

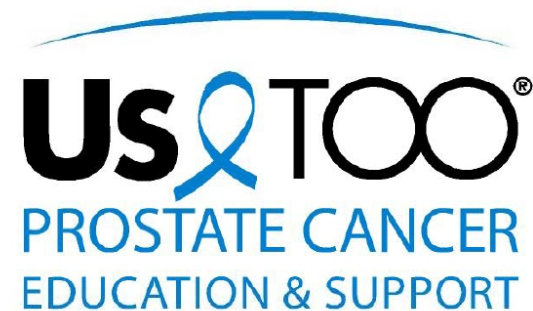


Us TOO University Presents: Estrogen Deficiency Side Effects Due to Androgen Deprivation Therapy

Today's speaker is Samir Taneja, MD

Program moderator is Pam Barrett,
Us TOO International

Made possible by a contribution from GTx, Inc.



Agenda

- 7:00 pm CT Welcome and introductions
- 7:04 pm CT Presentation by Dr. Taneja begins
- How ADT affects men treating prostate cancer
 - Role of estrogen and testosterone in men, and deficiencies associated with ADT
 - ADT estrogen deficiency side effects
 - Managing estrogen deficiency side effects of ADT
- 7:28 pm CT Live Q&A begins
- 7:48 pm CT Wrap-up
- 7:50 pm CT Call/webinar ends



Samir S. Taneja, MD

The James M. and Janet Riha Neissa Associate Professor of Urologic Oncology
Director, Division of Urologic Oncology
Department of Urology and NYU Cancer Institute
NYU Langone Medical Center
Chief, Urology Section, Veterans Administration Medical Center, Manhattan

Prostate cancer

- An estimated 192,280 new cases of prostate cancer will occur in the US during 2009
- Most frequently diagnosed cancer in men*
 - 1 in 6 men will be diagnosed with prostate cancer in their lifetime
- 2 million US prostate cancer survivors
 - More prostate cancer survivors than any other cancer
- Estimated 27,000 deaths in 2009
 - Second leading cause of cancer death in men
- Various treatment options
 - Surgery
 - External beam radiation
 - Radioactive seed implants
 - Watchful waiting (active surveillance)
 - Androgen Deprivation Therapy (ADT)
- Approximately 700,000 men are receiving ADT

*excluding skin cancers

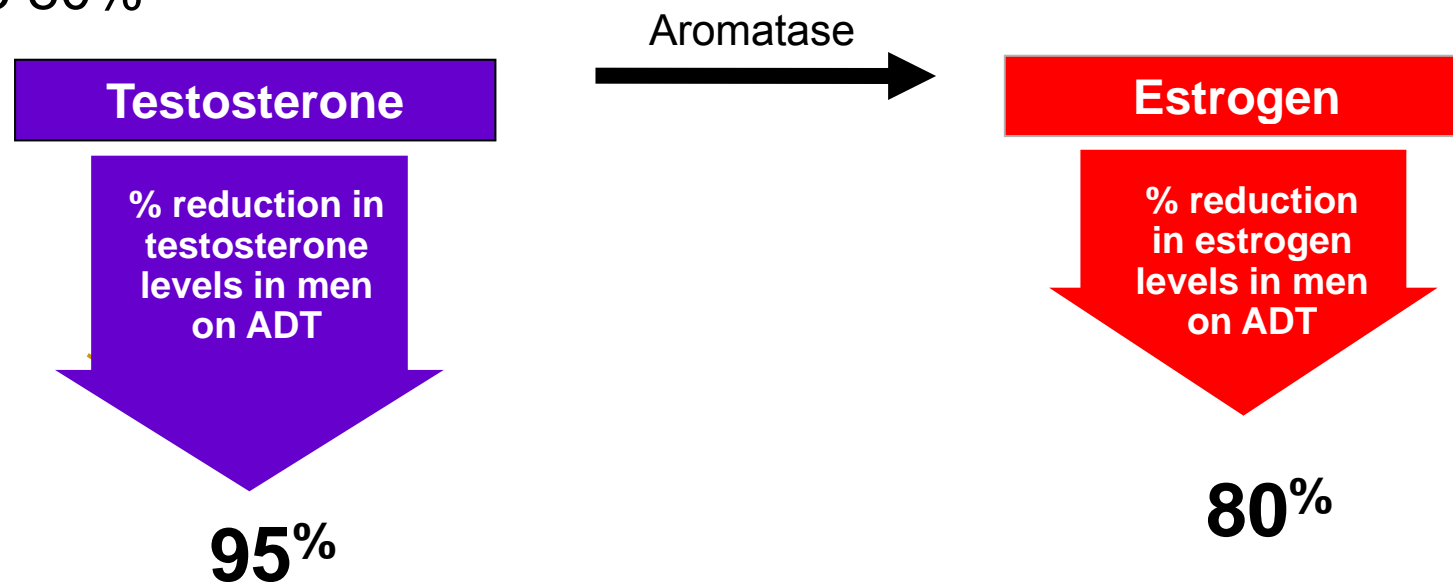
http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_prostate_cancer_36.asp

