the 70-79 age range.
- PSA screening practice has continued to increase in Italy and is often performed in elderly people without any scientific rationale.

% di uomini residenti che hanno fatto almeno una determinazione del PSA nel 2010-2011
Archivio prestazione Ambulatoriali Regione Veneto

Classe di età	%
25-34	1,2%
35-44	6.7%
45-54	29.6%
55-64	54,3%
65-74	70,6%
75-84	67,2%
85+	52,5%

Cortesia di M. Zorzi



Prevalenza in Italia

Figura 5 - Prevalence estimates by cancer site in Italy in the period 1970-2015. Crude proportion per 100,000 persons. Age 0-99 years, men.

Prevalenza in Umbria

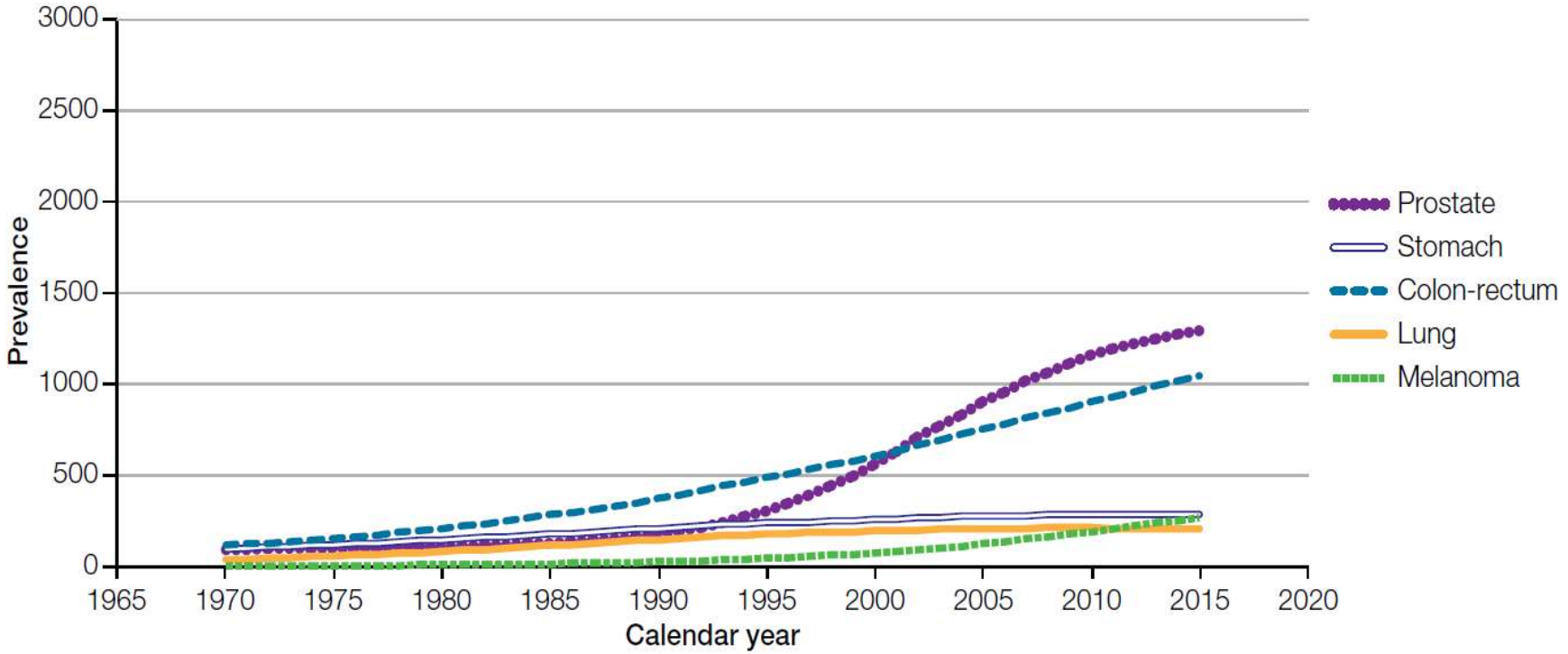


Figure 5 - Prevalence estimates by cancer site in Umbria in the period 1970-2015. Crude proportion per 100,000 persons. Age 0-99 years, men.

“The Popularity Paradox”

- Raffle and Gray have coined the term “The Popularity Paradox” for this situation:
- “The greater the harm from overdiagnosis and overtreatment from screening, the more people there are who believe they owe their health, or even their life, to the program.”
- Raffle AE, Gray JAM. Screening: evidence and practice. Oxford: Oxford University Press, 2007. pp 366

The Cost Implications of Prostate Cancer Screening in the Medicare Population

Xiaomei Ma, PhD[1,2]; Rong Wang, PhD[1,2]; Jessica B. Long, MPH[2,3]; Joseph S. Ross, MD, MHS[2,3,4]; Pamela R. Soulos, MPH[2,3]; James B. Yu, MD[2,5]; Danil V. Makarov, MD, MHS[6]; Heather T. Gold, PhD[7]; and Cary P. Gross, MD[2,3]

BACKGROUND: Recent debate about prostate-specific antigen (PSA)-based testing for prostate cancer screening among older men has rarely considered the cost of screening. **METHODS:** A population-based cohort of male Medicare beneficiaries aged 66 to 99 years, who had never been diagnosed with prostate cancer at the end of 2006 (n = 94,652), was assembled, and they were followed for 3 years to assess the cost of PSA screening and downstream procedures (biopsy, pathologic analysis, and hospitalization due to biopsy complications) at both the national and the hospital referral region (HRR) level. **RESULTS:** Approximately 51.2% of men received PSA screening tests during the 3-year period, with 2.9% undergoing biopsy. The annual expenditures on prostate cancer screening by the national fee-for-service Medicare program were $447 million in 2009 US dollars. The mean annual screening cost at the HRR level ranged from $17 to $62 per beneficiary. Downstream biopsy-related procedures accounted for 72% of the overall screening costs and varied significantly across regions. Compared with men residing in HRRs that were in the lowest quartile for screening expenditures, men living in the highest HRR quartile were significantly more likely to be diagnosed with prostate cancer of any stage (incidence rate ratio [IRR] = 1.20, 95% confidence interval [CI] = 1.07-1.35) and localized cancer (IRR = 1.30, 95% CI = 1.15-1.47). The IRR for regional/metastasized cancer was also elevated, although not statistically significant (IRR = 1.31, 95% CI = 0.81-2.11). **CONCLUSIONS:** Medicare prostate cancer screening-related expenditures are substantial, vary considerably across regions, and are positively associated with rates of cancer diagnosis. ***Cancer* 2013;000:000-000.** © *2013 American Cancer Society.*

TABLE 2. Average Annual Cost to Medicare for Prostate Cancer Screening During 2007 to 2009 (in 2009 US$)

Age Group	No. of Fee-For-Service Medicare Beneficiaries	PSA Rate (per 100)	Annual Screening Cost	
			Screening Cost Per Beneficiary	Total Screening Cost[a]
66-74 y	7,000,356	32.6	$43	$301 M
75-84 y	4,104,286	28.7	$31	$127 M
85-99 y	1,314,851	17.9	$14	$18 M
Total	12,419,493	29.8	$36	$447 M[b]

Four Flawed Arguments Against Prostate-specific Antigen Screening (and 1 Good One)

Andrew J. Vickers. Urology 2015

Nella classe d'età 55-69 (forse)!

