Validation of the Pitts unified theory of prostate cancer, late-onset hypogonadism and carcinoma: the role of steroid 5α-reductase and steroid aromatase

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INTRODUCTION
Without steroid 5α-reductase (5AR) I and II mRNA in Gleason 4, 5 prostate cancer there is no 5AR I and II in such disease [1]. Genetic and epigenetic factors lower 5AR and are associated with increased deaths from prostate cancer deaths. Pitts predicted [2–5] that finasteride (Prostate Cancer Prevention Trial, PCPT) and, in 2005 [6], dutasteride (Reduce with Dutasteride Cancer Events) would increase Gleason 4, 5 prostate cancer by lowering 5AR by 70–90%. The PCPT [7–11] used finasteride to lower 5AR by 70% and reported a 68% increase in the incidence and a 200% increase in the prevalence of Gleason 4, 5 prostate cancer (n.b. predicted prognosis of grade 4, 5 prostate cancer same with/without finasteride: “finasteride”/“native” prostate cancer equally malignant). The PCPT validated the “Pitts unified theory of prostate cancer”, i.e. Gleason 4, 5 prostate cancer is promoted by low 5AR and increased steroid aromatase [12,13].

EMBRYOLOGY
The prostate arises from the confluence of Müllerian (oestrogen receptors) and Wolffian (androgen receptors) elements. The urorectal septum separates the prostate from the rectum and the embryonic prostate becomes the posterior lobe of the adult prostate. Over 90% of prostate cancers arise on the posterior aspect of the prostate, where prostate cancer is compressed against the posterior prostatic capsule by BPH, and where digitally directed patterned biopsies have the best yield. Therefore, fewer than half of prostate cancers are totally within prostatic tissue [14–17].

BIOCHEMISTRY
Steroid 5AR converts testosterone to dihydrotestosterone; steroid aromatase converts testosterone to oestriadiol in males and females (androgen deprivation results in oestrogen deprivation). Oestradiol, the product of testosterone aromatization, binds to the androgen and oestrogen receptors. Dihydrotestosterone (DHT) mediates cellular apoptosis through the paracrine prostate stromal cell factors and autocrine prostate epithelial cell factors (alopecia, remodelling of the anterior urethral plate, and remodelling of the embryonic prostate). Oestrogen mediates cellular proliferation through the paracrine and autocrine factors. Decreasing 5AR by 90% results in DHT decreasing by 35 times, testosterone increasing by 20 times, and oestrogen increasing by 19 times. The same changes are found in Gleason 4, 5 prostate cancer. Oestrogen plus testosterone increases the oestrogen proliferation by a factor of 100. Low 5AR results in unchecked prostatic epithelial cell proliferation from increased oestrogen without the apoptosis mediated by DHT (i.e. carcinogenesis) [18–20].

STEROID 5AR II GENE
The prevalence of incidental prostate cancer is the same in low-risk (Asian) and high-risk (Black) men. The increased incidence of grade 4, 5 prostate cancer in Black men is explained by the genetic variations in 5AR activity. One amino acid substitution in V89L in the SR5aR2 gene coding for 5AR downregulates the 5AR gene. The prevalence of this polymorphism increases with depth of skin colour. Similar polymorphisms of the 5AR gene are found in breast, lung, endometrial and other adenocarcinomas [21,22].

DIETARY FAT
Dietary fats decrease the activity of 5AR and decrease the conversion of testosterone to DHT (i.e. increased testosterone and reduced DHT). Fair [23] showed, in the LNCaP nude-mouse model, that reducing fat from 40% to 2.8% stops the growth of implanted LNCaP (SSaR-positive). Blocking fatty acid synthetase in the nude mouse model halts the growth of implanted PC-3 (fatty acid synthetase high) more than LNCaP (fatty acid synthetase low) and is reversed by palmitate. Palmitate is the end product of fatty acid synthetase, and reduces 5AR by 76%, as does finasteride (decreased by 72%) [24,25]. This demonstration of the replacement of palmitate fulfils Koch’s postulates.

Japanese men have lower levels of DHT and 5AR secondary to polymorphisms of the SRD5A2 gene. The prevalence of incidental prostate cancer is the same in Japanese men, American men and Black men, but the prostate cancer death rate is low for Japanese men in Japan. First-generation Japanese men in the USA with a high-fat western diet had an increase in prostate cancer death rate from 1.7 to 12.9 deaths/100 000, the same as western men [26]. The epidemiology of breast cancer, colon cancer, renal cancer and endometrial cancer show the same increased cancer mortality related to dietary fat.