Guise TA, et al. *Rev Urol.* 2007;9(4):163-80.

<http://www.cancer.gov/cancertopics/pdq/treatment/prostate/patient/allpages/print>

ADT reduces testosterone and estrogen to castrate levels

- ADT (also called hormonal therapy) is the standard of care for men with advanced prostate cancer
- ADT is accomplished by either bilateral orchiectomy or using medications such as Lupron[®] or Zoladex[®]
- Testosterone is converted to estrogen by the aromatase enzyme
- ADT decreases testosterone by up to 95% and estrogen by up to 80%

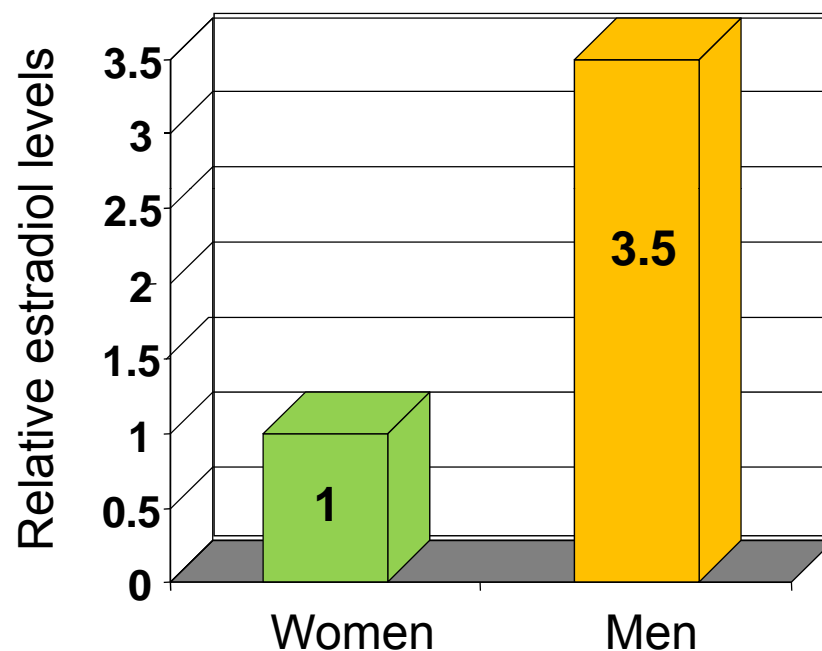


Smith MR, et al. *J Urol*. 2008;179(1):152-155.
Guise TA, et al. *Rev Urol*. 2007;9(4):163-80.
Zoladex is a registered trademark of Astra-Zeneca.

Stoch SA, et al. *J Clin Endocrinol Metab*. 2001;86:2787-2791.
Higano CS. *Urol Clin N Am*. 2004;31:331-352.
Lupron is a registered trademark of Abbott Laboratories.

Estrogen plays a vital role in men's health

- Estrogen is the principal hormone responsible for maintaining bone integrity in men and women
- Typically, elderly men (age 70 years) have higher levels of estrogen than women of similar age



The role of estrogen and testosterone in men

Estrogen

Thermoregulation & cognition

Libido

Cholesterol changes

Bone health

Testosterone

Mental & physical energy

Muscle strength

Body hair, deep voice

Erectile function

Prostate health

Gao W, et al. *Mol Interv.* 2007;7(1):10-13.
Higano CS. *Urology.* 2003;61(S2A):32-38.
Guise TA, et al. *Rev Urol.* 2007;9(4):163-180.

