

Prostate Cancer Health Center

Treatment May Speed Prostate Cancer

Study Shows Hormone Therapy Can Make Prostate Cancer More Deadly

By [Daniel J. DeNoon](#)

WebMD Health News

Reviewed by [Louise Chang, MD](#)

Aug. 28, 2008 -- Hormone therapy, the most common treatment for advanced [prostate cancer](#), can boomerang to make the [cancer](#) more deadly, mouse studies suggest.

The finding "may revolutionize the way we combat prostate cancer," suggest University of Rochester researchers Chawnshang Chang, PhD, Edward M. Messing, MD, and colleagues.

It's well known that male sex hormones promote the growth of prostate cancer. That's why doctors use hormone therapy -- chemical or physical castration -- to shut off these tumor-promoting androgens.

But Chang's team finds that in different types of prostate cancer cells, androgens actually inhibit prostate cancer. When these tumor cells don't get androgens, they become more aggressive and more invasive.

The lining of the prostate is made up of epithelial cells. The fibrous body of the prostate is made up of stromal cells. On their surfaces, both cell types have triggers -- androgen receptors -- that fire when they encounter sex hormones. Triggering androgen receptors has different effects in each cell type.

"The androgen receptor in the stromal cells always turns the cancer on," Messing tells WebMD. "The androgen receptor in the epithelial cells, at least in the animal models we studied, tends to inhibit cancer."

This, Messing says, helps explain why hormone therapy always works at first but then tends to lose its cancer-inhibiting effect over time.

Since the cancer-promoting effect of androgens is strongest in the earlier stages of cancer, hormone therapy does more good than harm. But as the cancer spreads to distant sites, Messing says, the cancer-inhibiting effect of androgens may become more important. At this point, hormone therapy may do more harm than good.

How can the same hormones have two opposite effects?

"Anyone who has been around teen boys and older men knows that androgen receptors in different parts of the body cause different effects," Messing says. "Androgen receptors on the scalp make older men lose their hair, while androgen receptors on the face make teenagers grow beards. So androgen receptors can do different things in different places."

Doctors have long known that hormone therapy has different effects at different times in different parts of the body, says Peter Nieh, MD, director of the Uro-Oncology Center at Emory University, Atlanta.

"We'd all like to find a silver bullet that attacks one thing but does not hurt anything else. The problem is there is always collateral damage," Nieh tells WebMD.

Chang's team demonstrated the opposite effects of androgen receptors in cell-culture studies and in studies of prostate-cancer-prone mice that lacked androgen receptors only in their prostate epithelial cells. These mice had much more aggressive cancer, apparently because they lost the ability to respond to the cancer-inhibiting effects of androgens.

The researchers also point to studies of prostate glands removed from men with prostate cancer. There were significantly fewer androgen receptors in metastatic prostate cancers than in early prostate cancers or in

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Prostate Cancer Health Center

Treatment May Speed Prostate Cancer

Study Shows Hormone Therapy Can Make Prostate Cancer More Deadly (continued)

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Nieh notes that human studies will be needed to confirm the suggestion that the cancer-stimulating effect of hormone therapy explains why the treatment often fails after succeeding at first. And he says that even if hormone therapy does stimulate cancer, its inhibitory effect is more important for some patients.

"The idea of continuous hormone therapy for very advanced prostate cancer has been with us for 60 years," Nieh says. "Patients with bone metastases and extensive disease probably have much more of the stromal part of the prostate, the part that is stimulated by androgen. So they will respond better to the cancer-inhibiting aspect of hormone treatment than to any cancer-stimulating aspect."

But the Chang team's mouse studies suggest that hormone therapy may exert a stronger effect on stromal cells early in the course of disease.

Nieh points to clinical trials of intermittent hormone therapy, in which patients go off treatment from time to time. The idea is to lessen the side effects of the treatment and to extend its anticancer effect.

"With intermittent hormone therapy, animal studies suggest you may be getting a balance between the inhibitory and stimulatory effects on the cancer, whereas continuous hormone therapy drives out the inhibitory effect and you are left with the stimulatory effect," he says. "We really won't know in humans for at least four or five years because the trial is just now being done."