(1) *Screening does reduce mortality*.

(2) High rates of overdiagnosis and overtreatment are not inevitable.

(3) Overdiagnosis and overtreatment are a big problem, hence [32,33]:

avoid

a. We restrict screening in older men, who are most prone to overdiagnosis.

b. We only biopsy men who have a strong chance of having a high-grade cancer.

c. We reserve treatment for men at above-average risk, with men at low risk being placed on active surveillance.

(4) Treatment-related morbidities are a problem so we refer those patients who do need treatment to high volume centers, where outcomes are known to be better.

(2) High rates of overdiagnosis and overtreatment are ~~not~~ inevitable.

- Our results can be interpreted as suggesting a substantial overlap between cases that contribute to mortality reduction achievable by screening and those that would remain undetected in the absence of screening
- …screen-detected cases include both tumors with indolent and progressive behavior, but we are currently unable to clearly discern the two. It is also consistent with trials showing only modest benefit from prostatectomy compared with expectant management in low-risk prostate cancer (13, 14) and very high cause-specific survival in patients treated with active surveillance (15), both indicating small advantage attainable by active treatment in men with a low-risk prostate cancer

Absolute Effect of Prostate Cancer Screening: Balance of Benefits and Harms by Center within the European Randomized Study of Prostate Cancer Screening. Auvinen A et al. Clin Cancer Res. 2016

Sovradiagnosi sostanziale

Nella classe d'età 55-69(74)

- The rate of overdiagnosis in the ERSPC study is estimated to be 41%, which would require that further detailed information

Table 1. Estimated size of the disease reservoir for three cancers, the lifetime risk of death or metastatic disease, and the probability of overdiagnosis where the entire disease reservoir detected

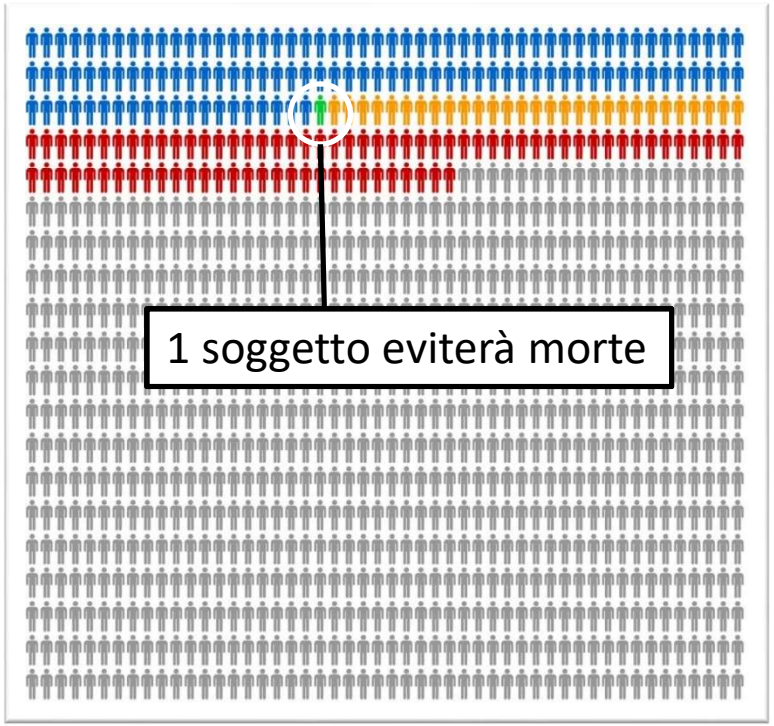
Cancer	Population	% With cancer (disease reservoir) (*a*)	Lifetime risk of death or metastatic disease* (*b*), %	Probability of overdiagnosis where entire disease reservoir detected† ($c = [a - b]/a$), %
Prostate	Men older than 60 y	30–70	4	87–94
Thyroid	Adults aged 50–70 y	36–100	0.1	99.7–99.9
Breast	Women aged 40–70 y	7–39	4	43–90

* The lifetime risk of death or metastatic disease was estimated by multiplying the lifetime risk of death reported by the Surveillance, Epidemiology, and End Results program (10) by 1.33, which more than accounts for the small proportion of patients diagnosed with metastatic disease who die from other causes (approximately 20%, 15%, and 10% of those with metastatic cancer of the prostate, thyroid, and breast cancer, respectively).

† This estimate is a lower-bound estimate because lethal and/or metastatic cancers do not always arise from prevalent cancers (those contained in the disease reservoir) but also from incident cancers (those not contained in the disease reservoir).

DISCUSSIONE: Screening tra i 55 e i 69 anni

Iter diagnostico-terapeutico, qualità di vita e danno da screening



1000 uomini sottoposti al test del PSA

230 pazienti sottoposti a biopsia

4.922 campioni bioptici

Cateterizzazione, sanguinamento, febbre,

120 nuove diagnosi e terapie

80 pazienti con complicanze

- Incontinenza urinaria e fecale
- Disfunzioni sessuali
- Ginecomastia, aumento di peso e perdita di massa muscolare
- Affaticamento e depressione

Conclusioni

Accordo su:

- Lo screening per il cancro della prostata **riduce la mortalità** (quasi accordo)
- Lo stesso screening è causa importante di **sovradiagnosi e sovratrattamento**
- Lo screening è **ampiamente diffuso** in forma **opportunistica** (sebbene con una discreta variabilità)
- Le persone dovrebbero essere informate correttamente sui benefici e i rischi dello screening (in tutte le classi d'età)

Conclusioni 2

- E' importante la ricerca di fattori che possono discriminare i tumori progressivi (Gleason >6; PSA>10ng/mL*; marcatori**)
- I benefici dello screening compaiono dopo molti anni (8-10)
- La sovradiagnosi aumenta e il beneficio dello screening si riduce in età avanzata
- Lo screening non dovrebbe essere effettuato in uomini oltre i 70 anni con speranza di vita<10 anni

PSA come test di screening dopo i 70 anni

- **Non si hanno evidenze** positive **di efficacia** dopo i 70 anni (RR circa 1.2 in ERSPC non significativo)
- I **benefici** dello screening compaiono **dopo** molti **anni (8-10)**
- La **sovradiagnosi aumenta e il beneficio dello screening si riduce in età avanzata**

quindi

- Lo screening non dovrebbe mai essere effettuato in uomini oltre i 70 anni

PSA come test di screening prima dei 70 anni

- Non vi è consenso ma da evidenze indirette sappiamo che lo screening è in atto

L'utilizzo attuale non va bene in quanto la diffusione opportunistica:

