Possibilities of cancer prevention, early detection and cancer care in males
Introduction

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Cancer in Males: Epidemiology

- **Cancer epidemiology (2008)**
  - Worldwide
    - Incidence
      - Men: 6,617,844; 203.8/100.000
      - Women: 4,219,626; 128.6/100.000
    - Mortality
      - Men: 6,044,710; 165.1/100.000
      - Women: 3,345,176; 87.6/100.000
    - M/I
      - Men: 81%
      - Women: 68%

Globocan 2008 (8.2011)

Cancer in Males: Epidemiology

- **Cancer epidemiology (2008)**
  - Estonia
    - Incidence
      - Men: 2,734; 285.7/100.000
      - Women: 2,822; 203.7/100.00
    - Mortality
      - Men: 1,905; 189.1/100.000
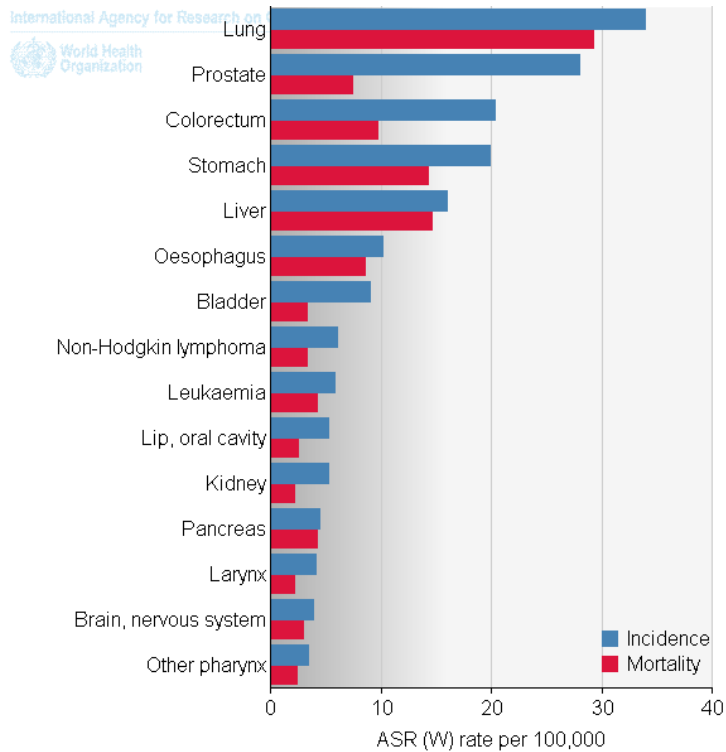   - Women: 1,630; 90.3/100.000
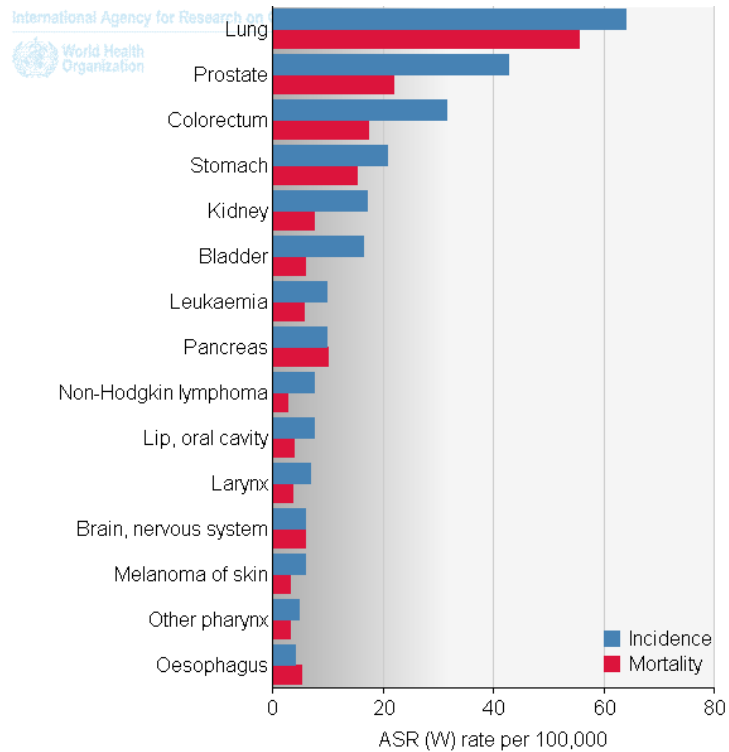   - M/I
      - Men: 65%
      - Women: 44%

Globocan 2008 (8.2011)

Cancer in Males: Epidemiology

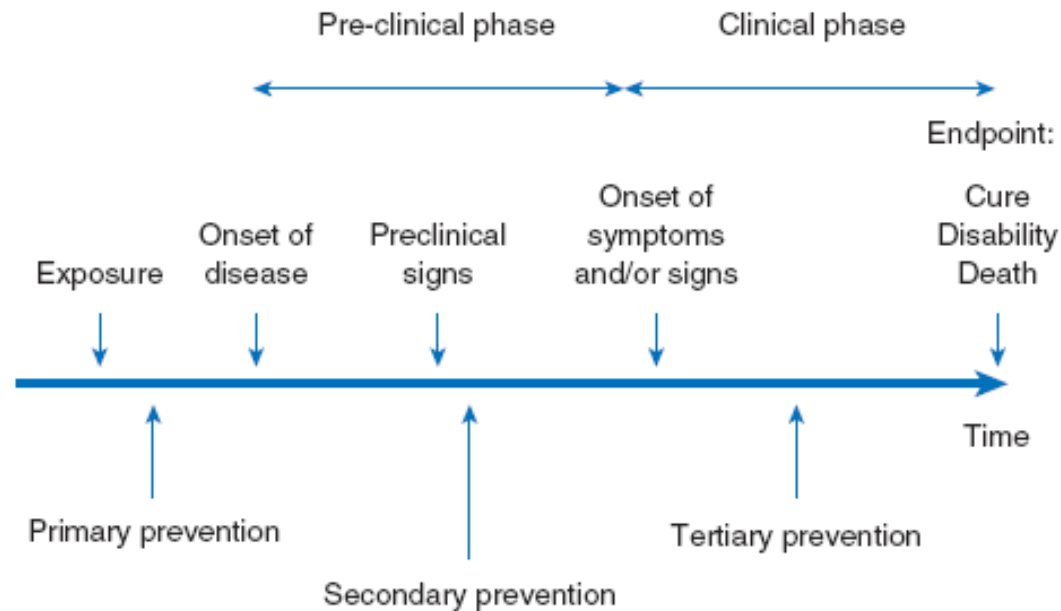- **Most frequent cancers: men**

Worldwide

Estonia

Globocan 2008 (8.2011)