CALCIUM, VITAMIN D, FISH OILS AND SELENIUM
Calcium binds with fat by saponification and inhibits the absorption of dietary fat, thereby effectively lowering the fat in the diet. Vitamin D is essential for the absorption of calcium, and selenium is an activating cofactor for vitamin D. Fish oils contain vitamin A and D. The confusion in the dietary studies of cancer prevention is explained by the lack of control of the dietary fat and the method of calcium supplementation. Milk is a
poor calcium source because of the dietary fat and lecithin that inhibit calcium absorption. In the Women's Health Initiative, those women who took calcium with vitamin D as prescribed, and who lowered their fat as prescribed, had a lower incidence of breast and colon cancer. The Women's Health Initiative also showed that T4M0N0 and T4M0N+ colon cancer increased with hormone-replacement therapy (i.e. oestrogen stimulation of cancers in other than reproductive organs). Note that other dietary/supplement 'chemoprevention' measures give inconclusive or erroneous results unless the dietary fat is lowered. Breast, colon and renal cancer show the same effects of vitamin D (sunlight/vitamin D), calcium, and hypertension (calcium-channel blockers?).

**LATE-ONSET HYPOGONADISM, OBESITY, ELEVATED OESTROGEN, LOW TESTOSTERONE AND DECREASED SPERM COUNT**

Obesity (body mass index, BMI, >30 kg/m²) was an independent predictor of Gleason 4, 5 prostate cancer and was associated with a higher risk of PSA failure (biochemical failure) after radical prostatectomy ($P = 0.03$). Black men have a higher BMI ($P < 0.001$) and a higher PSA failure rate ($P < 0.003$) than white men [27,28].

In obesity the adipose tissue has steroid aromatase that produces a high oestrogen level, which down-regulates the hypothalamic-pituitary gonadal axis, and both testosterone and sperm production decrease. Blocking the steroid aromatase conversion of testosterone to oestrogen with anastrozole lowered serum oestrogen in obese (BMI >35 kg/m²) infertile men, from 46.0 to 28.9 pg/mL, increased testosterone from 295 to 445 mg/dL, and increased the testosterone/oestrogen ratio (255%; $P < 0.001$ for all differences) without increasing bone turnover or osteoporosis from oestrogen/testosterone deprivation by LHRH agonists or orchidectomy [29–33].

Late-onset hypogonadism (decreased androgen and sperm production) could be treated by ‘resetting’ LHRH by lowering oestrogen and increasing testosterone with aromatase inhibitors, which would block the adverse effects of increased testosterone on incidental prostate cancer [12,13].

Breast, colon and renal cancer show the same adverse effects of obesity. Notably, the increased incidence of gynaecomastia and male breast cancer is related to the increased prevalence of obesity and the use of 5AR blockers such as finasteride and dutasteride.

Of interest, the ‘Fat Lady’ who sings last in the opera is a soprano; operatic tenors and sopranos are (often) obese, with increased steroid aromatase/oestrogen at the time of puberty, and have minimal masculinization of the larynx. Frequent operatic tenors are infertile.

Selective oestrogen-receptor modulators (SERMs) halt the growth of prostate cancer in the LNCaP nude mouse model, and reduced the cumulative risk of prostate cancer in 514 men with high-grade prostatic intraepithelial neoplasia (24.4% vs 31.2%; $P < 0.05$) [34]. Other dietary factors (β-carotene, omega fish oil, γ-vitamin E, cooked tomatoes) are probably SERMs, as only certain isomers are effective and have no effect without low-fat diets in trials of other than lung cancer. Lung cancer is high-grade, has no 5AR and is hormone-unresponsive.

**COROLLARY I**

All high-grade carcinomas have no 5AR and elevated steroid aromatase. After Boorjian et al. [35] reported no androgen receptors in high-grade TCC like those found in prostate cancer, and as predicted by the validated Pitts unified theory, Barocas et al. [36] found low or no 5AR in high-grade TCC, and the changes in 5AR were predictive of outcome. As predicted by the validated unified theory, Boorjian et al. [35] found elevated oestrogen receptors and elevated steroid aromatase in high-grade TCC and a higher incidence of high-grade TCC in females. These predicted results led to a literature review of all carcinomas. Not only were the epigenetic factors (fat, calcium, oestrogen, obesity) the same for breast, renal and colon cancer, but also low/absent 5AR was associated with high-grade carcinoma (prostate, bladder, breast, colon, gastric, oesophageal, thyroid, cervix, endometrial, lung) [35–38].