- Non consente alcun tipo di controllo dei risultati (non registriamo neanche la diffusione del test!)
- Non garantisce che le persone siano state correttamente informate

Table 1. Screening Recommendations of Major Societies in

Hayes JH, Barry MJ. Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. JAMA. 2014;311:1143-9

Organization	Who Should Be Screened	Screening Interval	Basis
US Preventive Services Task Force, 2012[14]	Screening should not be offered		Systematic review
American Urological Association, 2013[15-17]	Men aged 55-69 y or ≥70 y with >10- to 15-y life expectancy: use shared decision-making approach Men at higher risk <55 y: individualize approach	Consider 2-y interval over annual screening; may individualize intervals based on initial PSA	Systematic review and meta-analysis of the literature, 1995-2013
American Society of Clinical Oncology, 2012[18]	Men with life expectancy >10 y: use shared decision-making approach		Updating of Agency for Healthcare Research and Quality literature review; PubMed search through 2012; expert opinion
American Cancer Society, updated 2010[13]	Men aged >50 y at average risk with >10-y life expectancy: use shared decision-making approach Men at higher risk (black, first-degree relative diagnosed before 65 y) at 45 y Men at appreciably higher risk (multiple family members diagnosed before 65 y) at 40 y	Base interval on initial PSA: annual if ≥2.5 ng/mL; biannual if <2.5 ng/mL Biopsy recommended for all men with PSA>4 ng/mL Biopsy for PSA levels between 2.5 and 4 ng/mL should be individualized	Systematic review of the literature and consensus process
American College of Physicians, 2013[12]	Men aged 50-69 y with life expectancy >10-15 y: use shared decision-making approach Men at higher risk (black, first-degree relative diagnosed before 65 y) at 45 y Men at appreciably higher risk (multiple family members diagnosed before 65 y) at 40 y	Consider longer intervals than 1 y between screening PSAs	Review of available guidelines
Canadian Urologic Society, 2011[19]	Men ≥50 y with a 10-y life expectancy: use shared decision-making approach Men ≥40 y at high risk Consider baseline PSA in men 40-49 y	Consider intervals up to every 4 y	Systematic literature search 2004-2010
European Association of Urology, 2013[20]	Baseline PSA≥40-45 y	Risk-adapted strategy based on initial PSA in men with life expectancy >10 y Screening intervals every 2-4 y for men with serum PSA>1.0 µg/L at 45-59 y and up to 8 y in men with serum PSA <1 µg/L	Systematic literature review and meta-analysis

Conclusioni 3

Dibattito su:

- Nessuno raccomanda l'introduzione di uno screening organizzato nella classe d'età 55-69 anni (disequità)
- Linee guida sullo screening e sui percorsi diagnostico terapeutici dovrebbero essere concordate anche localmente
- Lo screening opportunistico dovrebbe essere modificato per consentirne la valutazione – un servizio pubblico deve essere in grado di selezionare e controllare gli interventi sanitari


Grazie dell’attenzione

Extended Mortality Results for Prostate Cancer Screening in the PLCO Trial With Median Follow-Up of 15 Years. Pinsky PF et al.

- rate ratio (RR) of 1.04 (95% confidence interval [CI], 0.87-1.24). The RR for all-cause mortality was 0.977 (95% CI, 0.950-1.004).
- It was estimated that 86% of the men in the control arm and 99% of the men in the intervention arm received any PSA testing during the trial, and the estimated yearly screening-phase PSA testing rates were 46% and 84%, respectively.
- CONCLUSIONS: Extended follow-up of the PLCO trial over a median of 15 years continues to indicate no reduction in prostate cancer mortality for the intervention arm versus the control arm.
- Because of the high rate of control-arm PSAtesting, this finding can be viewed as showing no benefit of organized screening versus opportunistic screening

Metastatic Prostate Cancer Incidence and Prostate-specific Antigen Testing: New Insights from the European Randomized Study of Screening for Prostate Cancer. *Buzzoni C et al. Eur Urol. 2015*

- DESIGN, SETTING, AND PARTICIPANTS: Information on arm, centre, T and M stage, Gleason score, serum PSA at diagnosis, age at randomisation, follow-up time, and vital status were extracted from the ERSPC database. Four risk categories at diagnosis were defined: 1, low; 2, intermediate; 3, high; 4, metastatic disease. PSA (≤100 or >100 ng/ml) was used as the indicator of metastasis…
- RESULTS AND LIMITATIONS: In the screening arm, 7408 PCa cases were diagnosed and 6107 in the control arm... The IRRs were elevated in the screening arm for the low-risk (IRR: 2.14; 95% CI, 2.03-2.25) and intermediate-risk (IRR: 1.24; 95% CI, 1.16-1.34) categories at diagnosis, equal to unity for the high-risk category at diagnosis (IRR: 1.00; 95% CI, 0.89-1.13), and reduced for metastatic disease at diagnosis (IRR: 0.60; 95% CI, 0.52-0.70).
- CONCLUSIONS: The results confirm a reduction in metastatic disease at diagnosis in the screening arm, preceding mortality reduction by almost 3 yr.

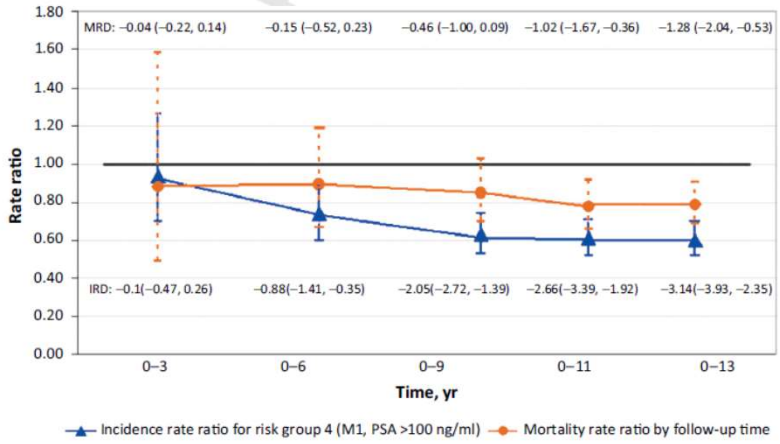


Fig. 1 – Cumulative incidence rate ratios for risk category 4 (after data imputation) and prostate cancer mortality rate ratio by time since randomisation (95% confidence intervals given in parentheses).
IRD = incidence rate difference per 1000 randomised men; MRD = mortality rate difference per 1000 randomised men.