Cancer in Males: How to Approach the Cancer Problem

- **Natural evolution of cancer and different approaches**

Cancer in Males: Prevention of Cancer

- **Types of cancer prevention**
  - Primary prevention
    - Controlling (avoiding) exposure to risk factors
    - Increasing an individual's resistance to these risk factors (by immunization or chemoprevention)
  - Secondary prevention
    - Detecting cancer at an early stage when treatment is
      - More effective
      - Leading to a higher rate of cure
      - Reduced frequency of the more serious consequences of disease
  - Tertiary prevention
    - Reducing the progress or complications (and death) of disease and of disability to improve the outcome of illness among affected individuals

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Cancer in Males: Primary Prevention

- **Risk factors**
  - Cancer risk factor = factor that modulate/influences cancer development
  - Types of risk factor
    - Modifiable
      - Behavioral
      - Environmental
    - Non-modifiable
      - Biological: age; gender
      - Genetic
  - Effect of risk factor on carcinogenesis depend on
    - Duration of exposure to the risk
    - Quantitative extent of exposure
    - Cumulative and synergistic effects of other factors

Cancer in Males: Primary Prevention

- **Preventable cancers by primary prevention**
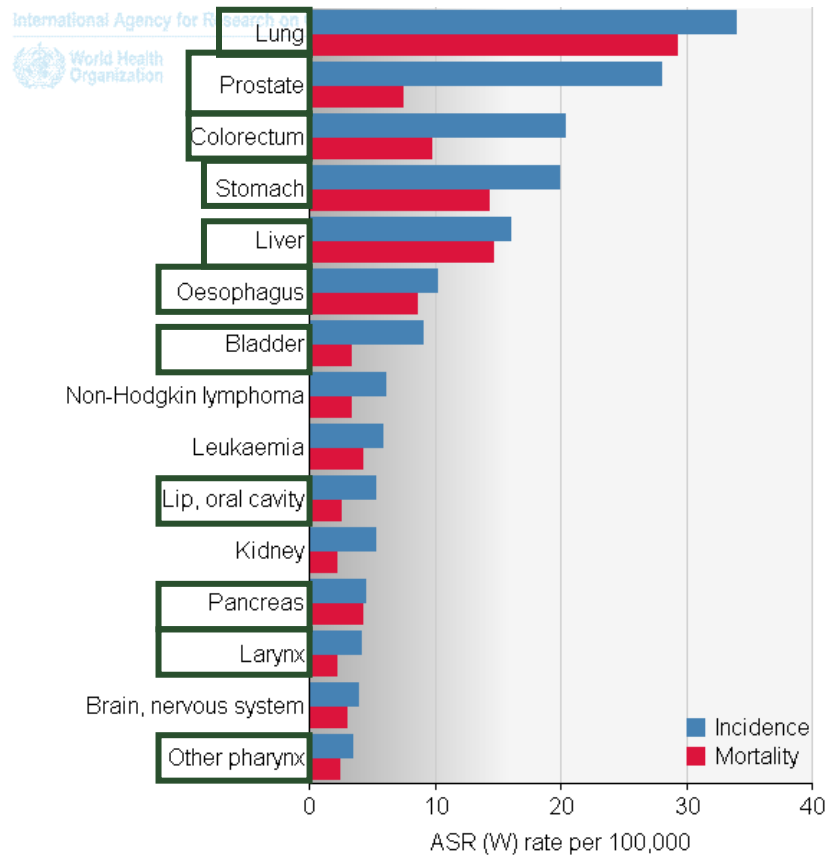
Cancer in Males: Primary Prevention Obesity

- **Nutritional status: overweight in men in Europe**

Country (year)	Age (Years)	Overweight (BMI: 25-29.9) (%)	Obesity (BMI > 30) (%)
Estonia (2004)	16-64	32.0	13.7
France (2006)	15+	35.6	11.8
Finland (2003)	25-64	48.0	19.8
Italy (2003)	18+	42.1	9.3
Lithuania (2002)	20-64	41.2	16.4
Poland (2002)	18-94	39.0	10.9
Portugal (2003)	18-64	49.1	14.5
Slovenia (2001)	25-64	50.0	16.5
UK-England (2004)	16+	43.9	22.7

IOTF. Global prevalence database 2007

Cancer in Males: Primary Prevention Obesity

- **Cancers in men associated with obesity**

| Cancer type	Incidence		Mortality	
	Strength of evidence	Effect on risk	Strength of evidence	Effect on risk
Colorectal	Consistent	Increased; RR 2.0	Inconsistent	Decreased survival
Renal	Consistent	Increased; RR 2.5	Inconsistent	Non conclusive
Esophageal	Consistent	Increased; RR 3.0	Modest	Decreased survival
Prostate	Controversial	Non-conclusive	Modest	Decreased survival
Pancreas	Controversial	Increased; RR 1.7	Inconsistent	Non conclusive
Gastric cardia	Controversial	Increased; RR 2.0	Inconsistent	Non conclusive
Liver	Controversial	Increased; RR 1.5-4.0	Inconsistent	Non conclusive
Gall bladder	Limited data	Increased; RR 2.0	Limited data	Non conclusive
Lymphoma	Limited data	Increased	Limited data	Non conclusive

RR: risk ratio

Cancer in Males: Primary Prevention
Obesity

- **Preventive measures**
  - Maintain a healthy weight throughout life
    - Balance caloric intake with physical activity
    - Avoid excessive weight gain throughout the life cycle
    - Achieve and maintain a healthy weight if currently overweight or obese
  - Adopt a physically active lifestyle
    - Engage in at least 30 minutes of moderate-to-vigorous physical activity (above usual activities) on at least 5 days/week (45 to 60 minutes of intentional physical activity are preferable)

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Cancer in Males: Primary Prevention
Tobacco Use

