Preventing prostate cancer through androgen deprivation may have harmful effects

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Mice deficient in PTEN in the prostate developed stable precancers. Androgen deprivation promoted progression to invasive prostate cancer. Patients with PTEN-deficient prostate precancers may not benefit from androgen deprivation chemoprevention therapy.

The use of androgen deprivation therapies to prevent precancerous prostate abnormalities developing into aggressive prostate cancer may have adverse effects in men with precancers with specific genetic alterations, according to data from a preclinical study recently published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"The growth and survival of prostate cancer cells are very dependent on signals that the cancer cells receive from a group of hormones, called androgens, which includes testosterone," said Thomas R. Roberts, Ph.D., co-chair of the Department of Cancer Biology at the Dana-Farber Cancer Institute and professor of biological chemistry and molecular pharmacology at Harvard Medical School in Boston, Mass.

Previous findings from two major randomized, placebo-controlled prostate cancer chemoprevention trials revealed that androgen deprivation therapy reduced the overall risk for low-grade prostate cancer. However, both trials also revealed a high cumulative risk for high-grade prostate cancers that has caused concern among experts.

High-grade prostatic intraepithelial neoplasia is a prostate abnormality

that is considered to be a major precursor to prostate cancer. Loss of the tumor suppressor PTEN is detected in 9 to 45 percent of clinical cases.

Using a mouse model of PTEN-driven high-grade prostatic intraepithelial neoplasia, Roberts and his colleagues investigated whether surgical or chemical androgen deprivation could prevent the cancer precursor from progressing to more aggressive disease.

"When we castrated the animals, we thought the tumors would shrink and they did initially," Roberts said. "However, they then grew back and became invasive."

The results of this preclinical study suggest that prophylactic reduction of the most active form of androgen, or blocking androgen receptor function, might have unintended consequences in some men.

"Stretching our data even further, these findings suggest that as men age and their testosterone levels decrease, loss of testosterone might actually encourage indolent prostate tumors to become more aggressive," Roberts said. "This suggests that testosterone supplements might be a good thing for the prostate, even though current wisdom suggests the opposite."

Roberts noted that these results should be interpreted with caution because the prostate glands of mice are different from their human counterparts. More data on human tumors are needed to evaluate whether the data from this mouse study are applicable to men.

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