Medical Hypotheses 72 (2009) 665–674

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Apocrine sweat gland obstruction by antiperspirants allowing transdermal absorption of cutaneous generated hormones and pheromones as a link to the observed incidence rates of breast and prostate cancer in the 20th century

Kris G. McGrath *

Northwestern University Feinberg School of Medicine, Division of Allergy and Immunology, 676 North St. Clair Street, Suite 14018, Chicago, IL 60611, United States

ARTICLE INFO

Article history:
Received 27 January 2009
Accepted 28 January 2009

SUMMARY

Breast and prostate cancer share similarities and likely represent homologous cancers in females and males, respectively. The role of hormones such as testosterone and estrogen in carcinogenesis is well established. Despite worldwide research efforts, the pathogenesis of these diseases is largely not well understood. Personal care products containing estrogens or xenoestrogens have raised concern as a breast cancer risk, especially in young African-American women. In the United States (US) there is a parallel rise in the incidence in breast and prostate cancer compared to selected non-hormone dependent tumors. Observed US and global breast and prostate cancer incidence increases were occurring before exogenous hormone replacement and xenoestrogen exposure were commonplace. An unintentional, inadvertent, and long term hormone exposure may occur from transdermal absorption of sex hormones and pheromones (androgens) from axillary apocrine sweat gland obstruction by aluminum-based antiperspirants. The global rise in antiperspirant use parallels rises in breast and prostate cancer incidence and mortality rates. A multi-disciplinary literature based set of evidence is presented on how such a link is possible, to prompt confirmatory investigations in the pursuit of unmet needs in breast and prostate cancer etiology and prevention.

Introduction

Breast and prostate cancer similarities are abundant and include: later in life occurrence, nearly equal lifetime risk, hormone dependent growth, western lifestyles risk factors, similar geographical variations, breast and prostate tissues contain estrogen and androgen receptors, familial genes account for 5% of incidence, both share biochemical markers, and both are treated with hormonal manipulation [1–8].

Registry data from 21 countries of age-adjusted rates for cancers had the highest correlation coefficient between prostate and breast cancer at 0.81 [2]. The hormone risk for breast cancer is the cumulative exposure to exogenous estrogen and estrogen/progesterone combinations and for prostate cancer the cumulative exposure to androgens [4,9–15]. The rise in incidence of these hormone dependent tumors began before and increased after the introduction of exogenous hormone therapies. The first estrogen–progesterone combination drug was approved in the US for regulation of menstruation in 1957, and as a contraceptive in 1960 [16,17].

Estradiol and synthetic estrogens are established carcinogens [18,19]. Combination therapy (estrogen plus progesterone) causes breast cancer and is classified as a carcinogen by the International Agency for Research on Cancer [20–22].

Breast cancer incidence rates have risen since at least 1935 until a drop was seen in 2003–2004. This decline followed the cessation in July 2002 of the Women's Health Initiative (WHI) estrogen-plus-progesterone trial after observing increased risks of breast cancer among women assigned to take estrogen plus progestrone [23,24]. A population-based tumor registry study observed that between the mid-1970s and the mid-1980s the incidence of estrogen receptor-negative breast cancers rose 22–27%, while the incidence of estrogen receptor-positive breast cancers increased an average of 131% [25]. The rise in breast cancer incidence rates through the late 1990s was consistent with the effects of mammography screening and increasing use of menopausal hormone therapy, and the recent decline in incidence is consistent with the drop in hormone use [23,26]. Further evidence in support of this relation between decrease in estrogen plus progestin prescribing comes from declines in incidence reported in New Zealand and Germany that parallel those in the US [20].

Prostate cancer incidence also increased throughout the 20th and into the 21st centuries with episodic surges in incidence attributed to screening practices [27–33]. Male hormone replacement in the US began in the 1940s followed by sparse usage, and limited formulations, indications and delivery systems. Sales stagnated around $18 million annually in 1988, until a 2200% increase

* Tel.: +1 312 695 8624/222 9500; fax: +1 312 222 9589.
E-mail address: k-mcgrath@northwestern.edu

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doi:10.1016/j.mehy.2009.01.025

occurred from 1993 to 2002, to an estimated $400 million annually [34,35]. Testosterone therapy has expanded beyond the use in hypogonadal men less than 65 years old to use in older men with low testosterone levels, which has been attributed to greater media and public attention [35].

Despite an increase in testosterone-treated men there has yet to be an observed associated increase in prostate cancer incidence [36]. A collaborative analysis of 18 prospective studies of endogenous hormones and prostate cancer risk, found that serum concentrations of sex hormones were not associated with the risk of prostate cancer [37]. Plasma testosterone and dihydrotestosterone concentrations determined prospectively or at the time of cancer diagnosis have not been convincingly associated with increased risk of prostate cancer [3,38]. Such observations prompted an editorial outcry from Carpenter in 2008, "Getting over Testosterone: Postulating a Fresh Start for Etiologic Studies of Prostate Cancer." He adds: "prostate cancer remains as enigmatic as it is burdensome ... an androgen etiology of prostate cancer would have immediate implications for prevention, such as screening for higher androgen levels... to focus instead on developing more sophisticated hypotheses and novel study designs..." [39]. Crawford ponders: "If androgens are indeed important in prostate cancer development, then measurement may need to be done in early adulthood, years before prostate cancer is actually detected" [3]. López-Otín focuses on the common features of breast and prostate cancer in an attempt to "possibly trigger new thinking into their pathogenesis and progression" [1].

