Bisphenol A as a Risk Factor in Prostate Cancer

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Abstract

Prostate cancer is a public health problem and the second leading cause of cancer-related death in men (1-3). Its etiology is not clear, although it is related to age, ethnicity and genetic factors (4). Its incidence has been increasing, not only because of early diagnosis but also because there seem to be other factors related to its pathogenesis, such as carcinogenic agents of the environment (5). Some of the food packaging found nowadays in supermarkets are made of plastic. There is controversy about the use of this material due to the possible adverse effects on health caused by the compounds forming them. In the first place, among the problems that plastic present for human health, we identified the migration of certain compounds forming them. Migration consists in the transfer of certain substances from the packaging into the food. Bisphenol A (BPA) can be found among these compounds. BPA is a monomer used in the production of plastic from carbonate sources that has been categorized as an endocrine-disrupting compound (EDC). Moreover, it is also used in the inner lining of other types of containers, such as cans. Some data associate the possible adverse effects derived from its exposure with the emergence of different diseases (e.g. diabetes, polycystic ovarian syndrome, metabolic syndrome, and obesity, among others). However, the International Agency for Research on Cancer (IARC) does not consider this element as a risk factor in the development of any type of cancer. Therefore, future studies are required to accurately assess the negative impact of BPA on the development of cancer in humans. This review attempts to examine the relation between this compound and the development of prostate cancer.

Keywords: bisphenol A, diet, cancer, prostate, disruptor, plastic.

1. Introduction

Bisphenol A (BPA), whose molecule can be observed in Figure 1 adapted from (6), is a compound that has been used over 50 years mainly as a monomer in the production of polycarbonate plastics and as an intermediary in epoxy resin synthesis (7). It has the property of acting as a prototypical xenoestrogen such as 17β-estradiol, and exposure to it causes different health problems. Its production has experienced a boom, increasing from one million metric tons to 7.7 million tons from 1980 to 2015 (8). This is why it accounts for some of the largest volumes of chemicals produced in the world (9). Due to the resistance it causes in the plastic material, this compound has been mainly used for the production of food packaging.

Furthermore, BPA is used as a component in polyester, polysulfone, and polyacrylate resins. These resins are used to make food containers (e.g. reusable baby bottles, baby bottles, dishes, cups, and storage containers. This compound can migrate into the food.

BPA is metabolized in the liver. Part of it becomes BPA glucuronide, a very soluble metabolite, whilst a smaller amount becomes BPA sulfate by reacting with sulfate (10). Once BPA is conjugated, its estrogenic activity is inactivated in such a way that a small part of the ingested BPA produces hormone level alterations and other types of adverse effects (11). When BPA is metabolized, it is removed from the body through urine. Nevertheless, although the detoxification process occurs successfully within a few hours after ingestion, the European Food Safety Authority (EFSA) decided in 2006 that, due to its toxicity, the Tolerable Daily Intake should diminish from 50 to 4 µg/kg bw/day. The main role of the EFSA is to provide scientific advice and to report existing and emerging risks associated with the food chain. This authority was established in 2002 and is based in Palma, Italy. In addition to the members, the Executive Director and the Management Board, the Scientific Committee, and its ten panels are in charge of the scientific endeavor. It is necessary to emphasize that some of the competencies of the EFSA are

food and feed safety, nutrition, animal health and welfare, plant protection, and plant health (12).

The main problem with exposure to food products is that BPA leaves some monomers unbound during polymerization and migrates some of them into the food. This leaching process increases if the container is stored in contact with acidic or basic foods, and also if the temperature rises (8).

There is extensive evidence that led to classify BPA as a very weak estrogenic compound and an endocrine disruptor. However, in addition to producing adverse effects on thyroid hormones, research has shown its relationship with diabetes (13); obesity (14); metabolic syndrome (15); effects on the reproductive system in animal studies (13, 16); and different types of cancer, such as liver (15), prostate (17, 18), breast (19), ovarian (20), uterine (21), testicular (22), and colon (23) cancer.

This review analyzes the relationship between human exposure to BPA due to diet and prostate cancer.