- **Tobacco use in men**

%
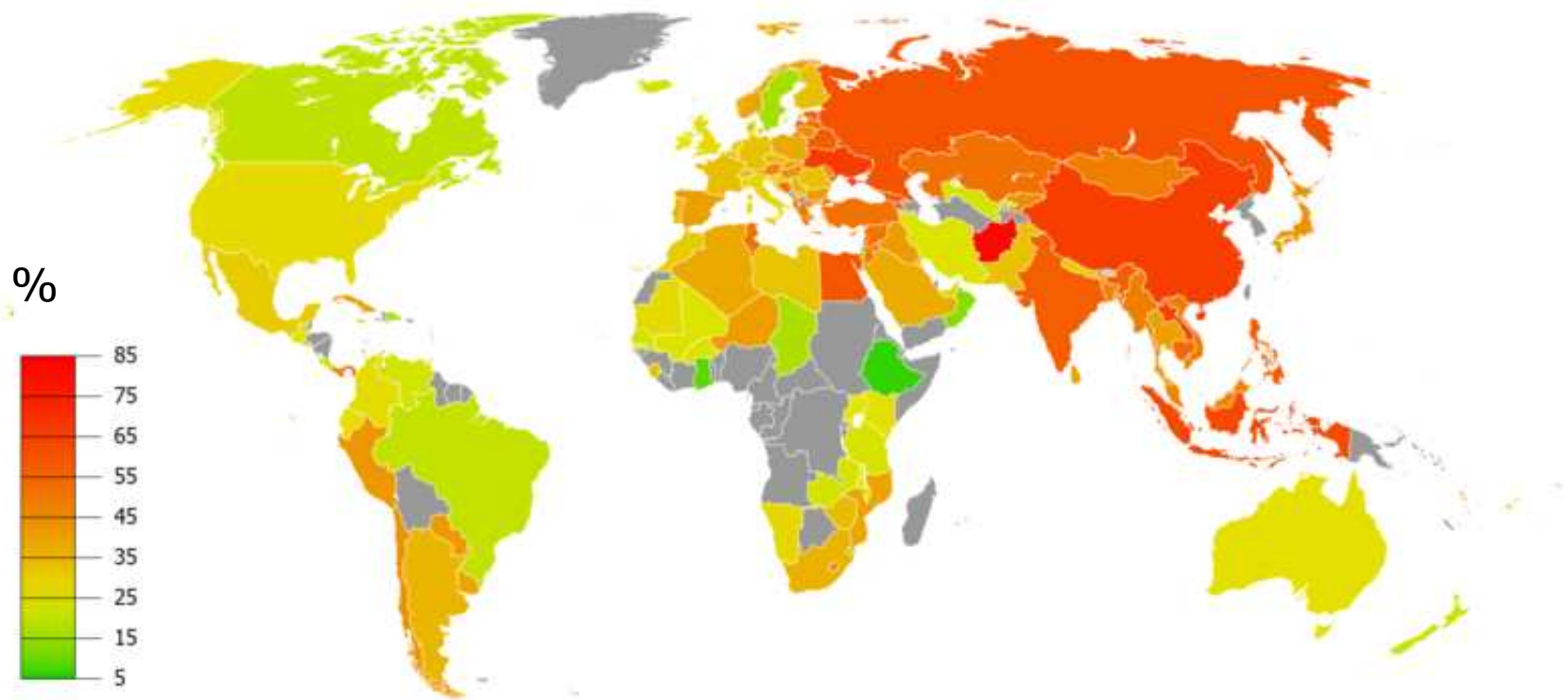
WHO Report on the Global Tobacco Epidemic, 2008

Cancer in Males: Primary Prevention Tobacco Use

- **Cancer types convincingly associated with smoking**
  - Respiratory tract
    - Lung cancer
    - Laryngeal cancer
    - Oropharyngeal cancer
  - Gastrointestinal tract
    - Esophageal cancer
    - Stomach cancer
    - Pancreatic cancer
  - Genitourinary tract
    - Kidney (renal) cancer
    - Bladder cancer

Cancer in Males: Primary Prevention
Tobacco Use

- **Cancer types probably associated with smoking**
  - Acute myeloid leukemia
  - Colorectal cancer
  - Liver cancer

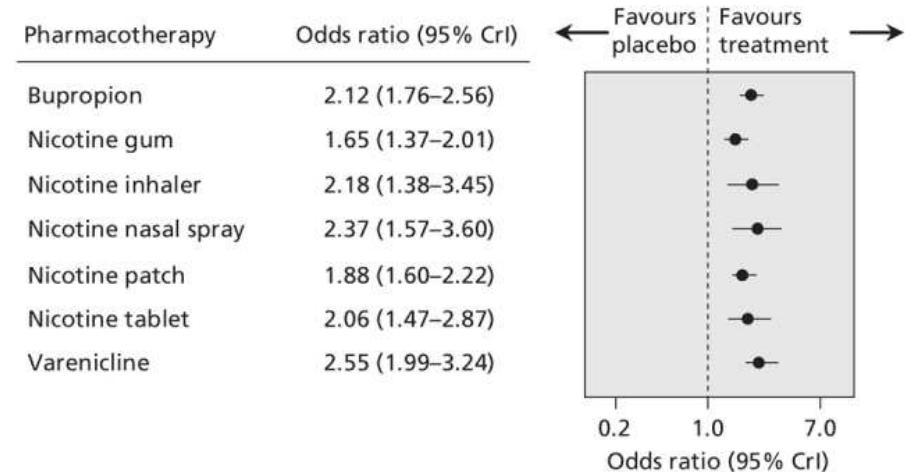# Cancer in Males: Primary Prevention
Tobacco Use

- **Proven tobacco control policies**
  - Monitor tobacco use and prevention policies
  - Protect people from tobacco smoke
  - Offer help to quit tobacco use
  - Warn about the dangers of tobacco
  - Enforce bans on tobacco advertising, promotion and sponsorship
  - Raise taxes on tobacco

Cancer in Males: Primary Prevention
Tobacco Use

- **Individual measures for tobacco control**
  - Self-help approaches
  - Counseling
  - Pharmacotherapy
  - Pharmacotherapy + psychological interventions

Pharmacotherapy	Odds ratio (95% CrI)	← Favours placebo	Favours treatment →
Bupropion	2.12 (1.76–2.56)		
Nicotine gum	1.65 (1.37–2.01)		
Nicotine inhaler	2.18 (1.38–3.45)		
Nicotine nasal spray	2.37 (1.57–3.60)		
Nicotine patch	1.88 (1.60–2.22)		
Nicotine tablet	2.06 (1.47–2.87)		
Varenicline	2.55 (1.99–3.24)		