Perhaps, unrecognized androgen and estrogen exposure begins early in the lives of males and females, linking an etiology to these very prevalent hormone-dependent malignancies.

An uncharted source of androgen and estrogen exposure to the breast and prostate may be from the skin, an exposure beginning early in the life, *in utero*, and through puberty to advanced age. Similar to the classical steroidogenic organs, the gonads and adrenal glands, the skin and appendages (including hair follicles, sebaceous glands, and sweat glands) have all of the enzymes required for androgen synthesis and metabolism. The apocrine sweat glands and sebaceous glands account for the vast majority of androgen metabolism in skin [40].

Androgens secreted by the apocrine sweat glands include the powerful behavior-altering pheromones. Apocrine sweat glands synthesize numerous additional androgens, including testosterone, dihydrotestosterone (DHT), androstanediol, as well as the glucuronide and sulfate conjugates of DHT, androstanediol, and androsterone. Apocrine type 1 5α-reductase irreversibly converts testosterone to DHT, the most potent tissue androgen. Through cutaneous sources of aromatase, testosterone and androstenedione are converted to estradiol and hair follicles aromatize androstenedione to estrone [40–43].

Underarm applied aluminum-salt-based antiperspirants obstruct sweat glands and do not discriminate between eccrine (thermal sweat) and apocrine (emotional/stress sweat) sweat glands [44]. Axillary apocrine glands outnumber eccrine glands 10:1 [45].

Apocrine glands have the potential to be obstructed one or more times daily over decades as >90% of Americans use antiperspirant/deodorants with a 3.1% global sales increase in 2007 to $9.4 billion, and an estimated increase by 17.3% to $11.1 billion in 2012. Antiperspirant/deodorant usage begins at least at (perhaps before) puberty, and is consistent into advancing years, with discontinuation unlikely during pregnancy [45–49].

A resultant epi and transdermal reservoir of a variety of androgens and estrogens is created for potential systemic absorption and disruption of hormonal homeostasis.

It has been previously hypothesized that *in utero* and early life exposures to exogenous estrogens, including those added to personal care products and those derived from the widespread estrogenic environmental contaminant, bisphenol A, are an overlooked and underestimated contribution both to premature sexual development and to breast cancer risk [50]. Underarm hygiene habit frequency has been associated with an earlier age of breast cancer diagnosis [46].

With so many similarities between breast and prostate cancer, it is not unreasonable to consider a common etiology, especially from potential hormone disruption occurring through the underarm, in an attempt to "possibly trigger new thinking into their pathogenesis and progression" [1].

The hypothesis

It has been established that a woman's lifetime risk of breast cancer increases with greater cumulative levels of estrogen, whether endogenous or exogenous. Case-control studies have confirmed that serum estrogen levels are higher in breast cancer cases when compared to controls [22,50]. Decreases in breast cancer rates have been related to reduction in use of hormone replacement therapy [24].

It also has been established that there is evidence suggesting that a man's lifetime risk of prostate cancer increases with greater cumulative exposure of the prostate to androgens [9–14]. However, this hormone relationship is not as apparent as with breast cancer. A collaborative analysis of 18 prospective studies, pooling pre-diagnostic measures on 3886 men with incident prostate cancer and 6438 control subjects, found no association between the risk of prostate cancer and the serum concentrations of testosterone, calculated-free testosterone, dihydrotestosterone sulfate, androstenedione, androstanediol glucuronide, estradiol, or calculated-free estradiol. Androstanediol glucuronide may most closely reflect intraprostatic androgen activity and this measure was not associated with the risk of prostate cancer [37]. Here it is hypothesized that *in utero*, early, and late life exposure from axillary generated sex-hormones and androgenic pheromones from chronic axillary apocrine sweat gland obstruction by aluminum-salt based antiperspirants is an overlooked contribution to the global parallel rise in breast and prostate cancer incidence and mortality. This hypothesis may also explain the numerous similarities between breast and prostate cancer as well as observed epidemiological differences between African-Americans and Caucasians. This potential unintentional and inadvertent exposure may also contribute to the increased lethality of breast cancer in young women in general and in African-American women of all ages. There is a higher incidence of breast cancer in young African-American women and a higher incidence of prostate cancer in African-American men of all ages [50,51]. Death rates from breast and prostate cancer are higher in African-Americans than Caucasians [52].

Apocrine sweat glands are more developed and occur more often in women. African-American individuals have more sweat glands per cm^3 than Caucasians [53,54]. Apocrine sweat glands are concentrated in the axillae, termed, "axillary organ", an independent organ of human odor and pheromone production [55]. This organ is a key component of the skin as an endocrine organ of steroidogenesis. These axillary generated sex hormones as well as apocrine generated androgen-based pheromones all have the optimal molecular weights ($\leqslant$500 Da) for transdermal systemic delivery [56], acting as potential endocrine disruptors. This lifelong exposure would begin *in utero* during critical windows of vulnerability of breast and prostate bud development and during breast, prostate, and apocrine sweat gland maturation, occurring at puberty.

Aluminum-salt based antiperspirant products are used by more than 90% of the US population. Use begins at least before the age of