ERSPC

- The ERSPC study used data from 7 centers in different European countries, with a total of 162,387 men undergoing randomization. Of these, 72,952 men were assigned to the screening group and 89,245 men were assigned to the control group…Slightly different methods and follow-up routines were used; **PSA cutoff varied from 3 to 4 ng/mL** and serum PSA levels necessitating further testing ranged from 2.5 to 3.9 ng/mL. ... Intervals for the screening group were large-4 years for 87% of patients.

Screening for Prostate Cancer: A Review of the ERSPC and PLCO Trials
Elisabeth Eckersberger et al Rev Urol. 2009 Summer; 11: 127–133.

ERSPC RC6

Future Risk Calculator*

Time = 0 (Now)

Age (years) 60

PSA (ng/ml) 3

DRE ○ Abnormal ◉ Normal

Family history * ○ Yes ◉ No

DRE volume class (cc) 40

Previous neg. biopsy ◉ Yes ○ No

Calculate

Time = 4 (4 years later)

Probability of NO Prostate Cancer: **97.3%**

Probability of potential LOW RISK Prostate Cancer: **2.1%**

Probability of potential AGGRESSIVE Prostate Cancer[2]: **0.7%**

---

* Has your father or brother has prostate cancer?

* Future risk implies 4 years after assessment of predictors and is based on a screening algorithm using a lateral sextant biopsy indication based on a PSA >= 3.0 ng/ml cut-off

[2] A prostate cancer with a clinical stage > T2b or Gleason score >= 7 or PSA > 10.0 ng/ml

Cut-off **3**

- A fifth of the detected cancers were in men with low PSA concentrations (1–3 ng/mL), who would normally not have had prostate biopsy samples taken

Prostate cancer screening in men aged 50–69 years (STHLM3): a prospective population-based diagnostic study Grönberg H Lancet Oncol 2015

Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, Minasian LM, Ford LG, Lippman SM, Crawford ED, Crowley JJ, Coltman CA Jr. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med. 2004 May 27;350(22):2239-46.

Towards “next-generation” prostate cancer screening

- Screening for prostate cancer with prostate-specific antigen (PSA) reduces cancer mortality as effectively as screening for breast and colorectal cancer.1,2
- Despite this, population-based screening with PSA is not recommended because of the high rates of false positive test results, overdiagnosis, and overtreatment.2
- The key to prostate cancer screening is finding ways to reduce these negative effects…
- Presently we do not have the means to accurately predict which low grade prostate cancers will progress, but genetic profiling methods look promising

Towards "next-generation" prostate cancer screening. Lamb AD, Bratt O. Lancet Oncol. 2015;16:1579-80

Loeb S et al. The prostate health index selectively identifies clinically significant prostate cancer. J Urol. 2015; 193:1163–9.

The PHI score is a panel of three biomarkers;

- Total PSA,
- free PSA and
- p2PSA, and has been previously shown to improve patient risk stratification before biopsy

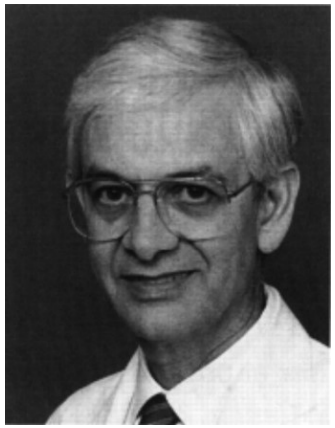
ERSPC risk calculator outperforms…

- The performance of the risk calculators in the present cohort shows that the ERSPC-RC is a superior tool in the prediction of PCa; however the performance of the ERSPC-RC in this population does not yet warrant its use in clinical practice.
- The incorporation of the PHI score into the ERSPC-PHI risk calculator allowed each patient's risk to be more accurately quantified.

The Added Value of Percentage of Free to Total Prostate-specific Antigen, PCA3, and a Kallikrein Panel to the ERSPC Risk Calculator for Prostate Cancer in Prescreened Men

- adding the 4k-panel to a previously developed PCa risk prediction model increased the predictive value in participants with PSA 3.0 ng/ml.
- Adding PCA3 increased the AUC in prescreened men regardless of their total PSA level at time of biopsy
- We found a very limited predictive value of %fPSA alone or combined with the RCs

INTERPRETAZIONE DELLE EVIDENZE



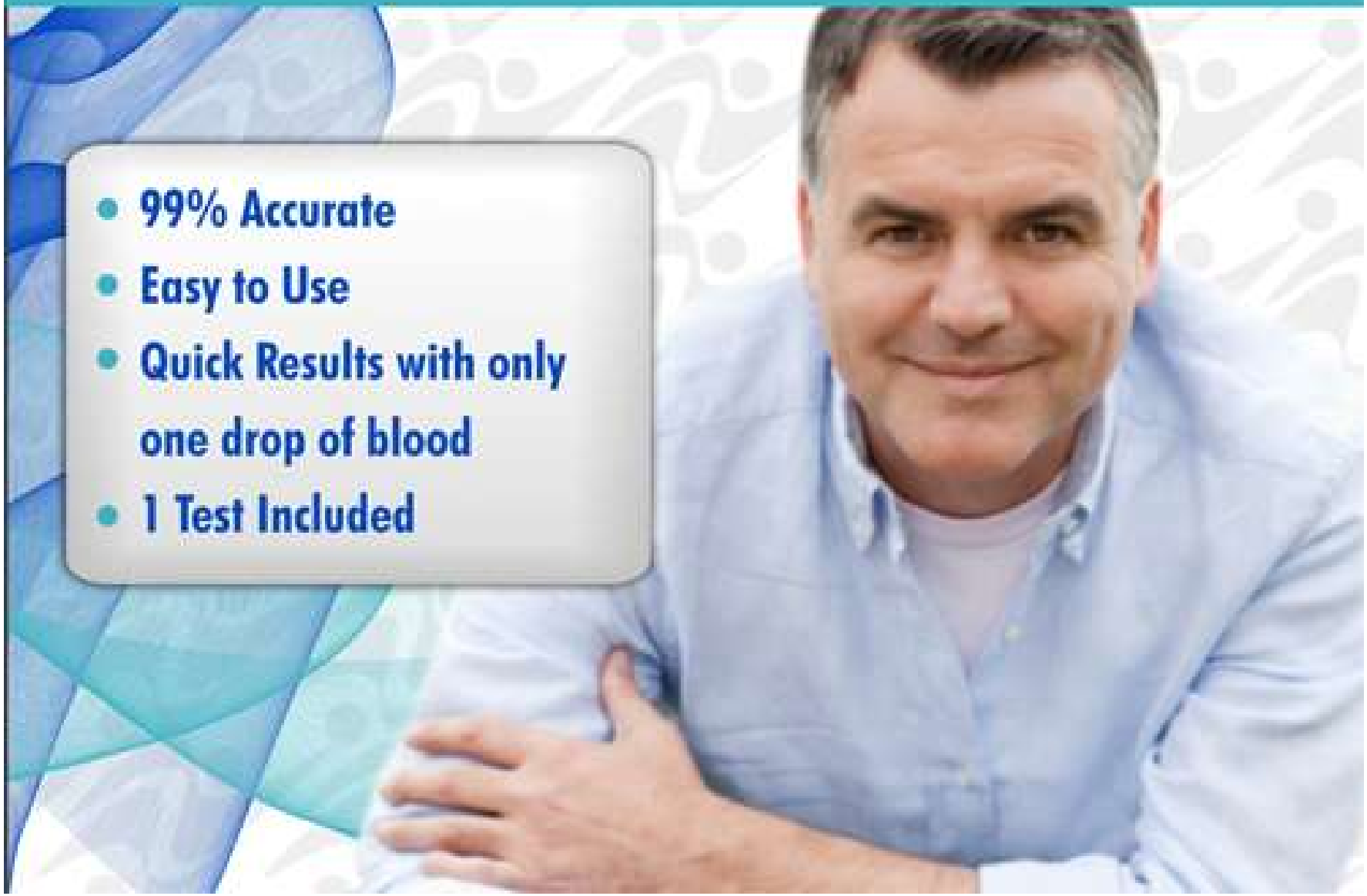
USPSTF Makes PSA Screening Recommendations Without Urology Representative

