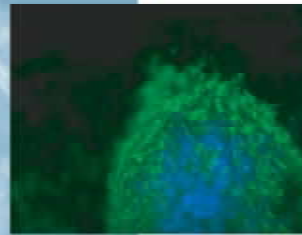


Epigenetic Basis for Increased Prostate Cancer Susceptibility due to Developmental Exposure to Estradiol or Bisphenol A

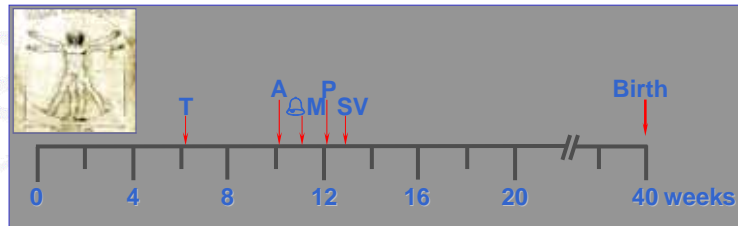


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PROSTATE CANCER The Magnitude of the Problem

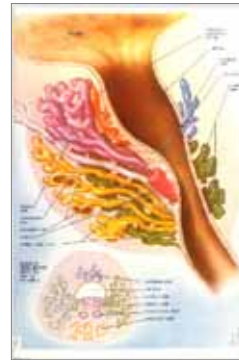
- The most prevalent non-cutaneous cancer in American males.
- Estimated 220,900 new cases; 28,900 deaths in US in 2005.
- Second leading cause of cancer deaths in males – of similar magnitude to breast cancer in females and AIDS.
- Ethnicity a major risk factor:
 - 2:1 incidence ratio in African-American males vs Caucasian in US.
 - Asian males have lowest incidence.
- Age-related incidence: up to 30% of males over 50 years harbor silent prostate cancer.
- % of men in US (1993-1995) developing invasive PCa with age:
 - Birth - 39 years: < 1 in 10,000
 - 40 - 59 years: 1.83 % (1 in 45)
 - 60 - 79 years: 14.79 % (1 in 7)
 - Birth to Death: 17.00 % (1 in 6)

Human Prostate Development



Morphogenesis:

- urogenital sinus (UGS), endodermal
- fetal week 12-28
- 2nd trimester; rising androgens
- 3rd trimester; falling androgens, rising maternal estrogens



DEVELOPMENTAL ESTROGENIC EXPOSURES

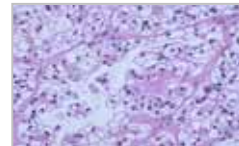
Elevated Maternal Estrogen (*Henderson, Ross, '88*)

AA women have a 40% higher level of estradiol during early PG compared to Caucasian women. A 2:1 AA-to-Caucasian ratio in prostate CA incidence is apparent by 45 yr of age



DES Exposure

- Taken by PG women b/t 1950 - 1975
- Increase in vaginal clear-cell carcinoma in exposed daughters
- Neonatal prostatic abnormalities in humans (*Driscoll & Taylor, '80*)
- Rodent models: predisposed to prostatic tumors (*Arai, '78*) and accessory sex gland dysplasia (*McLachlan, '75*)



Endocrine Disrupting Chemicals (EDC)

- methoxychlor (*Cooke, 90*); bisphenol A (*Nagel et al, '97*) affect prostate growth when given during developmental period
- bioaccumulation in mothers: placenta and breast milk

