COMMENTARY

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Endocrine disruptors and prostate cancer risk

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Abstract

There is increasing evidence both from epidemiology studies and animal models that specific endocrine-disrupting compounds may influence the development or progression of prostate cancer. In large part, these effects appear to be linked to interference with estrogen signaling, either through interacting with ERs or by influencing steroid metabolism and altering estrogen levels within the body. In humans, epidemiologic evidence links specific pesticides, PCBs and inorganic arsenic exposures to elevated prostate cancer risk. Studies in animal models also show augmentation of prostate carcinogenesis with several other environmental estrogenic compounds including cadmium, UV filters and BPA. Importantly, there appears to be heightened sensitivity of the prostate to these endocrine disruptors during the critical developmental windows including in utero and neonatal time points as well as during puberty. Thus infants and children may be considered a highly susceptible population for ED exposures and increased risk of prostate cancers with aging.

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Introduction

Prostate cancer is the most common solid cancer in males and is the second leading cause of cancer deaths in American men (Jemal *et al*. 2008). While rates today are markedly higher than rates observed three decades ago, the most recent statistics show that prostate cancer incidence rates have now stabilized which is thought to reflect changes in utilization of prostate-specific antigen (PSA) testing. In addition, benign prostatic hyperplasia (BPH) is the most common benign neoplasm, occurring in ~50% of all men by the age of 60. Despite extensive research, the basis for these high rates of abnormal prostatic growth is not well understood. It is recognized, however, that steroids play a role in the initiation and progression of prostate cancer which is the basis for hormonal treatment strategies. Eunuchs do not develop prostatic carcinoma (Moore 1947) and regression of the cancer can be initially achieved by castration and androgen blockade (Huggins & Hodges 1941). In addition to androgens, estrogen involvement in the etiology of BPH and prostatic cancer has been postulated and the use of anti-estrogens has been recently recognized to have a therapeutic role in prostate cancer management (Prins & Korach 2008, Raghow *et al*. 2002, Steiner & Pound 2003, Smith *et al*. 2008). Human and rodent prostates express both estrogen receptor α (ERα) and ERβ during development and into adulthood with ERα primarily found in stromal cells (Schulze & Claus 1990, Prins & Birch 1997) and ERβ in differentiated epithelium (Enmark *et al*. 1997, Prins *et al*. 1998). Furthermore, it is believed that early prostatic developmental events which are regulated by steroids may be linked to the predisposition of this structure to high rates of disease in adult men (Henderson *et al*. 1988, 1991). It is noteworthy that relative to adult estrogenic responses, the prostate gland is particularly sensitive to estrogen exposures during the critical developmental period (Prins *et al*. 2007).

The established risk factors for prostate cancer are age and race with African American men possessing the highest incidence of prostate cancer worldwide, at rates twofold of those for Caucasian-American counterparts. It is also recognized that genetics (family history), diet, and environmental factors can impact prostate cancer risk. In the human population, direct connections between endocrine disruptors (EDs) and prostate cancer risk have not been established. Nonetheless, due to the hormonal basis of this disease and the evidence that dietary compounds high in isoflavones (e.g., red clover, genistein) can control

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prostate cancer growth in humans (Jarred *et al*. 2002, Lakshman *et al*. 2008) and animal models (McCormick *et al*. 2007), there is reasonable cause to evaluate and understand any potential relationship between environmental EDs and prostate cancer risk. In addition to epidemiologic studies, there are *in vitro* studies with human prostate cells and *in vivo* studies in animal models that indicate associations between EDs and prostate cancer, carcinogenesis, and/or susceptibility. Due to difficulties in directly associating prostate cancer risk in humans with ED exposures, potential risk(s) will have to include research with animal models, particularly those that that are responsive to environmentally relevant exposures.