2. BPA and Diet

Exposure to BPA can occur both through environmental factors and through diet. According to the EFSA, the main source of human exposure to BPA is through food. Alarming amounts (over 1 mg/kg) (24) of this compound have been found in food. Several studies (34) quantified the amount of migrating BPA from some containers into the food. All of them agree that the greatest migration of BPA occurs in cans and water bottles. By analyzing other food groups and subgroups, including fresh food, numerous studies found the presence of BPA in all of them (25), and not only in long-term food products, such as those packaged in plastic bottles (26–28), bricks (29) or cans (30–32).

In order to find out the amount of BPA that gets into our bodies, the National Health and Nutrition Examination Survey (NHANES) was conducted in 2003-2004 in the US. This study (33) was promoted by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC). The total sample was composed of 2,517 US participants over the age of 6. The results revealed that 92.6% of the US population had BPA in their urine. In this study, which took into account the age, sex, and ethnicity of the participants, a urine sample was collected from one of the three daily examination sessions. The high number of participants with concentrations of BPA in urine demonstrated the continuous exposure of the population to this compound.

On the other hand, genistein (GEN) is a phytoestrogen present in soy with potentially protective effects against hormone-dependent cancers, including prostate cancer. In a study (35), pregnant rats were fed with or without soy and were administered 250 mg/kg bw/day of BPA via probes. Significant prostatic changes due to the exposure to this xenoestrogen could be quickly observed in the offspring of the soy-free litters. However, maternal feeding with GEN attenuated the adverse effects of BPA. In this way, it was possible to see a preventive action against the harmful effects of exposure to BPA through a soy-based diet in experimental animals.

3. Prostate Cancer and Pathogenesis

Prostate cancer is the most frequent cancer in men and the second most common in mortality worldwide (1, 3). It is related to many risk factors of a very diverse nature. Its incidence increases with age (36), and in those men with a family history of prostate cancer or even other hereditary types of cancer, such as breast cancer (4, 37). It is also more common in black men (38, 39), which has been related to dietary factors (39). Although some articles associate cancer development with endocrine disruptors (30, 32), it is true that their evidence remains uncertain and that human research is still scarce (17, 40).

This cancer is usually diagnosed in older men and its progression is often slow, so the benefit of early diagnosis is somewhat controversial (1). The normal growth of the prostate and its functionality are mainly regulated by androgens (24, 41). Prostate tumor cells act through the activation of the androgen receptor (AR), which will lead to an activation or inhibition of different molecular pathways. In addition to inhibiting the cell cycle, epigenetic changes take place in its regulatory proteins. In advanced cases of prostate cancer, overexpression of the epidermal growth factor receptor (EGFR) is observed. This transmembrane glycoprotein is a therapeutic target in many cancers (42). It is also believed that these genetic modifications affect the p53 protein, known as the "guardian of the genome", and that it could have a prognostic role because its presence leads to an increased risk of metastasis, also appearing in advanced stages (24, 43).

Most drugs used to treat prostate cancer act on the AR blocking, modulating, or reducing the production of the hormone. Initially, androgen deprivation therapy (ADT) is effective, but at a certain point it loses effectiveness (3, 24). Estrogen receptors (ER) play a fundamental role in the secretion of testosterone (T). This seems to be related to a possible subsequent malignization of prostate cells (3), since estrogens have been shown to induce cell proliferation in the prostate gland and favor carcinogenesis.

Therefore, it is thought that BPA can produce alterations at the level of the prostate gland by intervening or modifying its hormonal regulation. Mice studies proved its relation to the appearance of benign prostatic hyperplasia, as well as of prostate cancer (3). In these studies (17), BPA acts on the ER by altering cell proliferation. Until now, research has been inconclusive in humans, although it was proposed that BPA may increase the carcinogenic effect on aging on the prostate gland (44). Furthermore, in recent years it has been studied that exposure to intrauterine BPA could subsequently lead to a greater susceptibility to the development of neoplastic lesions in adulthood, and there are many endocrine disruptors to which the fetus is currently subjected (3).

Early exposure to BPA can lead to modifications in prostate cells in adulthood (1). Figure 2, adapted from (40), shows that exposure to BPA during fetal development increases the carcinogenic effect on aging (41).

4. BPA Action on the Prostatic Gland

The 5α-reductase enzyme metabolizes T in those tissues and organs where T is necessary, being overexpressed in prostate cancer (3). Its function is to synthesize dihydrotestosterone (DHT) from the circulating T, especially in the prostate and testicles. DHT has a higher affinity than T for the AR receptor.