Estrogen and testosterone deficiencies associated with ADT

Estrogen deficiency side effects

Hot flashes

Breast enlargement & tenderness

Elevated cholesterol

Bone loss & fractures

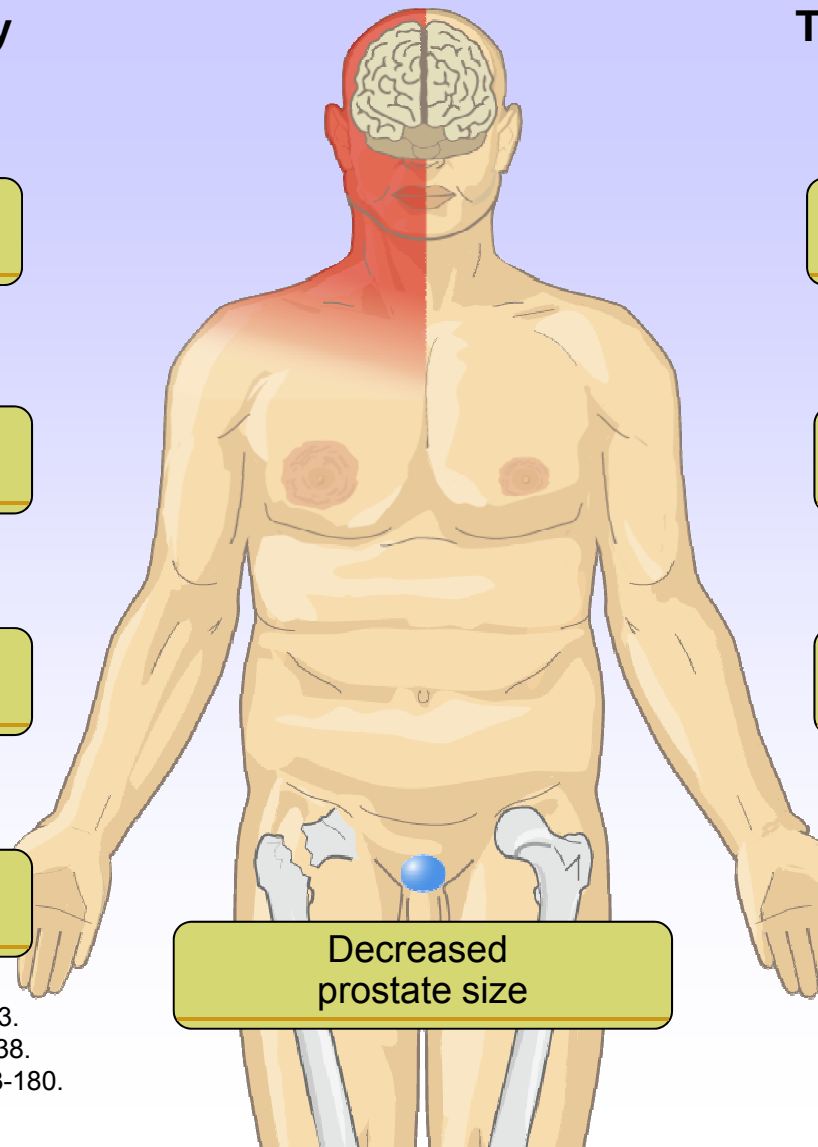
Testosterone deficiency side effects

Diabetes

Muscle weakness

Body composition changes

Erectile dysfunction



Gao W, et al. *Mol Interv.* 2007;7(1):10-13.
Higano CS. *Urology.* 2003;61(S2A):32-38.
Guise TA, et al. *Rev Urol.* 2007;9(4):163-180.

Key points on ADT estrogen deficiency side effects

- Fractures are highly prevalent in men on ADT, 1 in 5 men on ADT will have a fracture in four years
 - Most men on ADT do not know they are at higher risk for fractures
- Hot flashes and breast pain and enlargement are prevalent
 - Men on ADT complain about hot flashes but breast pain and enlargement not commonly assessed
 - Breast enlargement may be irreversible after first year
- ADT can increase risk for cardiovascular disease
 - Estrogen deficiency can worsen cholesterol
 - Testosterone deficiency may predispose to obesity and diabetes
 - ADT may impact arterial compliance (blood vessel health)

Shahinian VB, et al. *N Engl J Med*. 2005;352(2):154-64.

Guise TA, et al. *Rev Urol*. 2007;9(4):163-80.