Evidence and mechanisms

Farming and pesticides

Regarding links between prostate cancer and environmental factors in humans (outside of diet), the most compelling data come from the established occupational hazard of farming and increased prostate cancer rates (Morrison *et al*. 1993, Alavanja *et al*. 2003, Meyer *et al*. 2007). While several variables may contribute to higher prostate cancer rates in farmers, chronic or intermittent exposures to pesticides are the most likely explanation (Alavanja *et al*. 2003, Van Maele-Fabry *et al*. 2006). This is supported by a large epidemiology study (Agricultural Health Study) in a collaborative effort between the NCI, NIEHS, and EPA in the United States that has examined agricultural lifestyles and health in ~90 000 participants in North Carolina and Iowa since 1993 (www.aghealth.org). Evaluation of >55 000 pesticide applicators revealed a direct link between methyl bromide exposure, a fungicide with unknown mode of action, and increased prostate cancer rates. Furthermore, 6 pesticides out of 45 common agricultural pesticides showed correlation with exposure and increased prostate cancer in men with a familial history, suggesting gene–environment interactions. These six agents were chlorpyrifos, fonofos, coumaphos, phorate, permethrin, and butylate (Alavanja *et al*. 2003, Mahajan *et al*. 2006). The first four of these compounds are thiophosphates and share a common chemical structure. While these agents are regarded as acetylcholine esterase inhibitors and have not been shown to have direct estrogenic or antiandrogenic activities, a literature search revealed that these compounds have significant capacity as p450 enzyme inhibitors. In particular, chlorpyrifos, fonofos, and phorate strongly inhibit CYP1A2 and CYP3A4 which are the major p450s that metabolize estradiol, estrone, and testosterone in the liver (Usmani *et al*. 2003, 2006). Furthermore, the human prostate constitutively expresses CYP1A2 and CYP3A4 enzymes that are involved in intraprostatic metabolism of steroids, drugs, and dietary compounds (Finnström *et al*. 2001, Lawson & Kolar 2002, Sterling & Cutrineo 2004). This raises the possibility that exposure to these compounds may interfere with steroid hormone metabolism by the liver as well as the prostate and, in so doing, alter steroid balance and availability which in turn may contribute to increased prostate cancer risk. A similar mechanism of endocrine disruption *in vivo* has been identified for polychlorinated biphenols (PCBs) and polyhalogenated aromatic hydrocarbons (including dioxins, bisphenol A (BPA), and dibenzofurans) through potent inhibition of estrogen sulfotransferase which effectively elevates bioavailable estrogens in various target organs (Kester *et al*. 2000, 2002).

Environmental estrogens

In men, chronically elevated estrogens have been associated with increased risk of prostate cancer (Modugno *et al*. 2001). In rodents, estrogens in combination with androgens induce prostate cancer (Leav *et al*. 1988). For the sake of simplicity, we here refer to environmental estrogens as molecules with identified estrogenic activity (estrogen mimics), mostly through activation of ERs.

Diethylstilbestrol (DES)

DES exposure is considered an important model of endocrine disruption and provides proof of principle for exogenous estrogenic agents as disruptors of multiple endorgans. Maternal exposure to DES during pregnancy was found to result in more extensive prostatic squamous metaplasia in human male offspring than observed with maternal estradiol alone (Driscoll & Taylor 1980). While prostatic metaplasia eventually resolved following DES withdrawal, ectasia and persistent distortion of ductal architecture remained (Yonemura *et al*. 1995). This has lead to the postulation that men exposed prenatally to DES may be at increased risk for prostatic disease later in life although this has not been borne out in the limited population studies conducted to date (Giusti *et al*. 1995). However, extensive studies with DES in rodent models predict marked abnormalities in the adult prostate including increased susceptibility to adult-onset carcinogenesis following early DES exposures (Rajfer & Coffey 1978, Arai *et al*. 1983, Prins *et al*. 2001, Huang *et al*. 2004).

BPA

BPA is a synthetic polymer used in the production of polycarbonate plastics and expoxy resins and significant levels have been found in the urine of 93% of US population in a recent screen by the CDC (Calafat *et al*. 2008). The relative binding affinity of BPA for either ERα and ERβ or capacity for BPA to activate ER-dependent transcription is ∼10 000 lower than estradiol or diethylstilbestrol (Kuiper *et al*. 1998, Lemmen *et al*. 2004). While these data might suggest that BPA has minimal estrogenic activity, 1 μM BPA is 50% as efficacious as 1 μM 17β-estradiol in activating an estrogen-responsive luciferase reporter (Kurosawa *et al*. 2002). This indicates that, although BPA may have a significantly lower potency than endogenous estrogens *in vitro*, it is a full agonist for both ERα and ERβ. Furthermore, BPA induces ER through non-genomic pathways with an EC_{50} equivalent to 17β-estradiol suggesting that *in vivo* estrogenic activity of BPA may be due to non-genomic activation of ER (Song *et al*. 2002, Walsh *et al*. 2005).

The effects of BPA with regard to carcinogenic potential, including the prostate gland, have recently been reviewed by an expert panel (Keri *et al*. 2007). In short, there is evidence from rodent models and human prostate cell lines that BPA can influence carcinogenesis, modulate prostate cancer cell proliferation, and for some tumors, stimulate progression. The recent reports have provided evidence that early life exposure to BPA may increase susceptibility to hormonal carcinogenesis in the prostate gland, possibly by developmentally reprogramming carcinogenic risk (Ho *et al*. 2006, Prins *et al*. 2008). Studies using a rat model showed that brief neonatal exposure to a low dose of BPA (10 μg/kg BW/day) significantly increased the incidence and grade of prostatic intraepithelial neoplasia following adult estrogen exposure. This model of sensitivity to hormonal carcinogenesis is relevant to humans in that relative estradiol levels increase in the aging male and may contribute to prostate disease risk (Kaufman & Vermeulen 2005). The above studies further identified alterations in DNA methylation patterns in multiple cell signaling genes in BPA-exposed prostates which suggest that environmentally relevant doses of BPA 'imprint' the developing prostate through epigenetic alterations (Ho *et al*. 2006, Prins *et al*. 2008).