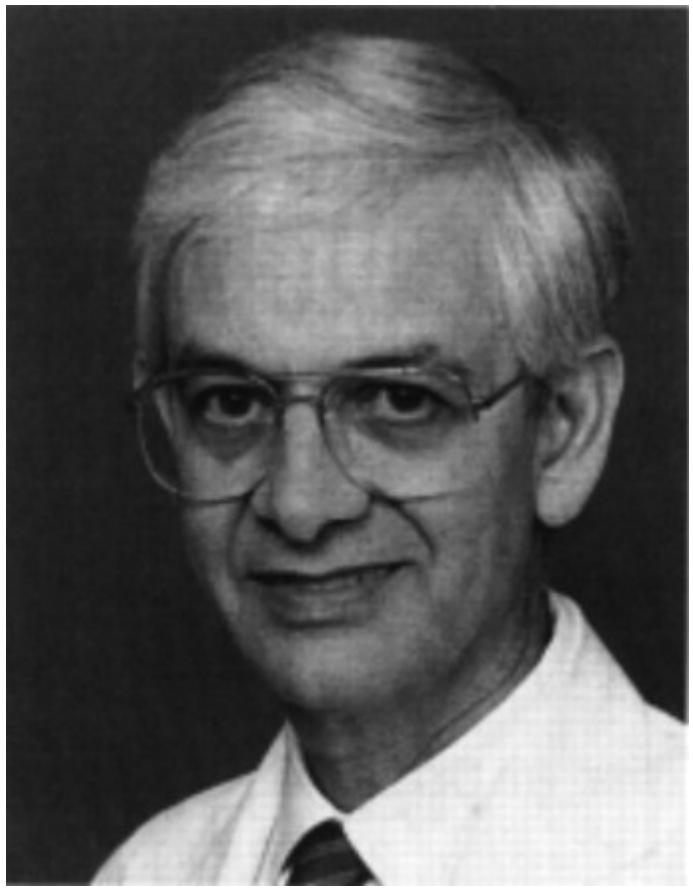
by William J. Catalona

www.drcatalona.com/quest/quest_fall09_5.htm

- The **US Preventive Services Task Force (USPSTF), with no urology representative**, reviewed what it considered the relevant literature and concluded that available evidence is insufficient to assess the balance between potential benefits and harms of using PSA to screen men less than 75 years old for prostate cancer and **has recommended against screening men over 75 years old** (even those at high-risk).
- A report (Moul et al) found that **78% of men surveyed at a screening clinic disagreed with this recommendation**. This study also presented evidence that older patients generally have more aggressive disease and worse outcomes…
- With respect to the 2008 USPSTF guideline, not all 75-year-old men are the same. Rather than discontinuing screening based solely upon chronological age, the decision to screen in this population should take into account the absolute PSA level and PSA trends over time, as well as general health status.

PROSTATE (PSA) SCREENING TEST





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Who and when should we screen for prostate cancer? Interviews with key opinion leaders

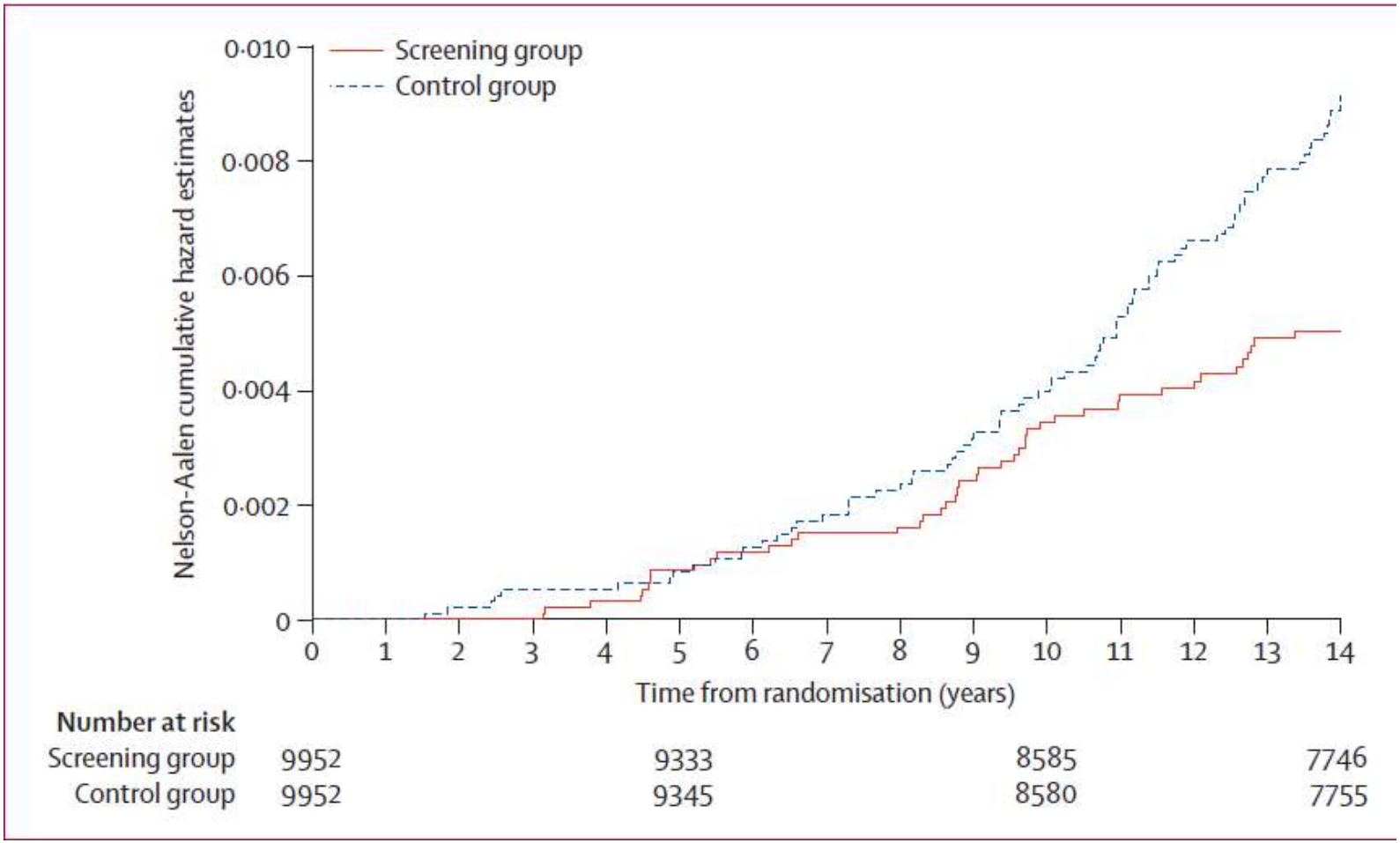
- Randomized screening trials, including the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Göteborg trial [4, 5] have provided evidence that regular PSA-screening can reduce prostate cancer mortality by 21–44 % at 13–14 years of follow-up;
- the age groups studied in these trials were 55–69 and 50–64 years, respectively.