Messing hopes that researchers will find a way to make future hormone therapy more specific so that it blocks the cancer-promoting functions of androgen receptors and enhances their cancer-inhibiting effects.

Chang, Messing, and colleagues report their findings in the Aug. 18 early online edition of the *Proceedings of the National Academy of Sciences*.

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1 | 2

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Edward M. Messing, MD, professor of urology, University of Rochester, N.Y.

Peter Nieh, MD, assistant professor of urology and director, uro-oncology center, Emory University, Atlanta.

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Treatment for prostate cancer can be self-defeating

Indo Asian News Service

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Washington, Aug 22 (IANS) Some of the drugs administered for treatment of prostate cancer can be self-defeating; they actually spur cancerous cells to grow, according to new research.

The findings could help explain why such failures have bedevilled patients for decades. Hormone therapy, a common treatment for advanced prostate cancer, fights the condition for a year or two.

But for reasons never fathomed by scientists, the treatment fails in patients with a worsening condition. The cancer begins to grow again, at a time when they have fewer treatment options.

These findings by Chawnsang Chang and his team at the University of Rochester Medical Center offers the explanation that the androgen receptor, through which male hormones like testosterone work, is much more versatile than previously thought.

Under certain conditions the molecule spurs growth, and at other times the molecule squelches growth - just like the same molecule does to hair in different locations on a man's head.

Chang said the molecule's versatility in the prostate should not come as a surprise, since the molecule's function elsewhere depends on its location.

For example, 'when the receptor is very active in the moustache area, more hair grows. When it's very active on the top of the skull, toward the front, hair falls out and men become bald. And the hair on the back of the head is insensitive to the receptor. The effects of hormones depend on the location'.

The new findings suggest the possibility that under some conditions, some treatments designed to treat prostate cancer could instead remove one of the body's natural brakes on the spread of the disease in the body.

The researchers stress that the results are based on lab studies and on findings in mice, and it's too soon to know yet whether the findings apply directly to prostate cancer in men.

Understanding the effects of the androgen receptor gives physicians a toehold in efforts to develop more effective treatment in prostate cancer. That would be welcome news for the one of every six men who will develop the disease during his lifetime.

More than 28,000 men die from the disease in the US every year, according to the American Cancer Society. Men's risk from prostate cancer is about the same as women's risk from breast cancer.

Every year both the genders face the risk of dying equally from their respective conditions, according to ACS.

Chang's findings are most relevant for patients with advanced prostate cancer, who typically receive hormone therapy after other treatments such as surgery or radiation.

With hormone therapy, physicians blunt the effects of male hormones like testosterone to bring the disease in the prostate to a halt. One form of hormone therapy works by blocking the androgen receptor.

The findings appeared online this week in the Proceedings of the National Academy of Sciences.

Why a common treatment for prostate cancer ultimately fails

• Prostate Cancer news • Aug 21, 2008

Some of the drugs given to many men during their fight against [prostate cancer](#) can actually spur some cancer cells to grow, researchers have found. The findings were published online this week in a pair of papers in the Proceedings of the National Academy of Sciences.

The results may help explain a phenomenon that has bedeviled patients for decades. Hormone therapy, a common treatment for men with advanced [prostate cancer](#), generally keeps the cancer at bay for a year or two. But then, for reasons scientists have never understood, the treatment fails in patients whose disease has spread – the cancer begins to grow again, at a time when patients have few treatment options left.

The new findings by a team led by Chawnschang Chang, Ph.D., director of the George Whipple Laboratory for Cancer Research at the University of Rochester Medical Center, help explain the process by showing that the androgen receptor, through which male hormones like testosterone work, is much more versatile than previously thought. Under certain conditions the molecule spurs growth, and at other times the molecule squelches growth – just like the same molecule does to hair in different locations on a man's head.