Knudsen *et al.* examined the influence of BPA on human prostate cancer cells that contained an androgen receptor (AR) point mutation (AR-T877A) frequently found in advanced prostate cancers of patients who relapsed after androgen deprivation therapy (Wetherill *et al*. 2005). They first observed that 1 nM BPA activates AR-T877A in transcriptional assays and leads to unscheduled cell cycle progression and cellular proliferation *in vitro* in the absence of androgen. Since BPA had no impact on wild-type AR, these data indicate that this gain-of-function AR mutant attained the ability to utilize BPA as an agonist. Subsequent *in vivo* analyses of the impact of BPA on human prostate tumor growth and recurrence were performed using a mouse xenograft of human cells containing the AR-T877A mutation (Wetherill *et al*. 2006). At low doses that fall within the reported ranges of human exposure, prostate tumor size increased in response to BPA administration when compared with placebo control and mice in the BPA cohort demonstrated an earlier rise in PSA (biochemical failure). These findings indicating that BPA significantly shortened the time to therapeutic relapse. These outcomes underscore the need for further study of the effects of BPA on tumor progression and therapeutic efficacy.

PCBs

Persistent organic pollutants, such as PCBs, are fat soluble chemicals that bioaccumulate in the human body. Many have estrogenic or anti-androgenic activity and as such, may perturb male reproductive activity. A recent analysis of adipose tissue concentrations of PCBs in Swedish men with and without prostate cancer revealed a significant association between PCB levels in the higher quandrants and prostate cancer odds ratio with the most marked associations for PCB153 and trans-chlordane (Hardell *et al*. 2006). A more extensive epidemiologic study of capacitor manufacturing plant workers highly exposed to PCBs revealed a strong exposure–response relationship for prostate cancer mortality (Prince *et al*. 2006). This supports previous findings of correlations between PCB 153 and 180 and prostate cancer risk in electric utility workers (Charles *et al*. 2003, Ritchie *et al*. 2003). While estrogenic activity of these compounds is a suspected mode of action, there is also evidence that PCBs inhibit estrogen sulfotransferase activity in the liver and effectively increase bioavailable estrogen in the body (Kester *et al*. 2000). Recently, Aroclor-1254, a mixture of 60 PCB pollutants, was tested on rat prostate cells *in vitro* and shown to disrupt gap junctions, expression of connexin 32 and 43 and increase double-stranded DNA breaks suggesting that PCBs may be able to transform prostate cells leading to carcinogenesis (Cillo *et al*. 2007). Further investigation using animal models is warranted for PCBs and prostate cancer risk.

Ultraviolet (UV) filters

There are a few recent reports that UV light filters that are used to protect against the sun have estrogenic activity (Schlumpf *et al*. 2004*b*). Specifically, 4-methylbenzylidene camphor and 3-benzylidene camphor (3-BC) are ERβ ligands (Schlumpf *et al*. 2004*a*). While little if any work has been done with regard to these UV filters and human prostate cancer, a few recent reports indicate that developmental exposure to the compounds can alter prostate gland development and estrogen target gene expression in the rat (Schlumpf *et al*. 2004*b*, Hofkamp *et al*. 2008). This raises the possibility that the fetal prostate may be affected following maternal use of these compounds.

Cadmium

Cadmium is known to ligand to ERs and function as an estrogenic mimic. While some large epidemiologic reports have indicated a relationship between cadmium exposure and prostate cancer rates, others have refuted these findings (Parent & Siemiatycki 2001). Nonetheless, there are intriguing reports in the literature which show that cadmium has proliferative action with human prostate cells *in vitro* through an ER-dependent mechanism and that this exposure is associated with acquisition of androgen independence (Benbrahim-Tallaa *et al*. 2007*b*). Furthermore, prostatic tumors have been shown to be experimentally induced by oral exposure to cadmium (Waalkes 2000). Since cadmium bioaccumulates in the body, further epidemiologic analysis of cadmium and prostate cancer risk is warranted, particularly in men with occupational exposures.

