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April 9, 2007

A common plastic molecule to which virtually all Americans are exposed may interfere with the standard medical treatment for prostate cancer, according to new experiments with human prostate tumors implanted into mice. The doses of the plastic molecule, [bisphenol A](#), were chosen specifically to be within the range of common human exposures. Tumor size and [PSA levels](#) were significantly greater in exposed animals just one month after treatment.

One of the principal [known sources of exposure](#) to bisphenol A in the U.S. is through its use to make a resin that lines the majority of food cans sold in markets. These new results by Wetherill *et al.* suggest men concerned about prostate cancer may want to reduce their consumption of canned goods and their use of polycarbonate water bottles, another common source of exposure.



Two former Presidential candidates who have suffered prostate cancer, Senator Bob Dole and Senator John Kerry.

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Context

The standard medical treatment for advanced prostate cancer takes advantage of the tumor's dependence upon androgens, like testosterone, to grow. As long as it remains androgen dependent, [androgen ablation therapy](#) (also known as androgen deprivation therapy) can keep the tumor under control by lowering testosterone levels or by decreasing sensitivity to testosterone. Up to 80% of patients initially respond positively to this intervention. But despite the initial

Prostate cancer

No cancer strikes men in the U.S. more frequently than prostate cancer. More than 40,000 die each year from the disease. It is the most commonly diagnosed cancer among U.S. men and the second leading cause of cancer-related death.

Older men and black men are at special risk, while native American men are comparatively at lower risk. Rates have increased steadily since careful

success of this approach, more than 50% of patients relapse after two years. This relapse is driven by a change in the tumor, as it gradually loses its dependence upon androgen stimulation and begins to respond to other hormones like estrogen.

Wetherill and her colleagues had [reported previously](#) on experiments with prostate tumor cells in cell culture that show bisphenol A speeds the rate at which the cells become androgen independent. This new round of experiments takes that *in vitro* effect and demonstrates its relevance in living animals.



Bottles made from polycarbonate

Bisphenol A has been known to be estrogenic since the mid-1930s. It is used to make polycarbonate plastic as well as dental sealants and a resin coating for food cans to separate food from metal. Exposure to BPA is ubiquitous. It has been detected in [95% of Americans](#) tested.

Beginning in the late 1990's, many research studies have linked BPA to a wide range of adverse effects in animals following low dose exposures, especially but not exclusively when exposure takes place in the womb. While initially characterized as a 'weak' estrogen, recent studies have found it to be just as powerful as estrogen at provoking certain types of physiological responses. [More on BPA...](#)

record keeping began in the U.S.

This increase is more than simply the fact that the U.S. population is gradually growing older and prostate cancer risk rises with age. It is due to an increase, controlling for age, in the risk of prostate cancer. And the change has been happening faster than could be explained by inheritance of mutations. Something is changing in the environment, including lifestyle, that is causing prostate cancer in more men. The race is on to find the cause, and environmental contaminants are emerging as a prime suspect.

While most prostate cancers are detected after a man passes into his 50's and beyond, animal and human studies indicate that prostate cancer isn't something that suddenly begins as men enter their senior years. Its origins most likely involve developmental errors very early in life, even in the womb. Something happens during that period that sets a cell off on the wrong track, but then it lies quietly, undetected for many decades.

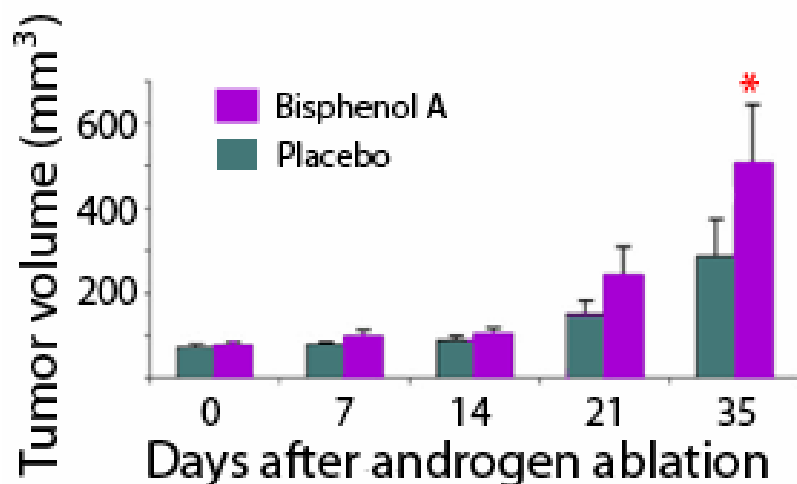
A [key diagnostic tool](#) for detecting prostate cancer is the prostate-specific antigen test, or **PSA test**. This test measures the levels of a protein produced by cells in the prostate gland. Prostate cancer and non-cancerous inflamed prostate conditions raise PSA levels in men's blood.

[More on prostate cancer](#)

What did they do? Wetherill *et al.* implanted human prostate tumor cells (called LNCaP cells) in a strain of mice with an immune system that does not resist transplants (called NCR/nu/nu mice). Tumor growth was monitored each week. Once the tumors had reached a specific volume, the mice were castrated and divided into two groups: one receiving a bisphenol A treatment, the other a placebo. Treatment and placebo were delivered using a subcutaneous 21-day release pellet. During the treatment period, the research team monitored serum PSA, testosterone and BPA levels. Thirty-five days later the mice were euthanized and the tumors were collected for detailed study.