Carlsson et al. BMC Medicine (2015) 13:288

Giovani

- There is a growing body of evidence on the benefits of commencing screening in the mid-40s.
- While the American Urological Association (AUA) bases its recommendation on the 55–69 age group based on the ERSPC results [6],
- the European Urological Association recommends a baseline PSA be obtained at 40–45 years of age [7].

Lo studio di Goteborg



Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, Pihl CG, Stranne J, Holmberg E, Lilja H. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. Lancet Oncol. 2010 Aug;11(8):725-32

Anziani

- we have shown that almost half of the excess incidence of cancer associated with PSA testing occurs in men over 70 [12] –
- a group in which screening is likely of little, if any, benefit [5, 13]
- guidelines in place at Memorial Sloan Kettering Cancer Center restrict screening in men over 60 to those with above average PSAs and dramatically restrict screening in men over 70 to a small number of men with exceptional health and high PSA

Shared decision making

- F Schröder: In my view, the time for population based screening has not come and may never do so.
- The main reason for my pessimistic view on this issue is the high probability (of approximately 40 %) of diagnosing cancers which will not progress clinically, cause symptoms, or lead to death (overdiagnosis)

Ilic D

- The ERSPC study authors concluded that, "…*the time for population-based screening has not yet arrived*…" [5]. Given that the current evidence does not support population-based prostate cancer screening,
- the question then turns to screening on an individual basis.
- For individual patients to make an informed decision, they must be aware of the benefits and harms associated with the diagnostic tests used when screening for prostate cancer

Ciò che bisogna sapere per decidere se sottoporsi allo screening per il cancro della prostata

Elementi fondamentali di informazione da fornire agli uomini per assisterli nella loro decisione in merito alla esecuzione dello screening per la prevenzione del cancro alla prostata.

Il cancro della prostata è una importante preoccupazione per la salute negli uomini:

1. Lo screening con il dosaggio dell'Antigene Prostatico Specifico nel sangue -da solo o in associazione con la Esplorazione Digitale del Retto (DRE)- individua il cancro in uno stadio precoce rispetto alla diagnosi non effettuata mediante esecuzione di test di screening.
2. Lo screening del cancro alla prostata può essere associato ad una riduzione del rischio di morire per cancro alla prostata. Tuttavia, i risultati degli studi sulla efficacia dello screening nel ridurre la mortalità per cancro della prostata sono contrastanti e gli esperti non sono d'accordo sulla validità dello screening.
3. Al momento non è possibile prevedere quali uomini ottengono un beneficio dal trattamento del cancro della prostata diagnosticato allo screening. Alcuni uomini grazie al trattamento potrebbero evitare morte e disabilità per cancro alla prostata. Altre persone che vengono sottoposte a trattamenti medici, sarebbero morte in assenza della diagnosi da screening per cause diverse dal cancro

Core Elements of the Information to be Provided to Men to Assist With Their Decision Regarding Prostate Cancer Screening.

Prostate cancer is an important health concern for men:

1. Screening with the PSA blood test alone or with both the PSA and DRE detects cancer at an earlier stage than if no screening is performed.
2. Prostate cancer screening may be associated with a reduction in the risk of dying from prostate cancer. However, evidence is conflicting and experts disagree about the value of screening.
3. For men whose prostate cancer is detected by screening, it is currently not possible to predict which men are likely to benefit from treatment. Some men who are treated may avoid death and disability from prostate cancer. Others who are treated would have died of unrelated causes before their cancer became serious enough to affect their health or shorten their lives.
4. Depending on the treatment selected,

http://www.rtup.unipg.it/rtupWebSiteNew/

Prevenzione Primaria: non ancora

- Selenio e vitamina E risultati negativi [Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009, 301:39-51.]
- The 5-α reductase inhibitors (5-ARIs) finasteride and dutasteride are the most promising to date, but also the most controversial. overall cancer risk reduction was driven entirely by the reduction in Gleason ≤6 tumors
- [Hamilton RJ, Freedland SJ. 5-alpha reductase inhibitors and prostate cancer prevention: where do we turn now? BMC Med. 2011 ;9(1):105.]

Klein EA, et al. **Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial** (SELECT). JAMA. 2011 12;306:1549-56.

CONTEXT: The initial report of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) found **no reduction in risk of prostate cancer with either selenium or vitamin E supplements** but a statistically nonsignificant increase in prostate cancer risk with vitamin E. Longer follow-up and more prostate cancer events provide further insight into the relationship of vitamin E and prostate cancer.

OBJECTIVE: To determine the long-term effect of vitamin E and selenium on risk of prostate cancer in relatively healthy men.