Arsenic

Exposure to arsenic has long been associated with a number of diseases including cancers (Chen *et al*. 1988, Watson & Yager 2007). A recent review of the epidemiologic data has shown an association between inorganic arsenic exposure from the environment and prostate cancer incidence and mortality in the human population (Benbrahim-Tallaa & Waalkes 2008). Importantly, it has been documented that arsenic may mediate some of these effects through endocrine disruption, specifically through interaction with ERs and activation of estrogen-regulated genes (Davey *et al*. 2007). In this context, there is a recent report that arsenic can induce malignant transformation of prostate epithelial cells *in vitro* and drive them toward an androgen-independent state (Benbrahim-Tallaa *et al*. 2007*a*). Interestingly, this was shown to be mediated through Ras-MAPK pathways and it is possible that membrane ERs may be involved in this process. Epidemiologic studies have shown an association between arsenic exposure and prostate cancer mortality in Taiwan (Chen *et al*. 1988), a finding that was substantiated by a later study in the United States (Lewis *et al*. 1999). Thus, it is possible that endocrine disruption by arsenic can contribute to prostate cancer risk.

Anti-androgens

While there are no known environmental androgens, EDs can also function through anti-androgenic pathways. Since prostate cancer is an androgen-dependent disease, we will briefly examine the known effects of some of these agents on the prostate gland.

Vinclozolin

Vinclozolin is a fungicide that is used as a pesticide on crops. It has known anti-androgenic properties by interfering with AR activity (Kavlok & Cummings 2005). Since vinclozolin effects are driven through AR antagonism, it is not surprising that there are no reported associations between this compound and prostate cancer, an androgen-dependent disease. Exposure of rats to vinclozolin during development results in reduced prostate gland growth and size which would be expected for an anti-androgen (Yu *et al*. 2004). Of interest, however, are recent studies with maternal (i.e. *in utero*) exposure to vinclozolin in rats which produce transgenerational effects on offspring through epigenetic alterations (Anway *et al*. 2005). These permanent perturbations include adverse consequences on the prostate gland such as premature acinar atrophy and aging-associated prostatitis for four generations (Anway & Skinner 2008). This may be particularly significant in light of recent evidence that chronic inflammation may play a role in prostate cancer initiation (Nelson *et al*. 2002).

Dichlorodiphenyltrichloroethane/dichlorodiphenyldichloroethylene (DDT/DDE)

DDT and its metabolic derivative p,p′-DDE were widely used as pesticides in the United States and their use is still in effect in other countries worldwide. In addition to AR antagonistic effects (Gray *et al*. 1999), p,p′-DDE at high concentrations has been shown to function as an inhibitor of 5α-reductase, the intraprostatic enzyme responsible for converting testosterone to the more potent androgen, dihydrotestosterone (Lo *et al*. 2007). While many reproductive abnormalities have been found with DDT/DDE exposure, including

reduced prostate growth, there is no known association between exposure to DDT/p,p′-DDE and prostate cancer risk.

Summary and key questions

There is increasing evidence both from epidemiology studies and animal models that specific endocrine-disrupting compounds may influence the development or progression of prostate cancer. In large part, these effects appear to be linked to interference with estrogen signaling, either through interacting with ERs or by influencing steroid metabolism and altering estrogen levels within the body. In humans, epidemiologic evidence links specific pesticides, PCBs, and inorganic arsenic exposures to elevated prostate cancer risk. Studies in animal models also show augmentation of prostate carcinogenesis with several other environmental estrogenic compounds including cadmium, UV filters, and BPA. Importantly, there appears to be heightened sensitivity of the prostate to these EDs during the critical developmental windows including *in utero* and neonatal time points as well as during puberty. Thus, infants and children may be considered a highly susceptible population for ED exposures and increased risk of prostate cancers with aging.

There are several key questions that must be addressed in the future studies in order to best appreciate and understand the risks of prostate disease as they relate to endocrine-disrupting chemicals.

1. What specific ED chemicals can influence the prostate gland and increase prostate cancer risk or progression?
2. What are their modes of action?
3. Are there epigenetic pathways that mediate developmental exposures to EDs and prostate disease with aging?
4. Is there an additive or synergistic effect from ED mixtures and prostate cancer risk or growth?
5. Does ED exposure influence prostate cancer susceptibility in subpopulations of men? Are there specific pathways with which ED chemicals synergize to influence prostate cancer incidence and/or progression?
6. Is the *in utero* developing human prostate sensitive to ED chemicals and do they influence prostate cancer risk in the aging male? What are the most appropriate life stages for examining ED and prostate cancer risk?
7. Is there a transgenerational risk for prostate cancer as a function of ED exposures?
8. Can we establish molecular markers for ED exposures as they relate to prostate disease risk?

Focused research on these and other specific questions is required in order to adequately evaluate the human risk for prostate disease from the growing accumulation of EDs in the environment. Insight into molecular mechanisms may help to provide biomarkers for prostate disease risk from ED exposure as well as to provide opportunities for therapeutic intervention.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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