Estrogens and Prostate Cancer: Etiology, Mediators, Prevention, and Management

Shuk-Mei Ho, PhD[a,b,*], Ming-Tsung Lee, MPhil[c], Hung-Ming Lam, PhD[b,c], Yuet-Kin Leung, PhD[a]

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- Estrogen receptor • Antiestrogens
- Selective estrogen receptor modulator (SERM) • Phytoestrogen
- Epigenetics • Chemoprevention • Prostate cancer risk
- Hormonal therapy

Androgens are traditionally recognized as the major hormone promoting normal and aberrant growth of the prostate. However, recent literature suggests that estrogen could also be an important mediator of these processes. Estrogen alone or in synergy with androgen is responsible for the pathogenesis of prostate cancer (PCa). More importantly, recent experimental data suggest that estrogen or its mimics could determine the risk of PCa development as early as the prenatal stage via a process known as estrogen imprinting. This article (1) reviews research findings that support a role for estrogens, estrogen mimics, and estrogen metabolites in prostate carcinogenesis; (2) discusses how different estrogen receptors (ER) mediate the action of estrogen in promoting the development and progression of PCa; and (3) evaluates the potentials

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[a] Department of Environmental Health, Center for Environmental Genetics, Cancer Institute, College of Medicine, University of Cincinnati, 3223 Eden Avenue, Kettering Laboratory Complex, Cincinnati, OH 45267, USA
[b] Cincinnati Veterans Affairs Medical Center, 3200 Vine Street, Cincinnati, OH 45220, USA
[c] Department of Environmental Health, College of Medicine, University of Cincinnati, 3223 Eden Avenue, Kettering Laboratory Complex, Cincinnati, OH 45267, USA
* Corresponding author. Department of Environmental Health, College of Medicine, University of Cincinnati, Room 128, Kettering Complex, 3223 Eden Avenue, Cincinnati, OH 45267.
E-mail address: shuk-mei.ho@uc.edu

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of estrogens, xenoestrogens, phytoestrogens, antiestrogens, and selective ER modulators (SERMs) for prevention and treatment of PCa.

EPIDEMIOLOGIC AND ANIMAL-MODEL STUDIES OF THE RELATIONSHIP BETWEEN ESTROGENS AND PATHOGENESIS OF PCA

Results from epidemiologic studies have suggested a role for estrogen in the pathogenesis of PCa. Racial/ethnic and geographic differences in the levels of estrogens provide a probable explanation for the disparity in the prevalence of PCa among various populations throughout the world.[1–3] Apropos to this view is the finding that levels of circulating estrogens in African American men, whose incidence of PCa is the highest in the United States, are higher than those in white Americans throughout their adult lives.[4–8] In contrast, Japanese men, whose incidence of PCa is low, have lower circulating levels of estrogen than do Dutch-European men.[9] A global study on 5003 men aged 65 years or older showed that black people (in the United States and in West Africa) had higher estrogen levels than white or Asian people (in the United States and in their homelands), with levels of total and free estradiol-17β (E2) 10% to 16% higher and levels of estrone (E1) 27% to 39% higher than in the Asian group.[10] Moreover, the ratios of total E2 to total testosterone (T) and E1 to androstenedione were higher in black people than in the other groups.[10] A comprehensive analysis of the levels of androgens, estrogens, and their metabolites in circulation led to the conclusion that 2 fundamental metabolic processes, increased aromatase activity and reduced androgen glucuronidation, are major factors governing the ratio of estrogen to androgen in elderly men.[10]

Age is also a key risk factor for PCa.[1] The prevalence of PCa increases dramatically as men age; this is paralleled by a significant increase in the ratio of circulating estrogen to androgen levels, which may increase by up to 40%.[11–17] This age-related hormonal change, often referred to as andropause, is caused by several endocrine events, including a decline in testicular function, and increases in adiposity, extragonadal aromatization, and the production of sex hormone–binding globulin (SHBG) as men age.[12,18–21] The level of 5α-dihydrotestosterone (DHT) was found to decrease, whereas those of estrogen (both E2 and E1) in the epithelial cells increase in the aging prostate (**Fig. 1**).[22] Because estrogens can be synthesized de novo via aromatase activity in the prostate,[23] tissue estrogen levels may be more important than circulating estrogen levels in promoting prostate carcinogenesis and progression. In this regard, recent studies using laser capture microdissection samples showed that stromal rather than epithelial aromatase activity may be important in upregulating the E2/T ratio in the tumor site via an alternative promoter activation mechanism during prostate carcinogenesis.[24,25] Furthermore, aromatase-knockout mice, which cannot produce E2 locally in the prostate, have increased levels of circulating T and DHT and, with age, are prone to the development of benign prostatic hyperplasia (BPH) but not PCa.[26] Collectively, increased estrogenic influences on the prostate caused by racial differences or andropause[27] may increase the risk of neoplastic transformation of the prostatic epithelium in men.[3,28,29]

Experimental models also support the suggestion that estrogens, alone or synergistically with androgens, are potent inducers of aberrant growth and neoplastic transformation in the prostate.[1,2,30–33] Prenatal exposure to maternal estrogens, or adult exposure to pharmacologic doses of estrogens, induces a benign lesion termed squamous metaplasia, which is derived from the basal-cell proliferation of the prostates of various species, including humans.[34] In a susceptible rat strain (Noble rats), chronic exposure to T plus E2 in adulthood promoted the evolution of a precancerous lesion similar to