BPA acts by increasing DHT and estradiol levels, as well as by activating various signaling pathways, such as extracellular signal-regulated kinases (ERKs), via ER or AR, or even EGFR directly, as discussed in the previous section. This leads to the proliferation of the prostate tumor cell. Furthermore, in the endothelial cell it also leads to an inflammatory response and the production of cytokines and various growth factors (24). Aromatase participates in the synthesis of estrogens.

Figure 3 adapted from (24) discusses the possible effect of BPA on prostate cancer. It summarizes the most well-known pathways of action of BPA, which lead to cell proliferation and to an inflammatory response in the endothelial cell. Different studies support the hypothesis of these authors. Even though there is not enough evidence in humans, it seems to be a sufficient basis to develop future publications and research. The action of BPA on the prostate gland, specifically on prostate stem cells, does present scientific evidence, but it is not possible to generalize this to the development of cancer itself in humans (3, 24, 44).

5. Other BPA Actions

BPA has been linked to other hormone-dependent cancers, such as breast or ovarian cancer. Regarding breast cancer, BPA interacts with growth factors, such as bone morphogenetic proteins (BMP), and these induce tumor proliferation or metastasis through various pathways. In addition, as it also happens with prostate cancer, it could generate resistance to chemotherapy, as has been seen to occur with EGFR tyrosine kinase inhibitors (EGFR-TKI) (3, 24).

Some authors associate BPA with many effects (28), such as an increase in fat mass index, obesity, depressive behavior, or behavioral disorders during childhood, among others. However, there is insufficient evidence to corroborate it. This is also the case of women with polycystic ovary syndrome, endometriosis, or those with greater difficulty in becoming pregnant, in whom high levels of BPA were observed (45, 46). On the contrary, some studies do show "some concern" about the consequences of BPA in the brain, in behavior, and in the prostate gland of fetuses, infants, and children (28).

Recent studies (24) focus on the effects of BPA at the genomic level on prostate cells, specifically on epithelial cells. There has been an increase in hormone receptor transcriptions in the cell nucleus, as well as in methylation.

6. Conclusions

There is a growing number of studies supporting the relationship between the development of prostate cancer and BPA consumption, although many of them have limited human evidence. Future studies are thus required, since we currently do not have enough evidence.

Given that prostate cancer is a slow-growing neoplasm, its diagnosis will be carried out mostly during the last decades of life (1). For this reason, it is necessary to conduct further research not only exposing the prostate cell to different concentrations of BPA (47), but also assessing the evolution over time of these effects.

Finally, nutritional studies would be useful to estimate the positive impact that a healthy diet would have against this xenoestrogen.

Statements

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Ethical concerns

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Conflicts of interest

The authors of this paper declare no conflicts of interest.

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Annex I: Figures

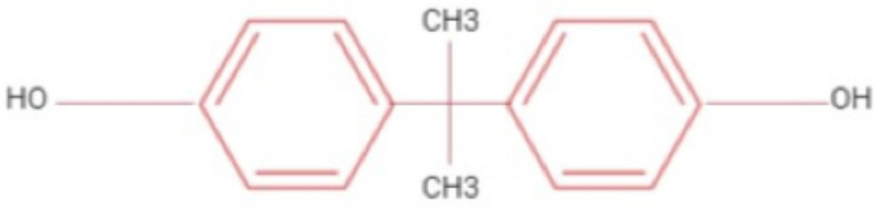


Figure 1. Bisphenol A molecule. Adapted from (6).