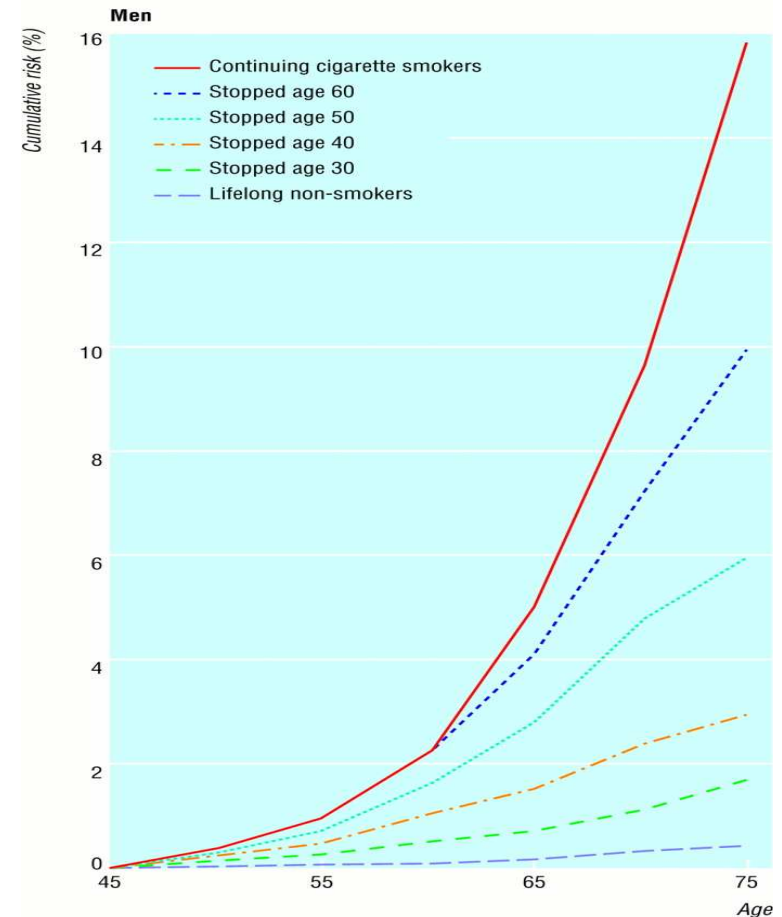0.2   1.0   7.0
Odds ratio (95% CrI)

Ranney et al. Ann Intern Med 2006; Eisenberg et al. CMAJ 2008

Cancer in Males: Primary Prevention
Tobacco Use

- **Effect of stopping smoking**

Effects of stopping smoking at various ages on the cumulative risk (%) of death from lung cancer up to age 75, at death rates for men in UK in 1990

Peto et al. BMJ 2000

Men

Cumulative risk (%)

— Continuing cigarette smokers
--- Stopped age 60
···· Stopped age 50
-·- Stopped age 40
-- Stopped age 30
-- Lifelong non-smokers

Age

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Cancer in Males: Primary Prevention
Alcohol Use

• **Pure alcohol consumption in L/capita $\geq$15 year in Europe**
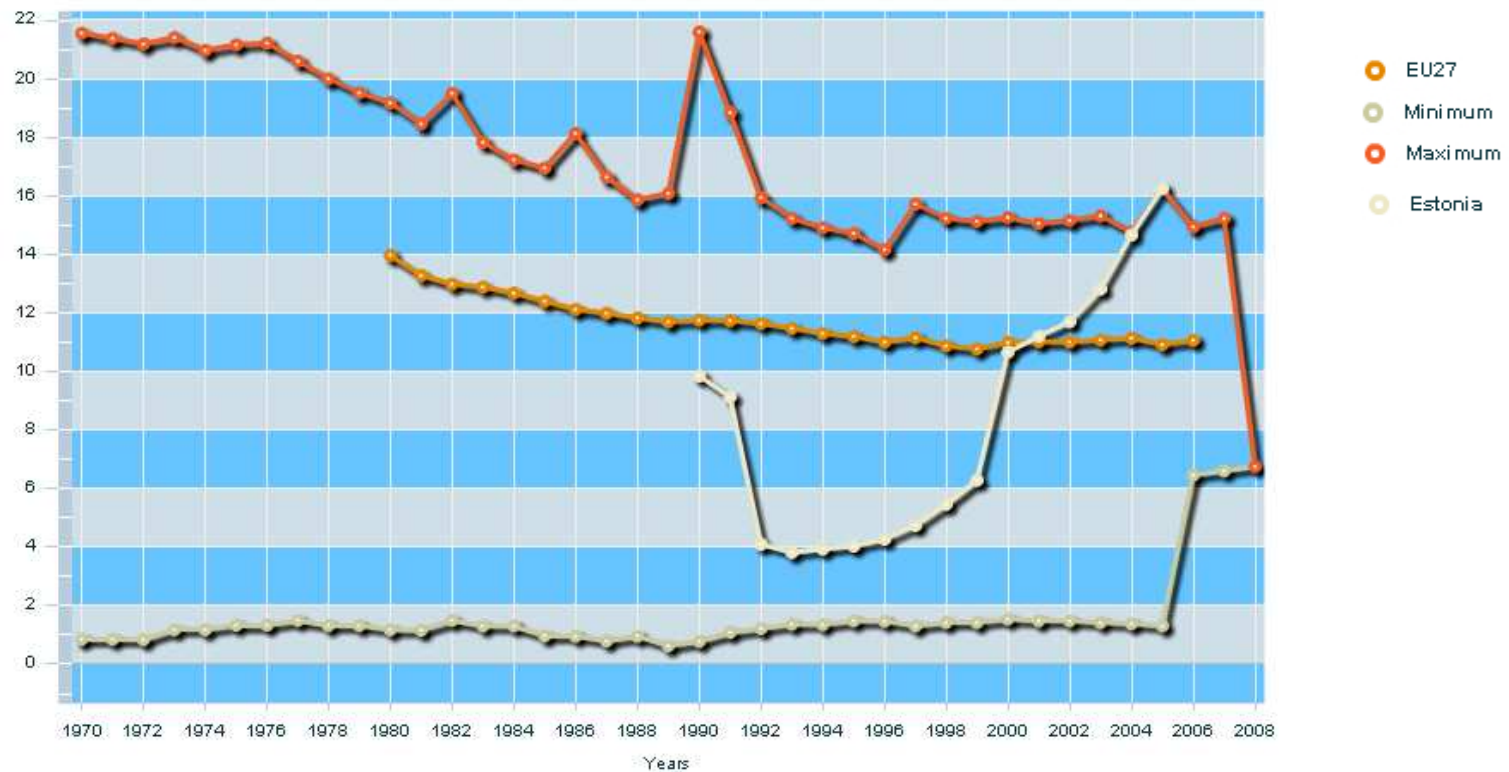
Cancer in Males: Primary Prevention Alcohol Use