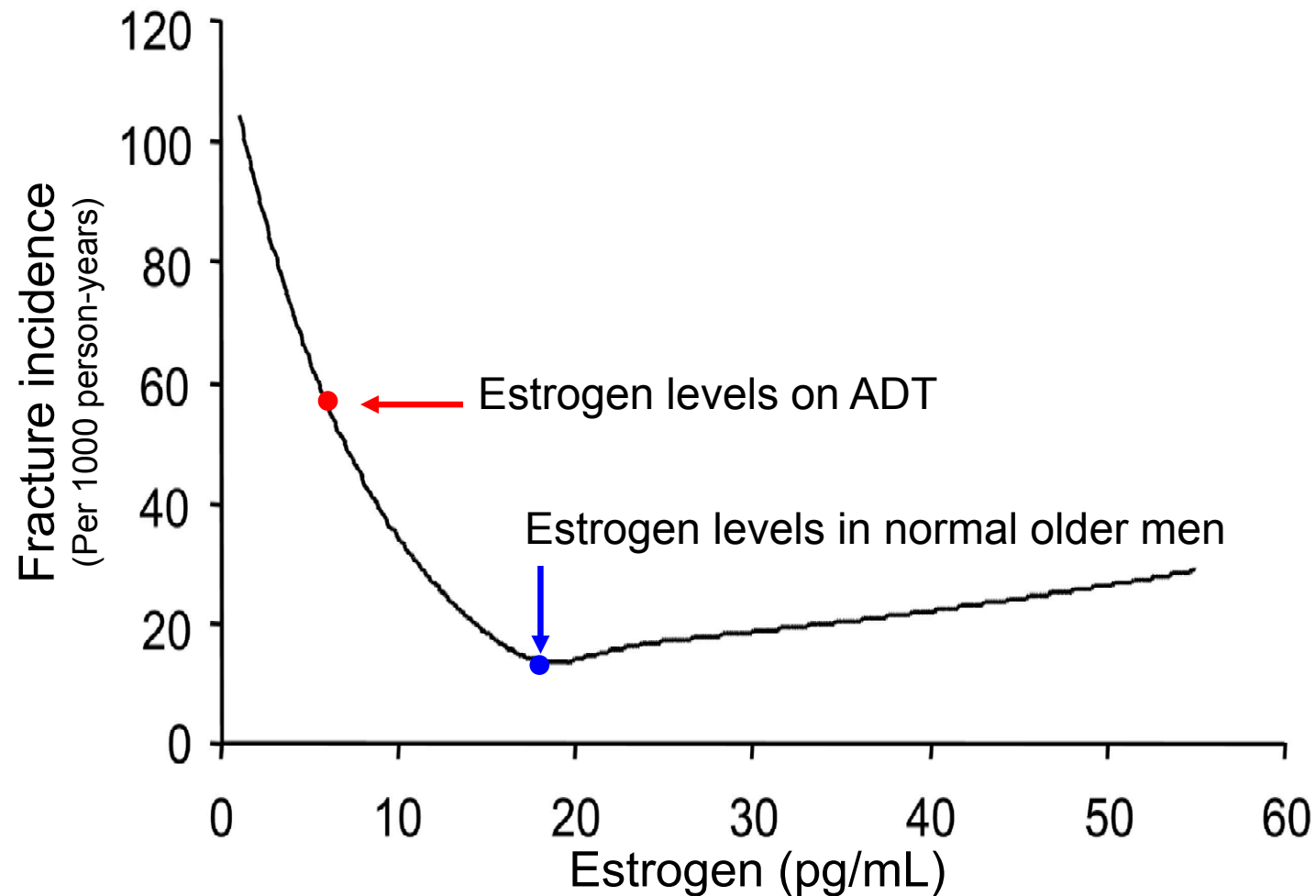
Keating NL, et al. *J Clin Oncol*. 2006;24(27):4448-56

Increased fracture risk in men on ADT

Classification of fractures

- Vertebral fractures
 - Determined by measuring the shape of vertebral bodies (spine) on lateral view X ray
- Fragility fractures
 - Non-traumatic fractures that occur as a result of a fall from a standing height or less (e.g. slipping on ice)
 - Typical sites are vertebral fractures, hip fractures and wrist fractures
- Traumatic fractures
 - Fractures resulting from falls from a distance greater than standing height or fracture that occur from some traumatic injury (e.g. car accident or falling off a ladder)

Low estrogen levels are associated with greater fracture incidence



Graph adapted from Mellström D, et al.