The new findings raise the possibility that under some conditions, some treatments designed to treat [prostate cancer](#) could instead remove one of the body's natural brakes on the spread of the disease in the body. The researchers stress that the results are based on laboratory studies and on findings in mice, and it's too soon to know yet whether the findings apply directly to [prostate cancer](#) in men.

Understanding the effects of the androgen receptor gives physicians a toehold in efforts to develop more effective treatments for men with [prostate cancer](#). That would be welcome news for the one of every six men who will get the disease during his lifetime. More than 28,000 men die from the disease in the United States each year, according to the American Cancer Society. Men's risk from [prostate cancer](#) is about equal to women's risk from [breast cancer](#): Each year, about the same number of men get [prostate cancer](#) as women get [breast cancer](#), and their risk of dying from the diseases is about equal, according to ACS.

Chang's findings are most relevant for patients with advanced [prostate cancer](#), who typically receive hormone therapy after other treatments such as surgery or radiation. With hormone therapy, physicians blunt the effects of male hormones like testosterone to bring the disease in the prostate to a halt. One form of hormone therapy works by blocking the androgen receptor. Androgen deprivation therapy is generally very effective for a year or two, but for reasons that no one has understood, the cancer ultimately returns.

"When a man receives hormone therapy, initially the treatment works well, and his PSA (prostate specific antigen) level goes down," said Edward Messing, M.D., a urologist and an author of the paper. "But inevitably, the PSA will start climbing again, and that is usually the first sign that the treatment is beginning to fail. It's a sign that the cancer in the prostate is making a comeback."

In work funded by the National Cancer Institute, Chang's team found that blocking the receptor indeed prevents some cells in the prostate from growing, just as scientists expected. But Chang's team unexpectedly found that blocking the receptor actually spurs other prostate cells to grow.

"The androgen receptor acts differently in different cells in prostate tissue," said Chang. "It's always been assumed that blocking the androgen receptor will stop all prostate cells from growing, but we have found that that's not the case. Since current treatment acts non-specifically on all the cells having androgen receptors in the prostate, blocking the androgen receptor will give mixed results."

The team found that, as expected, the androgen receptor in prostate support cells known as stromal cells stimulates growth of cells, including cancer cells, in the prostate. He also found, surprisingly, that the receptor actually acts as a tumor suppressor in epithelial cells known as basal cells in the prostate.

Then Chang's team knocked out the androgen receptor in specific sets of prostate cells and studied the results. As expected, when the molecule is turned off in stromal cells, growth of cancer cells in the prostate slows. But when the molecule is turned off in the epithelial cells, it removes one of the body's natural inhibitors that prevents [prostate cancer](#) cells from spreading, making cells more likely to invade other tissues.

"While the androgen receptor is really driving [prostate cancer](#), in another sense it appears that the receptor also normally inhibits the spread of cancer cells. It seems to have a dual role. Manipulating the androgen receptor can increase or decrease either of these actions depending on precisely how it's done," said Messing.

Chang says the molecule's versatility in the prostate should not come as a surprise, since the molecule's function elsewhere depends on its location.

"The effects of the androgen receptor on hair growth in men vary dramatically depending on where in the body the receptor is working," said Chang. "When the receptor is very active in the mustache area, more hair grows. When it's very active on the top of the skull, toward the front, hair falls out and men become bald. And the hair on the back of the head is insensitive to the receptor. The effects of hormones depend on the location.

"We found that the same is true within the cells of the prostate itself," said Chang, who is a faculty member in the departments of Urology and Pathology and the James P. Wilmot Cancer Center.

Chang says it's likely that the androgen receptor works differently in different cells partly because the assortment of molecular colleagues it works with within the body changes from situation to situation. Like a foreman turning to a pool of employees to get certain jobs done, the androgen receptor taps different molecules in different situations, forming intricate complexes or groupings that then accomplish various tasks. The receptor works very quickly, assembling a team within seconds, accomplishing a task, then disbanding and making its helpers available to form a brand new team for another task.