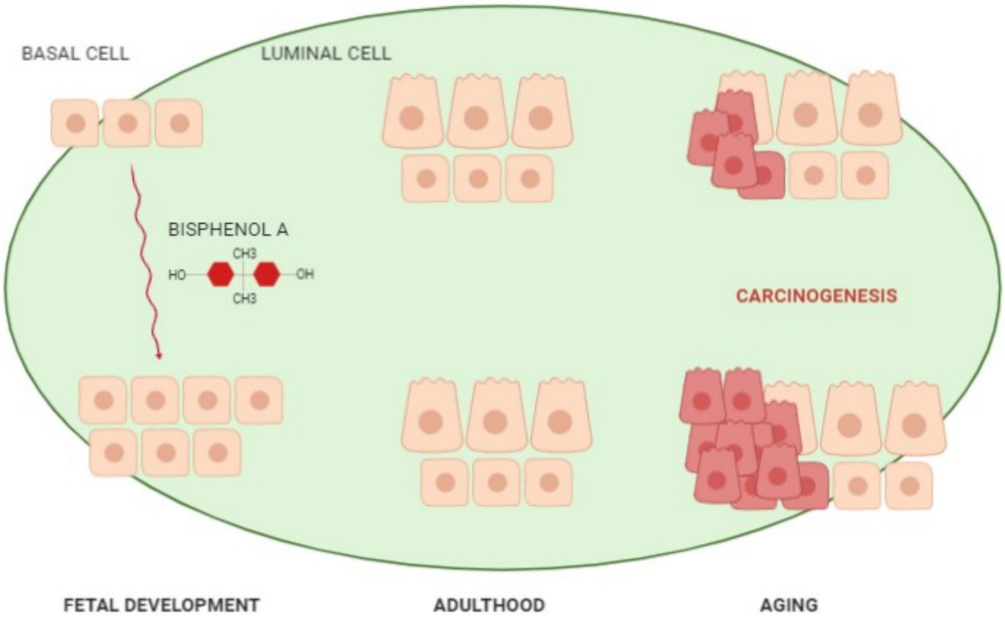
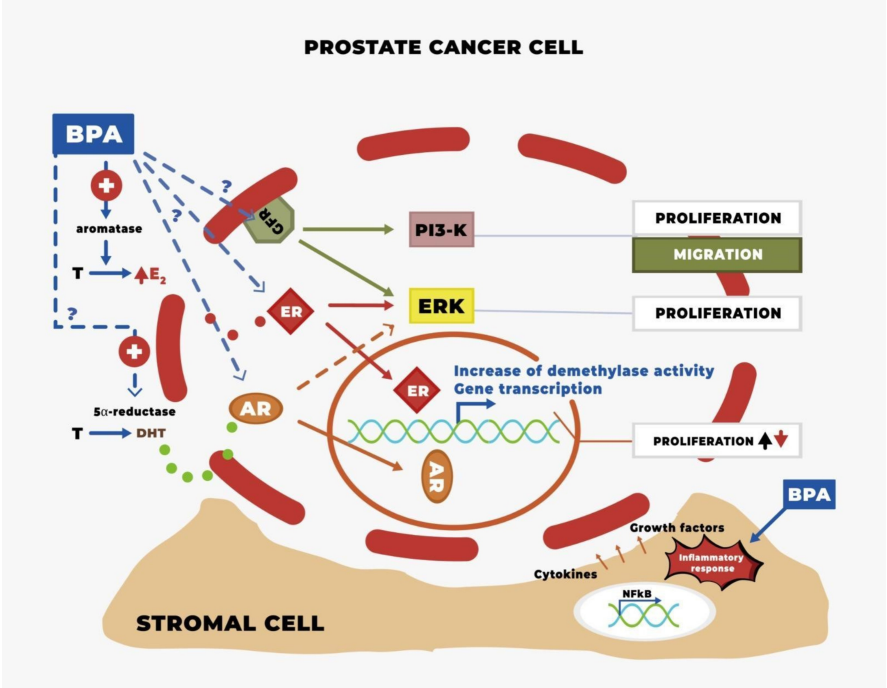


Figure 2. Effect of bisphenol A in the destination of stem cells. Adapted and authorized from (40). The exposure of prostate cells to endocrine-disrupting compounds can produce an abnormal effect on their growth, leading to cancer.



AR: androgen receptor; BPA: bisphenol A; DHT: dihydrotestosterone; ER: estrogen receptor; ERK: extracellular signal-regulated kinase; E2: estradiol; GFR: growth factor receptor; NFkB: nuclear factor kappa B; P13-K: phosphatidy-inositol-3-kinase; T: testosterone

Figure 3: Possible mechanisms of BPA action on the prostate cancer cell. Adapted and authorized from (24). It would act stimulating the AR, ER and EGFR receptors of the cell, which would activate different molecular signaling pathways leading to cell proliferation. It could also have epigenetic effects through ERs, modifying the transcription of genes in the nucleus, that would amplify this proliferative effect.