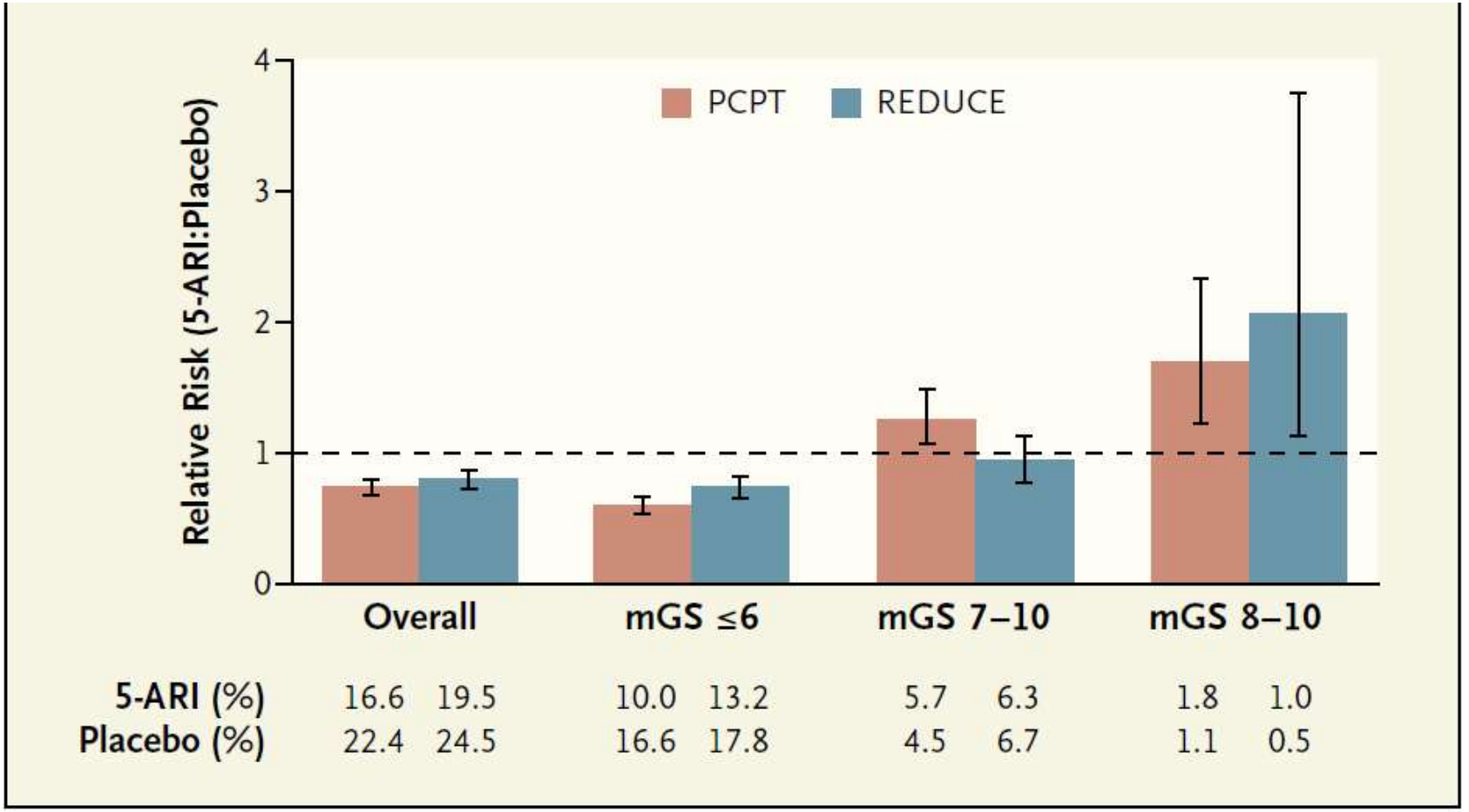
DESIGN, SETTING, AND PARTICIPANTS: A total of 35,533 men from 427 study sites in the United States, Canada, and Puerto Rico were randomized between August 22, 2001, and June 24, 2004. Eligibility criteria included a prostate-specific antigen (PSA) of 4.0 ng/mL or less, a digital rectal examination not suspicious for prostate cancer, and age 50 years or older for black men and 55 years or older for all others. The primary analysis included 34,887 men who were randomly assigned to 1 of 4 treatment groups: 8752 to receive selenium; 8737, vitamin E; 8702, both agents, and 8696, placebo. Analysis reflect the final data collected by the study sites on their participants through July 5, 2011.

INTERVENTIONS: Oral selenium (200 μg/d from L-selenomethionine) with matched vitamin E placebo, vitamin E (400 IU/d of all rac-α-tocopheryl acetate) with matched selenium placebo, both agents, or both matched placebos for a planned follow-up of a minimum of 7 and maximum of 12 years.

MAIN OUTCOME MEASURES: Prostate cancer incidence.

RESULTS: This report includes 54,464 additional person-years of follow-up and 521 additional cases of prostate cancer since the primary report. Compared with the placebo (referent group) in which 529 men developed prostate cancer, 620 men in the vitamin E group developed prostate cancer (hazard ratio [HR], 1.17; 99% CI, 1.004-1.36, P = .008); as did 575 in the selenium group (HR, 1.09; 99% CI, 0.93-1.27; P = .18), and 555 in the selenium plus vitamin E group (HR, 1.05; 99% CI, 0.89-1.22, P = .46). Compared with placebo, the absolute increase in risk of prostate cancer per 1000 person-years was 1.6 for vitamin E, 0.8 for selenium, and 0.4 for the combination.

CONCLUSION: **Dietary supplementation with vitamin E significantly increased the risk of prostate cancer among healthy men.**



Relative and Absolute Risk of Prostate Cancer According to Modified Gleason Score (mGS), PCPT and REDUCE Trial.

The abbreviation 5-ARI denotes 5α-reductase inhibitors. I bars indicate 95% confidence intervals.

Established risk factors for prostate cancer

The established risk factors for prostate cancer are age, ethnicity, family history of the disease and some genetic factors. (*tobacco*)

- Increasingly, **obesity** has been linked to aggressive prostate cancer risk.
- …prostate cancer risk may be elevated by diets rich in meat, dairy products or fat, and may be lowered by diets high in fibre, fruit, vegetables and various micronutrients

Da Prostate cancer risk related to foods, food groups, macronutrients and micronutrients derived from the UK Dietary Cohort Consortium food diaries. Lane JA et al. European Journal of Clinical Nutrition (2017) 71, 274–283

Micronutrients

- The epidemiological evidence for selenium and vitamin E was judged sufficient to commence a randomized supplementation trial, but this was stopped early due to no benefit… guidelines currently identify
- the carotenoid **lycopene**, a pigment found in tomatoes and other fruits as having a ‘probable’ protective effect on prostate cancer risk, whereas
- diets rich in calcium were classed as ‘probably’ increasing prostate cancer risk

Conclusioni

- …revealed no association with diet and prostate cancer,
- but a reduction with a Mediterranean-style diet rich in monounsaturated fatty acids and vegetables/fruits and low in red meats.
- A recent meta-analysis of adherence to a Mediterranean diet and overall cancer risk showed a 4% risk reduction for prostate cancer incidence