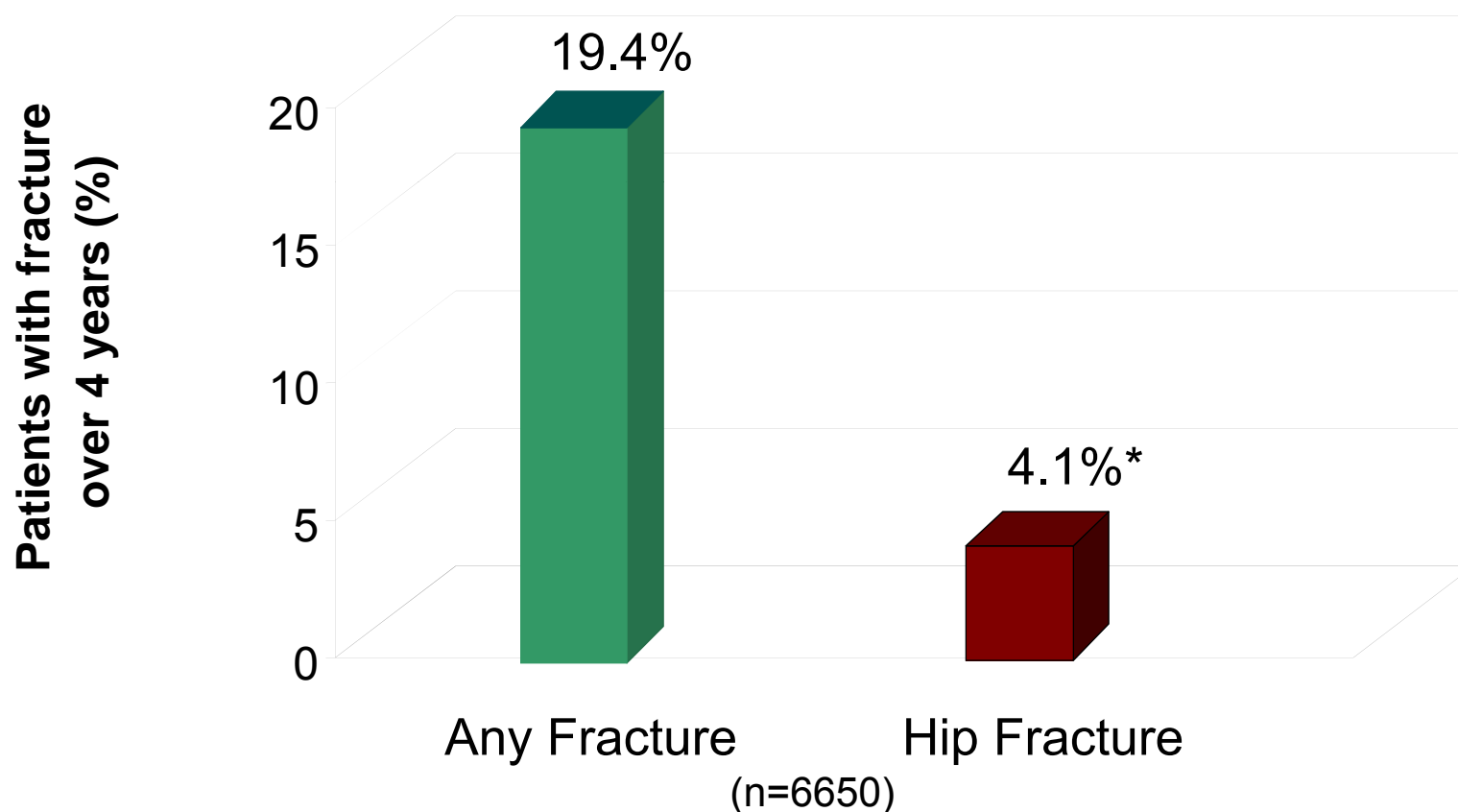
Mellström D, et al. *J Bone Miner Res.* 2008;23(10):1552-60.

Magno C, et al. *Eur Urol.* 2005 May;47(5):575-80;

Orwoll E, et al. *J Clin Endocrinol Metab.* 2006 Apr;91(4):1336-44

Smith MR, et al. *N Engl J Med* 2001;345:945-955.