- **Relative risk for cancer associated with average drinking category**

	Drinking category		
Cancer type	I	II	III
Oral cavity/Oropharynx	1.45	1.85	5.39
Esophagus	1.8	2.38	4.36
Liver	1.45	3.03	3.6
Other cancers	1.1	1.3	1.7

I: 0-39.99 g of pure alcohol/d; II: 40-59.99 g pure alcohol/d; > 60 g pure alcohol/d

Cancer in Males: Primary Prevention
Alcohol Use

- **Alcohol control policies**
  - Supply-oriented measures = limiting access to alcohol
    - Price policy: increasing the price of alcoholic beverages
    - Outlet density: higher density leads to higher alcohol sales
    - Hours of sales: increased drinking is associated with number of sale hours
    - Age restrictions: minimum age for purchase

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Cancer in Males: Primary Prevention
Alcohol Use

- **Alcohol control policies**
  - Demand-oriented measures
    - School-based education: little effect
    - Family-based interventions: may reduce alcohol abuse or risk factors for substance use
    - Community action: reduce drunken driving and accidents
    - Mass media campaigns: no impact on self-reported drinking
    - Warning labels on beverage containers: low impact; no change in the perception of risk; no change in behavior
    - Restrictions on advertising

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Cancer in Males: Primary Prevention
Alcohol Use

- **Alcohol control policies**
  - Individual approach
    - Screening for at-risk drinkers by screening instruments
    - If screening and assessment indicate increased risk
      ⟶ brief intervention by the healthcare provider significantly reduces alcohol use and associated problems
      - Various protocols for brief interventions
      - Providing advice
      - Counseling
      - Pharmacotherapy to
        - Alleviate acute withdrawal symptoms
        - Prevent re-abuse of alcohol
  - Recommended limitation of alcohol
    - 20 g of alcohol or two standard drinks per day for men

Cancer in Males: Primary Prevention Chemoprevention

- **Chemoprevention**
  - Use of agents that prevent
    - Induction
    - Growth
    - Progression of cancer
  - Agents
    - Dietary interventions
      - Vitamins
    - Medication
      - Anti-hormones
      - Anti-inflammatory drugs
  - Tested in different tumor types
    - Breast
    - Prostate
    - Colorectal/Lung/Head and neck cancer

Cancer in Males: Primary Prevention Chemoprevention in Prostate Cancer

- **Dietary products in the prevention of prostate cancer**

Author (year)	Nutritional component	Type study	Effect prevention
Giovannucci (2002)	Tomato products	Cohort	Protective effect
Kavanaugh (2007)	Tomato products/lycopene	FDA review	No effect
Kristal (2011)	Lycopene	Case control	No effect (case control)
Virtamo (2003)	Alpha-tocopherol/beta-carotene	Randomized	Alpha-tocopherol 32% decrease Beta-carotene 23% increase No long term effect
Duffield-Lillico (2003)	Selenium	Randomized	Protective effect
Jian (2004)	Green tea	Case control	Protective effect
Van Poppel (2011)	Phyto estrogens	Non-prospective	Possible protective effect

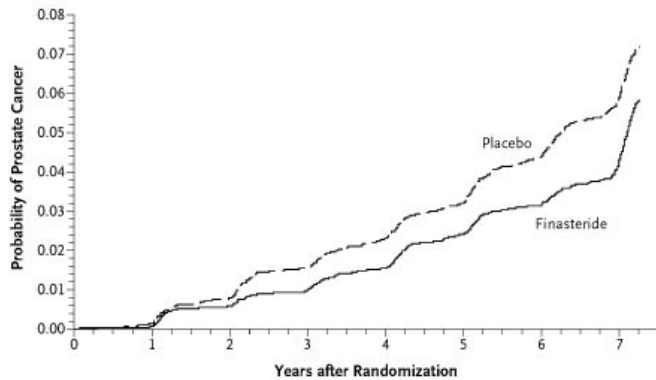# Cancer in Males: Primary Prevention Chemoprevention in Prostate Cancer

- **5-α Reductase inhibitors**

	PCPT	REDUCE
Patient number	18,882	8,336
Patient risk factors	Age ≥55 years Normal DRE Serum PSA ≤3 ng/mL	Age 50-75 years Serum PSA 2.5-10.0 ng /mL 1 negative prostate biopsy (6 to 12 cores) within 6 months
Treatment	5 mg finasteride/day vs placebo for 7 years	0.5 mg dutasteride/day vs placebo for 4 years

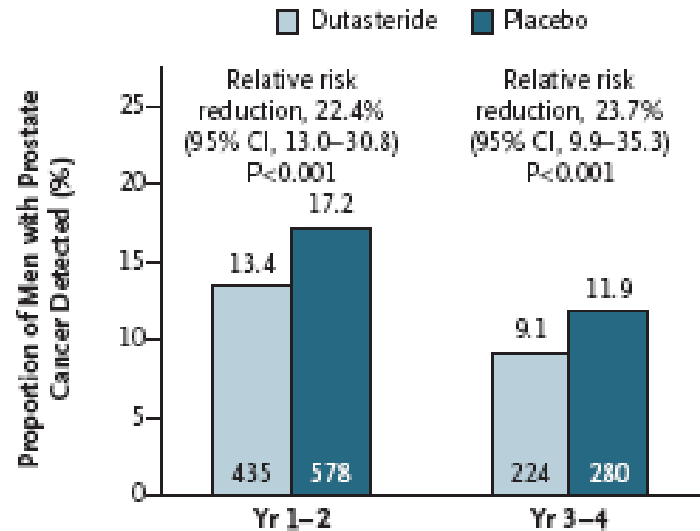DRE: digital rectal examination; SA: prostate-specific antigen; vs: versus