The validated Pitts unified theory of prostate cancer can be extended to all carcinomas, i.e. decreased 5AR and increased steroid aromatase increase the incidence of both Gleason 4, 5 prostate cancer and high-grade carcinomas.

**COROLLARY II**

Females (oestrous cycle) have a higher age-adjusted death rate from cancers (other than lung) than males, and a greater incidence of lung cancer with less pack-years of smoking. Lung cancer is high-grade and hormonally unresponsive, as is Gleason 4, 5 prostate cancer and high-grade breast cancer.

**COROLLARY III**

Androgen/oestrogen deprivation reduces the age-adjusted death rates from cancers (in the following discussion, other than of the lung) in males and females. From 1950 to the present, the female cancer death rate has been declining as oestrogen deprivation for breast cancer continues as primary therapy. The male age-adjusted cancer death rate is lower than in females and declined in parallel with the female age-adjusted death rate until the 1970s. Androgen/oestrogen deprivation primary therapy for prostate cancer was abandoned after the Veterans Administration Cooperative Urology Research Group report I (in 1968) showed the cardiovascular risks of diethylstilbestrol (DES) 5–10 mg; male cancer deaths plateaued. As androgen/oestrogen deprivation therapy increased in the 1990s, the male age-adjusted cancer death rate has begun to decline in parallel with the continuing decline of the female age-adjusted cancer death rate. In 2003 and 2004, age-adjusted cancer deaths decreased in both years in males and females for the first time in >30 years [39] (Table 1) [40].

**COROLLARY IV**

Steroid aromatase inhibitors lower oestrogen and increase testosterone without the stimulation of latent/incidental prostate cancer by the increased testosterone. The treatment of late-onset hypogonadism with steroid aromatase inhibition has the potential of chemoprevention of prostate cancer and non-lung cancer (as shown in breast cancer) [41].

**COROLLARY V**

Females have a much higher incidence of ‘auto-immune’ benign disease (multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, arteritis, etc.) because of
the oestrogen stimulation of the oestrus cycle. Adding steroid aromatase inhibitors might improve the results of standard therapy (with low-dose postmenopausal hormone replacement therapy to protect the bones and cardiovascular system?).

Females have a higher incidence of fatty liver/alcoholic cirrhosis with less alcohol intake, increased incidence of lung cancer with fewer pack-years secondary to the oestrous cycle, and might be helped by steroid aromatase inhibition.

COROLLARY VI

There are genetic (e.g. polymorphisms of the 5AR gene and down-regulation of the 5AR gene by HPV-18) and epigenetic (fat, cigarette smoking-carbon monoxide, Rous sarcoma virus, HTLV-I, Epstein Barr virus, Plasmodium falciparium, HPV-18, hepatitis C, B and D, Helicobacter pylori, Chlamydia pneumoniae, etc.) that increase the incidence both of Gleason 4, 5 prostate cancer and carcinomas [42]. No matter what the origin of the low/absent 5AR and increased steroid aromatase increase the incidence of both Gleason 4, 5 prostate cancer and carcinoma. There are many ways to start a car (key, remote, ‘hot wiring’, cables, coaching) but only the accelerator causes the car to move. 5AR is the ‘brake’ and steroid aromatase is the ‘accelerator’.

CONCLUSIONS

The PCPT validated the Pitts unified theory of prostate cancer, carcinoma, and late-onset hypogonadism; low/absent 5AR and increased steroid aromatase increases the incidence of both Gleason 4, 5 prostate cancer and high-grade carcinoma. The decrease in cancer-specific death rates with the increased use of androgen deprivation validates the Pitts unified theory of carcinoma. Steroid aromatase inhibition increases testosterone and decreases oestrogen without the stimulatory effect on incidental prostate cancer by the increased testosterone. Low/absent 5AR is a molecular marker for high-grade carcinoma, is predictive of clinical outcomes, and can be expressed as a percentage decrease to avoid the variations in immunohistochemistry (i.e. low Pitts score of percentage 5AR means high-grade/poor prognosis carcinoma) [43]. Adding oestrogen deprivation using steroid aromatase inhibitors, LHRH agonists (plus/minus bisphosphonates/low-dose postmenopausal hormone replacement therapy) or DES 1 mg to existing chemotherapy regimens should improve the results in carcinoma and many benign conditions such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, arteritis, familial polyposis, fatty liver, etc.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: 5αR, 5α-reductase; PCPT, Prostate Cancer Prevention Trial; DHT, dihydrotestosterone; BMI, body mass index; SERM, selective oestrogen-receptor modulator; DES, diethylstilbestrol.