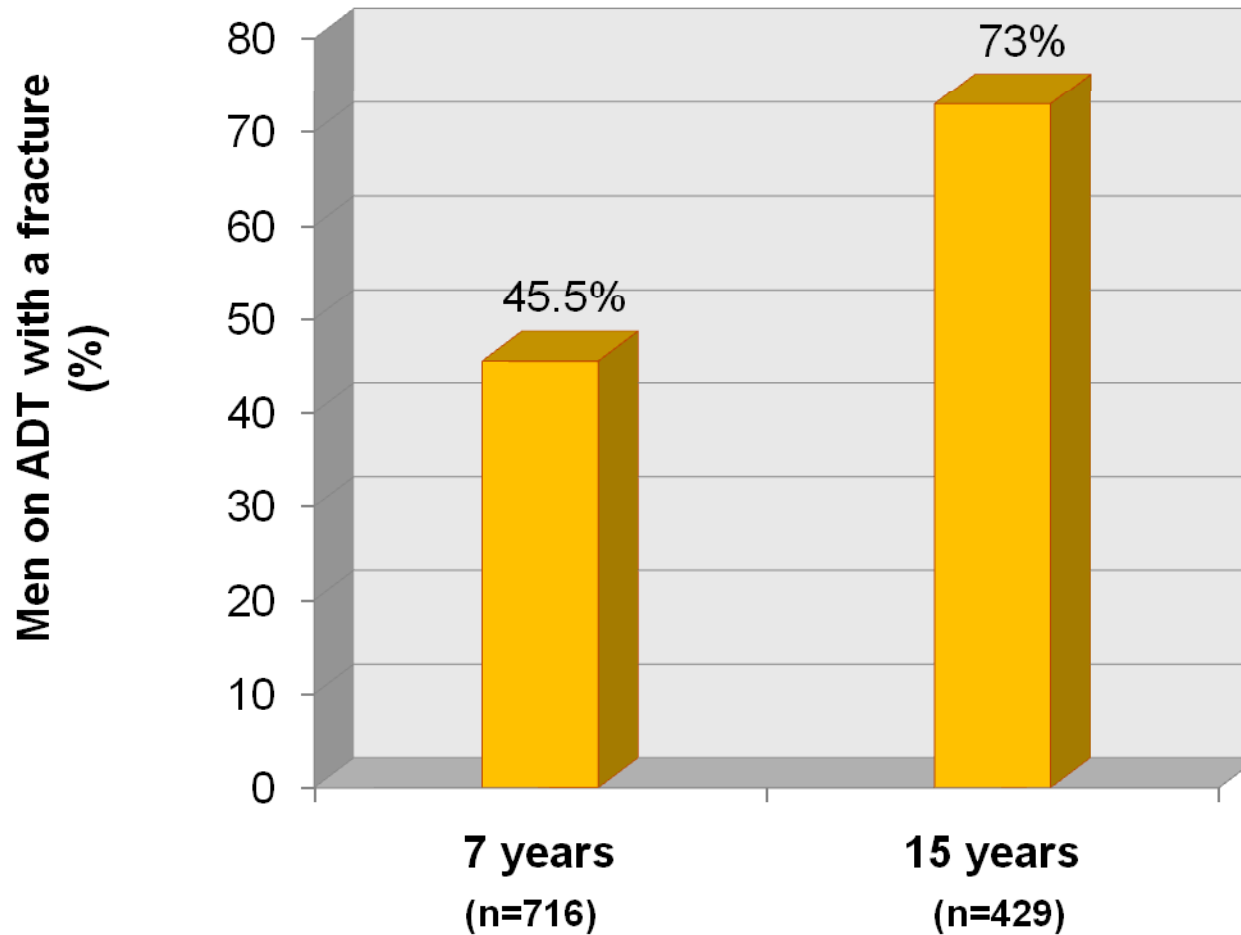
1 in 5 men on ADT fractured over four years, most common fracture was hip fracture



*Men in the study had multiple fractures. The total percentage of men with a fracture was 19.4%. Hip fracture occurred in 4.1% of men in the study.