Cancer in Males: Primary Prevention Chemoprevention in Prostate Cancer
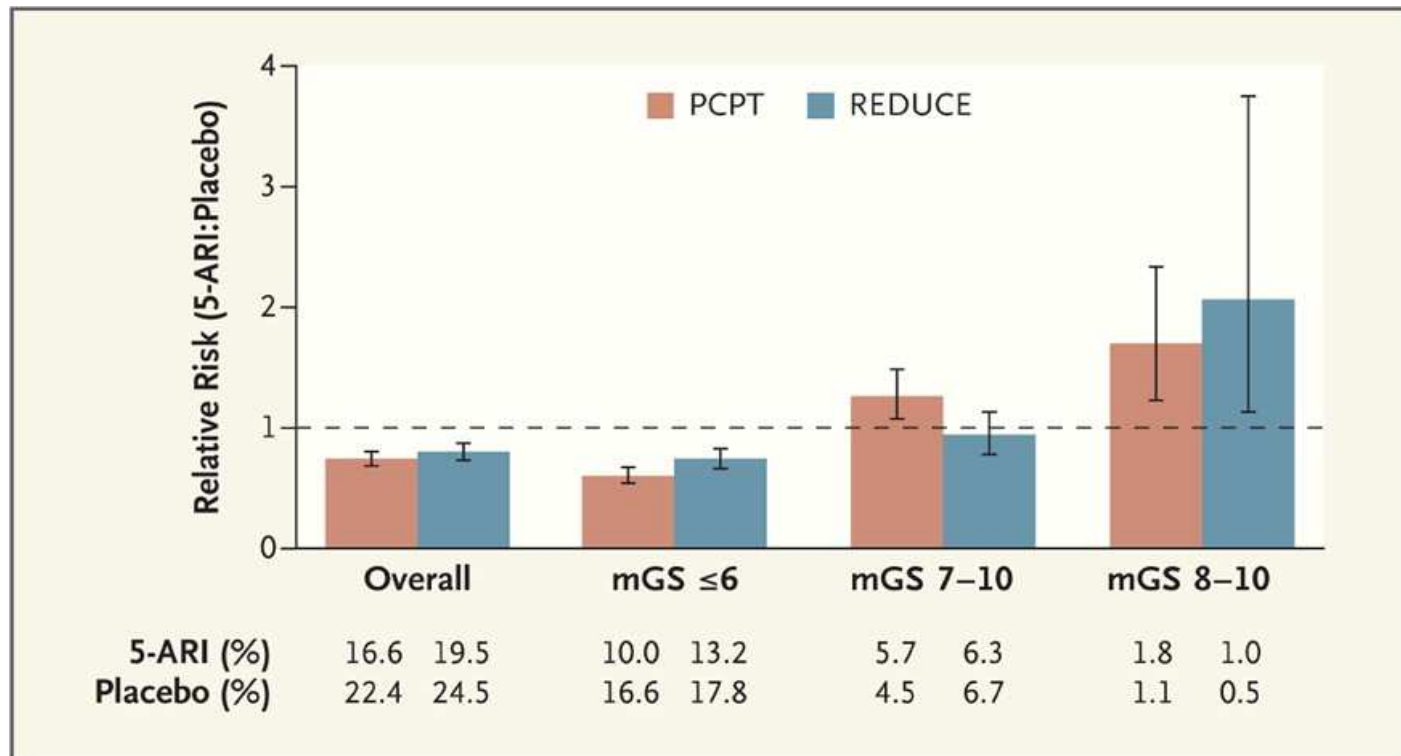
- **5-α Reductase inhibitors**

PCPT: Thompson et al. N Engl J Med 2003

Reduce: Andriole et al. N Engl J Med 2010

Cancer in Males: Primary Prevention Chemoprevention in Prostate Cancer

- **5-α Reductase inhibitors**

Theoret et al. N Engl J Med 2011

Cancer in Males: Primary Prevention Chemoprevention in Prostate Cancer

- **5-α Reductase inhibitors**

	PCPT		REDUCE	
	Finasteride	Placebo	Dutasteride (%)	Placebo (%)
Decreased libido	65.4	59.6*	3.3	1.6*
Erectile dysfunction	67.4	61.5*	9.0	5.7*
Gynecomastia	4.5	2.8*	1.9	1.0*
Urinary retention	4.2	6.3*	1.6	6.7*

*: $p < 0.05$

Cancer in Males: Secondary Prevention
Screening for Prostate Cancer

- **Conditions to start screening program (WHO)**
  - Condition represents a major cause of death and has a substantial prevalence in the population
  - Natural history of disease, from latency to overt disease, is well characterized
  - Screening test acceptable to population
  - Treatment of latent or early stage disease improves outcome
  - Effective treatments available with overt disease
  - Facilities for diagnosis and treatment available
  - Agreement among clinical guidelines on whom to treat
  - Screening should be cost-effective
  - Screening tests with a high positive predictive value, negative predictive value, sensitivity and specificity

http://www.who.int/cancer/detection/variouscancer/en/index.html

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Cancer in Males: Secondary Prevention Screening for Prostate Cancer

Advantages

Early disease highly curable; advanced disease generally incurable

Screening relatively simple (PSA, DRE, TRUS)

Positive trials

Disadvantages

Suboptimal sensitivity, specificity, predictive value of tests (DRE, PSA, TRUS)

Not all prostate cancers clinically significant

- Psychological and economic burden of diagnosis
- Morbidity of potentially unnecessary treatment

Rimer et al. Cancer: Principles & Practice of Oncology. 6th ed. 2001

Cancer in Males: Secondary Prevention Screening for Prostate Cancer

	PLCO3	ERSPC2	Goteborg 56
Period	1993–2001	1994–2006	1995–2008
Number of men	76,693	162,243	20,000
Age (years)	55–74 (13% >70)	55–69	50–64
Site	Multiple centers (USA)	7 countries	1 city (Goteborg, SW)
Methods	PSA >4 ng/mL Abnormal DRE	PSA >3 ng/mL Abnormal DRE	PSA >2.5 ng/mL (>2005) PSA >2.9 ng/mL (1999–04) PSA >3.4 ng/mL (1995–98)
Follow-up	Every 1 year × 6 11 years median follow-up	Every 4 years 9 years (complete)	Every 2 years 78% had 14-year follow-up

PLCO: Prostate, Lung, Colorectal, and Ovarian screening trial; ERSPC: European Randomized Study of Screening for Prostate Cancer trial; PSA: prostate specific antigen; DRE: digital rectal examination