The line of tumor cells used are androgen-dependent but following androgen ablation, like prostate tumors in men, become androgen independent over time, i.e., they grow even in the absence of androgen. In 31% of advanced human prostate tumors, androgen independence is tied to the presence of a specific androgen receptor (AR) mutant, called AR-T877A. This mutant is also present in the LNCaP cells used in this experiment. The mutation allows the receptor to respond not just to androgens, but an array of other hormones, including estrogen, progestins and anti-androgens.

What did they find? Testosterone was virtually undetectable in the mice after castration, as expected.



By day 21 after castration, tumors in both the placebo animals and BPA-treated animals were growing. By day 35, tumors in the BPA-treated animals were significantly larger than the controls ($p < 0.01$).

By day 35, tumors in the BPA treated animals were significantly larger than they had been on day 21 ($p < 0.001$).

Androgen ablation therapy

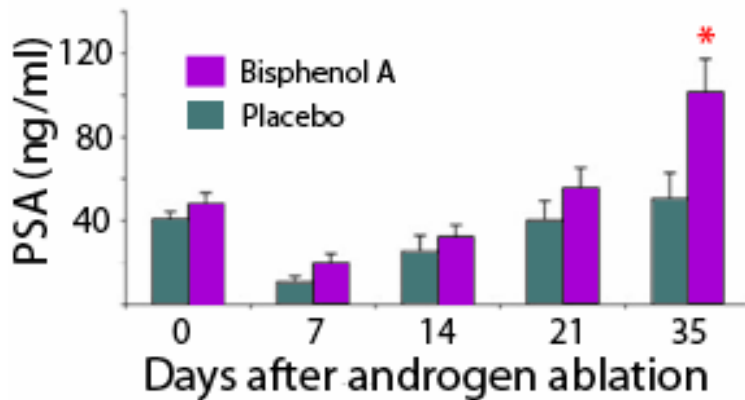
For much of the life of a human prostate tumor, it requires stimulation from an androgen, such as testosterone, to proliferate or grow by cells dividing. Without androgen stimulation, it grows only very slowly, if at all. As long as the tumor remains dependent upon androgens to proliferate (called 'androgen-dependence'), physicians can use 'androgen ablation therapy' to keep a prostate tumor under control.

Androgen ablation therapy proceeds either by reducing circulating levels of testosterone or by administering drugs that reduce the prostate's responsiveness to testosterone.

Castration: Testicles are the major source of testosterone in men. Removing them can reduce circulating testosterone levels by 90-95%. Alternatively, physicians can administer drugs that block the signals in the brain that guide testosterone synthesis in the testicles.

Anti-androgens: Drugs that block the androgen receptors can prevent testosterone from stimulating tumor proliferation.

Their histological studies revealed no significant differences between treated and placebo animals in the structure of the tumors. They did find, however, that proliferation rates were higher in BPA-treated animals than in placebo animals. A higher percentage of cells in BPA treated tumors were actively dividing than in controls ($p < 0.01$).



Immediately following androgen ablation by castration, PSA levels dropped by 75%, as expected (figure to left).

Also as expected, PSA levels in both placebo and BPA treated animals rose over time. The immediate drop followed by a gradual rise tracks what is observed in men following androgen ablation therapy.

By day 35, however, PSA levels were significantly greater in animals exposed to BPA than those in the control group ($p < 0.01$).

Prostate cancer

27 September [The problem with plastic](#). During the first few years of life, when babies' cells continue to undergo "programming," exposure to certain toxic chemicals can disrupt the delicate process. [US News & World Report](#).

25 September [New study raises doubts: Annual physicals worth it?](#) A new study led by the University of Pittsburgh School of Medicine may fuel the simmering debate on whether the annual physical exam itself is an outdated ritual that wastes time and money. [Philadelphia Inquirer](#), Pennsylvania.

24 September [Single gene linked to many cancers](#). A gene has been found to play an important role in tumour growth in nearly three quarters of cancers, raising hopes for potential new treatments for the disease, scientists will say

What does it mean? The results obtained in this study show that environmentally-relevant levels of bisphenol A may promote prostate cancer growth in those men who have the mutant form of the androgen receptor AR-T877A, present in 31% of advanced prostate tumors. Wetherill *et al.* note that other mutant forms may respond similarly, but that their study doesn't address those cases. So at a minimum, almost one-third of advanced prostate cancer patients may be vulnerable to incidental exposure to BPA and its interference with androgen ablation therapy.

The rise in PSA levels is particularly important, as in people, progression from a form of prostate cancer that responds to androgen ablation therapy to one that is resistant is often associated with rapidly rising PSA levels.

Their previous work in cell culture has shown that this impact of BPA can be countered by application of androgen receptor antagonists, such as bicalutamide. Hence treatment may negate the adverse effects of BPA. Whether this still holds following long-term exposure to BPA is currently under study.

Most of the low-level adverse impacts of BPA have emerged in research examining the consequences of developmental exposures, including on [prostate](#) and [breast cancer](#). This research joins a small number of other studies, for example, on [insulin resistance](#) and [sperm count](#), that have identified potential risks

today. [London Times](#), England.

23 September [Study of epigenetics seeks to control genes' functions](#). A new science is turning the medical world on its Darwinian ear. Epigenetics is about the factors that turn genes on and off, including contaminants. Worldwide, interest is booming. [Kansas City Star](#), Missouri.

20 September [House passes bill giving more power to the F.D.A.](#) The House overwhelmingly passed legislation on Wednesday that is expected to give federal drug regulators significantly more money and power to ensure the safety of the nation's drug supply. [New York Times](#).

[More news about prostate cancer](#)

resulting from adult exposures.

Resources:

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