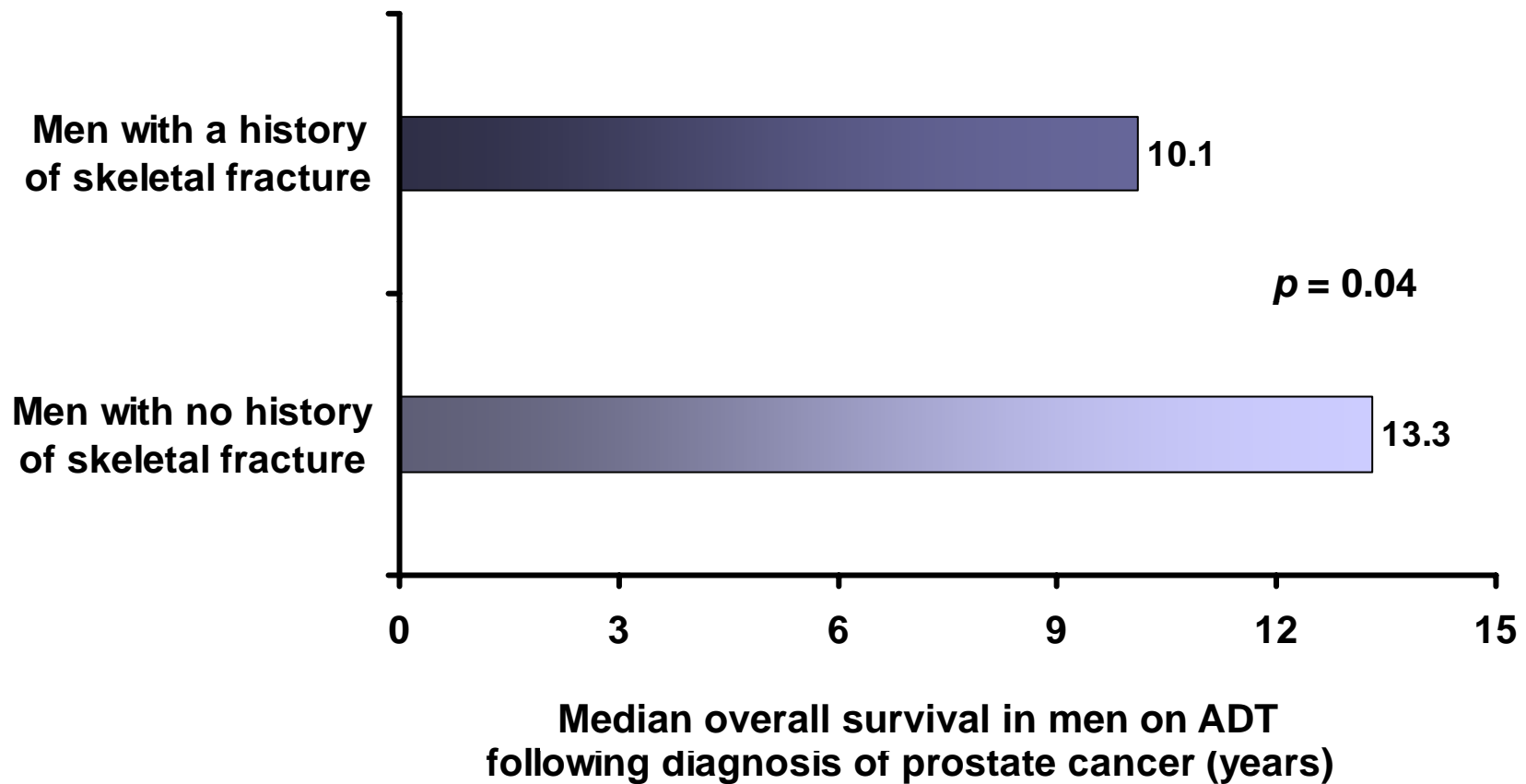
Shahinian VB, et al. *N Engl J Med.* 2005;352(2):154-64.

The fracture risk persists during ADT treatment



Krupski TL, et al. Cancer. 2004;101(3):541-9.
Melton LJ 3rd, et al. J Urol. 2003;169(5):1747-50.

Fractures in men on ADT can significantly reduce survival by more than 3 years



Oefelein MG, et al. *J Urol.* 2002;168(3):1005-7.

National Osteoporosis Foundation (NOF)

Five steps to bone health

1. Get your daily recommended amounts of calcium and vitamin D
2. Engage in regular weight-bearing and muscle strengthening exercise
3. Avoid smoking and excessive alcohol
4. Talk to your healthcare provider about bone health
5. Have a bone density test and take medication when appropriate

Treatment of osteoporosis

- National Osteoporosis Foundation (NOF) medication treatment guidelines
 - Postmenopausal women or men over 50 with osteoporosis or with a prior hip or spine fracture should be treated
 - Postmenopausal women or men with osteopenia should be treated if
 - 10-year probability of hip fracture that is $\geq 3\%$ OR 10-year probability of a major osteoporosis related fracture that is $\geq 20\%$
- Men with prostate cancer treated with ADT typically meet criteria for treatment
 - In one study, men on ADT exceeded hip fracture rate and met total fracture rate at 4 years, not 10 years
 - Vast majority of elderly men on ADT (77%) have osteoporosis or osteopenia