Izawa et al. Can Urol Assoc J 2011

Cancer in Males: Secondary Prevention Screening for Prostate Cancer

	PLCO3	ERSPC2	Goteborg 56
Compliance (%)	85	82	76
Contamination (%)	52	Not known	3
Prostate cancer Control/ Screened (%)	6/7.3	4.8/8.2	7.2/11.4
Prostate cancer deaths Control/Screened	50/44	326/214	78/44
Risk ratio (%)	NS	20 (p = 0.04)	44 (p = 0.002)
NNS		1:1410	1:293
NNT		1:48	1:12

PLCO: Prostate, Lung, Colorectal, and Ovarian screening trial; ERSPC: European Randomized Study of Screening for Prostate Cancer trial; NNS: number needed to screen; NNT: number needed to treat

Izawa et al. Can Urol Assoc J 2011

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Cancer in Males: Secondary Prevention Screening for Prostate Cancer

Organization	Screening	Screening technique	Screening interval	Age limits (years)
AUA (2011)	Yes	DRE/PSA	1/year	40-life expectancy > 10 years
NCCN (2011)	Yes	DRE/PSA	1/year	40
EAU (2011)	No			
ACS (2011)	No			
ESMO (2011)	No			

AUA:American Urology Association; EAU: European Association of Urology; ACS: American Cancer Society; ESMO: European Society for Medical Oncology; NCCN: National Comprehensive Cancer Network; DRE: digital rectal examination; PSA: prostate specific antigen

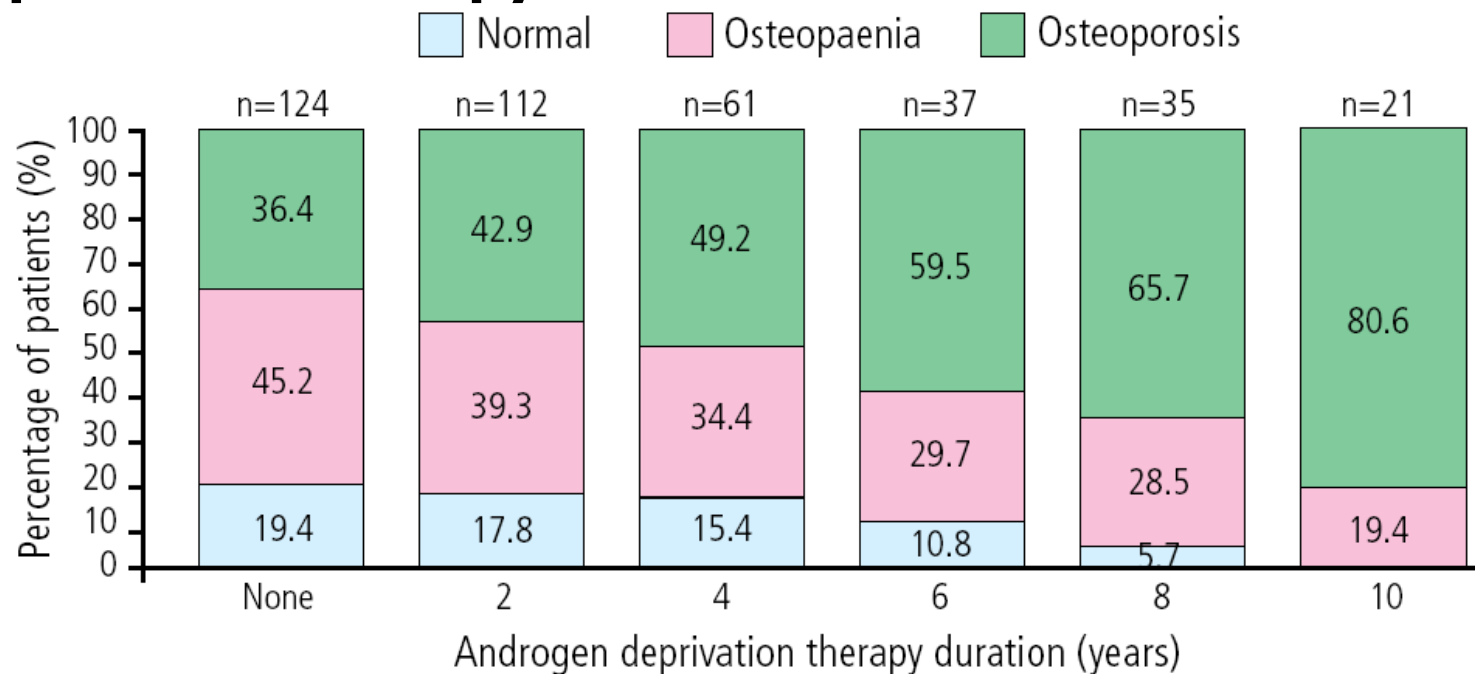# Cancer in Males: Tertiary Prevention Osteoporosis in Prostate Cancer

- **Osteoporosis = skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture**
- **Diagnosis**
  - Dual energy x-ray absorptiometry (DXA)
    - Bone mineral density compared to a young adult reference population translated in a T-score
      - T-score: $\geq$ - 1.0 = normal
      - T-score: <-1.0 and > -2.5 = ostopenia
      - T-score: $\leq$ -2.5 = osteoporosis

http://www.e-radiography.net/radpath/o/osteoporosis.htm; WHO 2007

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Cancer in Males: Tertiary Prevention
Osteoporosis in Prostate Cancer

- **Prevalence of osteoporosis and osteopenia in patients with non-metastatic prostate cancer: effect of Androgen Deprivation Therapy**

Morote et al. Actas Urológicas Españolas 2011

Cancer in Males: Tertiary Prevention
Fractures in Prostate Cancer

Author (year)	Number pts	Study type	Treatment	Fractures
Shahinian (2005)	50,613	Retrospective cohort	ADT vs no treatment	ADT: 19.4% No ADT: 12.7% p<.001
Smith (2005)	3,887 treatment vs 7,774 controls	Retrospective cohort	ADT vs no treatment	ADT group: 7.88 per 100 person-year Control group: 6.51 per 100 person-year HR, 1.21; p<.001
Dickman (2004)	17,731 in orchiectomy with prostate cancer 362,354 controls	Retrospective cohort	Orchiectomy vs no treatment	Relative risk of orchiectomy: 2.11 (95% CI, 1.94-2.19)

pts: patients: ADT: androgen deprivation therapy; vs: versus:
CI: confidence interval