Frequenza regionale 2009-2013

3435 casi nel periodo 2009-2013

In media 687 casi per anno

Tasso standardizzato per 100,000 abitanti, popolazione Italia 2011:
71.08

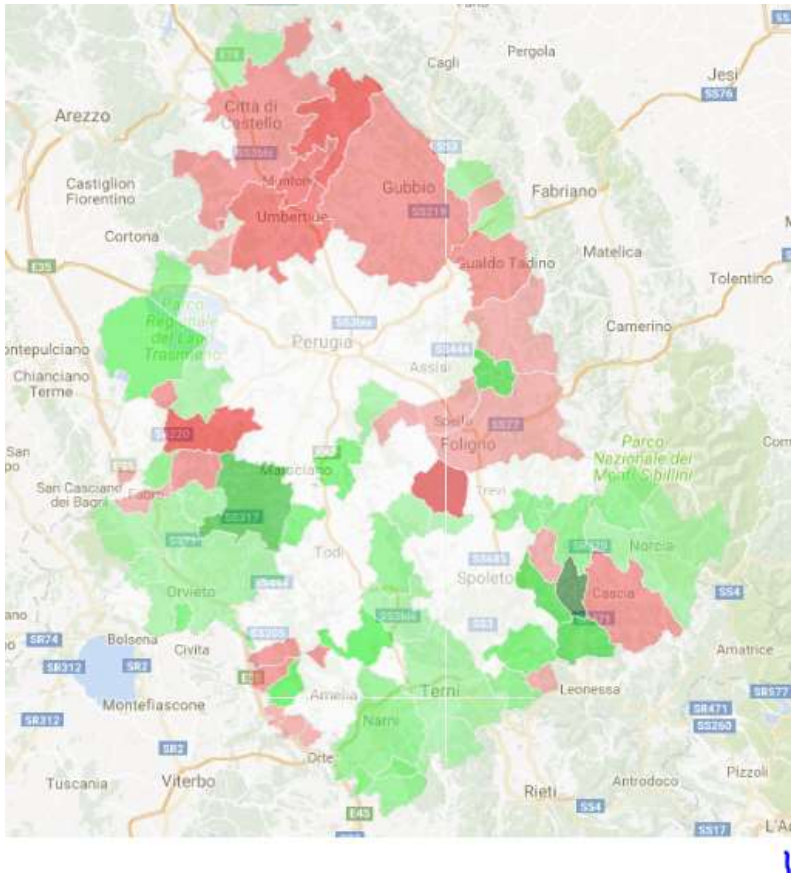
Primi cinque tumori più frequentemente diagnosticati in Umbria e proporzione sul total

Periodo completo: 1994 - 2013 | Ultimi 10 anni: 2004 - 2013 | **Ultimi 5 anni: 2009 - 2013**

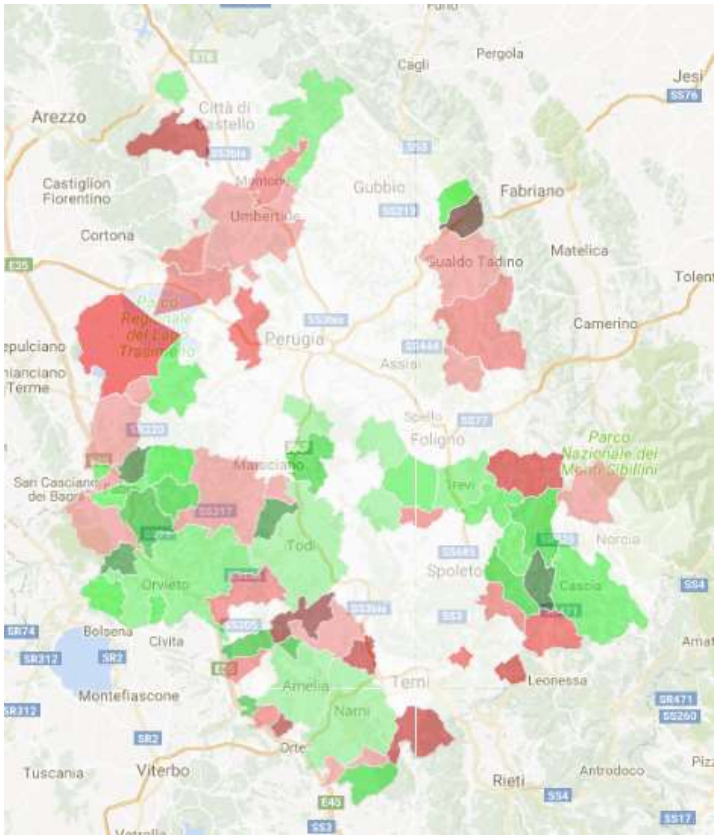
Rank	Maschi	Rank	Femmine	Rank	Tutta la popolazione
1	Prostata 687 casi per anno - 17.9%	1	Mammella 761 casi per anno - 23.9%	1	Colon retto 837 casi per anno - 11.9%
2	Colon retto 468 casi per anno - 12.2%	2	Colon retto 369 casi per anno - 11.6%	2	Mammella 769 casi per anno - 10.9%
3	Bronchi e polmoni 436 casi per anno - 11.4%	3	Bronchi e polmoni 171 casi per anno - 5.4%	3	Prostata 687 casi per anno - 9.8%
4	Vie urinarie 265 casi per anno - 6.9%	4	Stomaco 146 casi per anno - 4.6%	4	Bronchi e polmoni 608 casi per anno - 8.7%
5	Stomaco 185 casi per anno - 4.8%	5	Corpo dell'utero 137 casi per anno - 4.3%	5	Vie urinarie 334 casi per anno - 4.8%

Mappa dell'incidenza

2001-2009



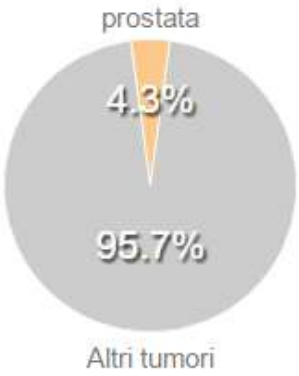
2010-2013



Mortalità regionale 2010-2014

676 casi nel periodo 2010-2014

In media 135 casi per anno



Prime cinque cause di morte per tumore più frequenti e proporzione sul totale dei decessi

Tasso standardizzato per 100,000 abitanti, popolazione Italia 2011:
12.45

Periodo completo: 1994 - 2014 | Ultimi 10 anni: 2005 - 2014 | **Ultimi 5 anni: 2010 - 2014**

Rank	Maschi	Rank	Femmine	Rank	Tutta la popolazione
1	Bronchi e polmoni 362 casi per anno - 20.6%	1	Mammella 175 casi per anno - 12.9%	1	Bronchi e polmoni 500 casi per anno - 16.0%
2	Colon retto 186 casi per anno - 10.6%	2	Colon retto 149 casi per anno - 10.9%	2	Colon retto 335 casi per anno - 10.7%
3	Prostata 135 casi per anno - 7.7%	3	Bronchi e polmoni 138 casi per anno - 10.1%	3	Stomaco 223 casi per anno - 7.1%
4	Stomaco 129 casi per anno - 7.3%	4	Pancreas 98 casi per anno - 7.2%	4	Pancreas 182 casi per anno - 5.8%
5	Vie urinarie 88 casi per anno - 5.0%	5	Stomaco 94 casi per anno - 6.9%	5	Mammella 178 casi per anno - 5.7%
				6	Prostata 135 casi per anno - 4.3%

Mortalità in riduzione