Hot flashes and breast pain/enlargement

ADT estrogen deficiency side effects: breast enlargement and pain

- ADT induced breast enlargement and pain results from the relative changes in the estrogen to testosterone ratio (testosterone drops more than estrogen)
 - Breast enlargement and pain is more common in men treated with Casodex[®] for complete androgen blockade
- Natural progression of ADT induced breast enlargement
 - Glandular changes begin within 6 to 12 months of treatment and may be reversible early
 - After one year, breast tissue may undergo fibrosis and breast enlargement may become irreversible

Higano CS. *Urology*. 2003;61(S2A):32–38.

Van Poppel H, et al. *Eur Urol*. 2005;47(5):587-92.

Casodex is a registered trademark of Astra-Zeneca

ADT estrogen deficiency side effects: hot flashes

- Hot flashes are one of the most common and most distressing side effects of ADT (occur in 50% to 80% of men)
- ADT induced hot flashes is thought to be in part related to a decline in estrogen levels
- Low estrogen alters the pituitary and brain feedback loop which stimulates the thermoregulatory center
- Abnormal stimulation of the thermoregulatory center may cause hot flashes
- Hot flashes persist with hot flashes reported in 50% of patients on ADT beyond 5 years

Increased risk of cardiovascular events in men on ADT

ADT estrogen and testosterone deficiency side effects: cardiovascular disease

- Surveillance, epidemiology and end results (SEER) Medicare data
 - Men on ADT (LHRH) had an 11% increased incidence of MI (heart attack) and 16% increase in sudden cardiac death*
 - Men on ADT (LHRH) had a 44% increased risk for diabetes and a 16% increased risk for coronary heart disease*
- Low testosterone is associated with the development of insulin resistance, type 2 diabetes and metabolic syndrome
- Estrogen deficiency increases cholesterol

* compared to age matched men

Keating NL, et al. *J Clin Oncol*. 2006;24(27):4448-56.

Saigal CS, et al. *Cancer*. 2007;110(7):1493-500.

Basaria S. *J. Androl* 2008; 29:534-539.

There are many factors associated with the development of coronary heart disease

- Known risk factors for coronary heart disease include:
 - High blood pressure
 - High cholesterol
 - Smoking
 - Physical inactivity
 - Obesity
 - Diabetes
 - Family history of heart disease is a risk factor for you in developing heart disease
 - Men develop heart disease at an earlier age than women
- Men on ADT should be carefully monitored for changes during therapy and may require intervention

Saigal CS, et al. *Cancer*. 2007;110(7):1493-500.

Basaria S. *J. Androl* 2008; 29:534-539.

Lloyd-Jones D, et al. *Circulation*. 2009 Jan 27;119(3):480-6.

Key Points in managing the estrogen deficiency side effects of ADT

- Men with prostate cancer on ADT are at a high risk for fractures and bone loss resulting in an increased risk of early mortality
 - While the NOF guidelines for management of increased fracture risk are not specific to men on ADT, these men have a fracture risk that exceeds the high risk definition (4% for hip fracture)
 - Early implementation of the NOF five steps to bone health may therefore be advisable for all men on ADT
- Men on ADT should discuss hot flashes, breast enlargement or breast pain with their physician early in their therapy
- Men on ADT should be aware of their baseline cardiovascular risk and discuss lifestyle/risk factor modification with their physician
- Men should know their baseline lipid and sugar levels and ask about any changes in lipid or metabolic profile with their physician during therapy

Questions/Discussion

- Web participants can ask a question by typing it in the CHAT box
- Callers can ask a question by pressing *1 on their telephone keypad, and will initially talk with Jackie from Us TOO



For More Information

- An audio and video archive and transcription of this presentation will be available at www.ustoo.org
- Read these Us TOO educational brochures:
 - *Prostate Cancer Patient's Guide to Hormone Therapy*
 - *What You Need to Know for Better Bone Health*
 - *What now? Hope and options when experiencing a rising PSA*
 - *The Prostate Cancer Playbook: For Prostate Cancer Recurrence, Rising PSA, and Advanced Disease*
- Participate in an online discussion group
- Thank you!

www.ustoo.org

1-800-80-Us TOO (1-800-808-7866)