VanderWalde et al. CA Cancer J Clin 2011

Cancer in Males: Tertiary Prevention
Osteoporosis in Prostate Cancer

- **FRAX**
  - = fracture risk assessment tool estimates the 10-year risks of any major fracture and hip fracture
  - Based on age, race, nationality, body mass index, medications, medical history, family history, smoking and alcohol consumption
  - http://www.shef.ac.uk/FRAX

VanderWalde et al. CA Cancer J Clin 2011

Cancer in Males: Tertiary Prevention
Prevention of Osteoporosis in Prostate Cancer

- **Lifestyle modifications**
  - Calcium and vitamin D intake
    - Calcium 1500 mg/d PO
    - Vitamin D 800 IU/d PO
  - Smoking cessation
  - Exercise
  - Moderating alcohol and caffeine intake

Egerdie et al. Can Urol Assoc J 2010

Cancer in Males: Tertiary Prevention
Prevention of Osteoporosis in Prostate Cancer

Author (year)	Treatment	Duration	Number of pts	Effect on BMD	Side effects
Greenspan (2007)	Alendronate 70 mg q 1 week vs placebo	1 year	112	Alendronate > placebo (spine, FN)	NSS
Smith (2003)	ZA 4 mg IV q 3 m vs placebo	1 year	106	ZA > placebo (spine, FN, TH)	NSS
Ryan (2006)	ZA 4 mg IV q 3 m vs placebo	1 year	122	ZA > placebo (spine, FN, TH)	More nausea ZA
Israeli (2007)	ZA 4 mg IV q 3 m vs placebo	1 year	215	ZA > placebo (spine, TH)	NSS
Smith (2009)	Denosumab 60 mg SC q 6 m vs placebo	36 months	1,468	Denosumab > placebo	NSS

FN = femoral neck; NSS = not statistically significant; q: every: ZA: zoledronic acid; IV: intravenous; SC: subcutaneously TH = total hip; vs: versus; m: months: BMD: bone mineral density; pts: patients

Egerdie et al. Can Urol Assoc J 2010

Cancer in Males: Tertiary Prevention
Prevention of Fractures in Prostate Cancer

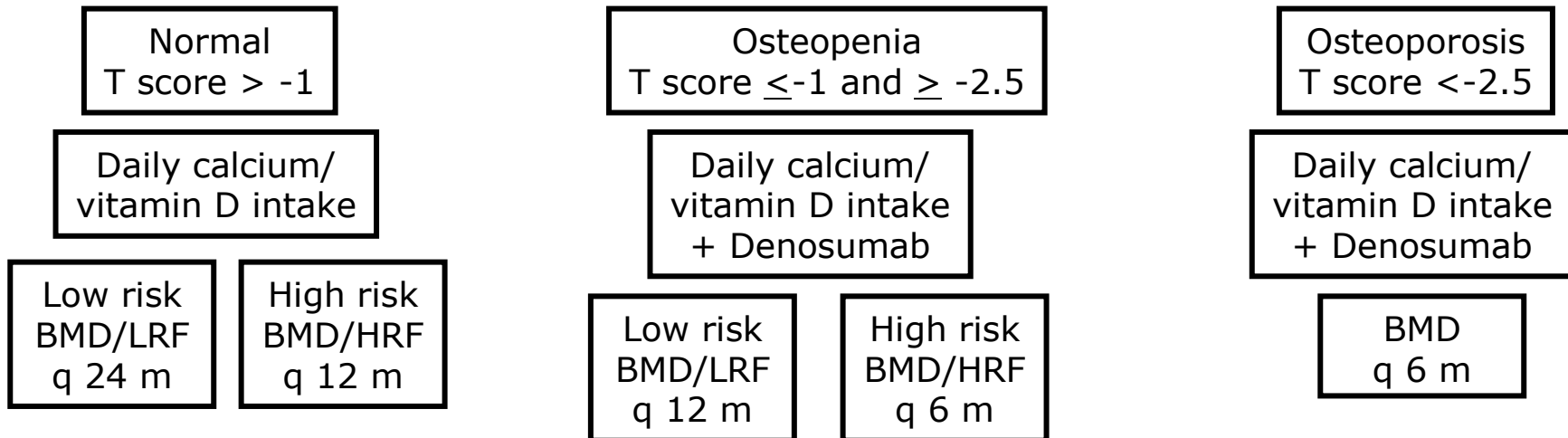| Author (year)	Treatment	Duration	Number of pts	Effect on fractures
Smith (2009)	Denosumab 60 mg SC q 6 m vs placebo	36 m	1,468	Denosumab 1.5% VF vs 3.9% with placebo; $p = 0.006$
Smith (2010)	Toremifene 80 mg OD vs placebo	48 m	1,389	Toremifene 2.5% VF vs 4.9% with placebo; $p < 0.05$

SC: subcutaneously; OD: once daily; VF = vertebral fractures; vs: versus; m: months; pts: patients

Cancer in Males: Teritary Prevention Management of Osteoporosis in Prostate Cancer

- **Patients on ADT**
  - Determine risk group
    - Low risk: no high-risk characteristics (LRF)
    - High risk (HRF): 1 or more of the following risk factors: duration of ADT more than 6 months; previous fractures; family history of osteoporosis; low BMI; tobacco use; alcohol consumption; corticosteroid use; medical co-morbidities; low vitamin D level
  - Measure baseline BMD

Normal T score > -1	Osteopenia T score ≤-1 and ≥ -2.5	Osteoporosis T score <-2.5
Daily calcium/ vitamin D intake	Daily calcium/ vitamin D intake + Denosumab	Daily calcium/ vitamin D intake + Denosumab
Low risk BMD/LRF q 24 m / High risk BMD/HRF q 12 m	Low risk BMD/LRF q 12 m / High risk BMD/HRF q 6 m	BMD q 6 m

After Higano. Nat Clin Pract Urol 2008

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Cancer in Males: Prevention Conclusions

- **Several types of prevention can be used in men to**
  - Reduce the incidence of cancer
  - Reduce the mortality of cancer
  - Reduce the morbidity related to cancer treatment
- **These types of prevention should be distributed among men at risk by**
  - Government-supported campaigns
  - Individual contacts with patients
- **Men should not be deprived of cancer prevention initiatives to improve their cancer-related outcome**