Chang's team is working on ways to focus on these molecular "co-factors" as a way to target the androgen receptor differently in different cells, for instance, turning off the receptor in some cells while keeping it on in others, to fight [prostate cancer](#). That type of cell-specific targeting is currently not possible.

The research in the laboratory involved tracking the disease in mice and also analyzing human [prostate cancer](#) cells in culture. Nevertheless, the work might include some hints for improving patient care. Possibilities include studying whether androgen suppression therapy might be used to target only

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specific cells within the prostate, as well as checking whether drugs designed to prevent cancer from spreading should be used in concert with hormone therapy.

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Chang's team included researchers Yuanjie Niu; Saleh Altuwaijri; Kuo-Pao Lai; Chun-Te Wu; William A. Ricke, Ph.D., assistant professor of Urology; Jorge Yao; Shuyuan Yeh, Ph.D., associate professor of Urology; Shengqiang Yu; Kuang-Hsiang Chuang; Shu-Pin Huang; and Edward Messing, M.D., professor and chair of Urology. Henry Lardy of the University of Wisconsin is an author on one of the papers.

Contact: Leslie White

Leslie_White@urmc.rochester.edu

585-273-1119

University of Rochester Medical Center

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Why a Prostate Cancer Treatment May Fail

Posted on: Friday, 22 August 2008, 15:00 CDT

Some drugs given to men to help treat prostate cancer may actually spur some cancer cells to grow, U.S. researchers said.

The study, published online in two papers in the Proceedings of the National Academy of Sciences, said hormone therapy, a common treatment for men with advanced prostate cancer, generally keeps the cancer at bay for a year or two. But then, for reasons scientists have never understood, the treatment fails in patients whose disease has spread.

Chawnschang Chang, director of the George Whipple Laboratory for Cancer Research at the University of Rochester Medical Center, said that the androgen receptor -- through which male hormones like testosterone work - is much more versatile than previously believed.

Under certain conditions the molecule spurs growth, and at other times the molecule squelches growth, just like the same molecule does to hair in different locations on a man's head.

The findings raise the possibility that under some conditions, some treatments designed to treat prostate cancer could instead remove one of the body's natural brakes on the disease. However, the researchers stress the results are based on laboratory studies in mice and it's too soon to know whether the findings apply to men.

Source: United Press International

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治療會惡化前列腺癌

(2008/09/16)



老鼠研究顯示，惡化前列腺癌最常用的荷爾蒙治療，反而會使此癌症更致命。

研究者、羅徹斯特大學的Chawnsang Chang博士、Edward M. Messing醫師等人認為，此一發現會使我們治療癌列腺癌的方式產生革命。

已知男性性荷爾蒙會促進前列腺癌生長，因此醫師使用荷爾蒙治療—化學或者生理去勢—來關掉這些促進腫瘤的雄性素。但是Chang博士的團隊發現，在不同類型的前列腺癌細胞中，雄性素實際抑制前列腺癌，當這些腫瘤細胞無法獲得雄性素，它們變得更有侵犯性。

前列腺內側由上皮細胞組成，前列腺的纖維體是由基質細胞組成，兩種細胞在它們的表面都有雄性素受體—當遇到性荷爾蒙時啟動功能，啟動這兩種細胞的雄性素受體會有不同結果。

Messing醫師向WebMD表示，基質細胞的雄性素受體會啟動腫瘤，而在動物研究中，上皮細胞的雄性素受體會抑制癌症。

Messing醫師表示，這有助於解釋何以一開始荷爾蒙治療有效，但之後會隨著時間失去其抑制癌症的效果。

因為雄性素的促進癌症效果在癌症早期最強，荷爾蒙治療的好處大於傷害；Messing醫師表示，但是當癌症擴散到遠端部位，雄性素的癌症抑制效果變得更重要，此時，荷爾蒙治療的弊大於利。

為何同樣的荷爾蒙會有兩個截然不同的效果？

Messing醫師表示，不論是青少年還是老人，都知道身體不同部位的雄性素受體會引起不同的效果，頭皮的雄性素受體使得年長男性失去頭髮，臉部的雄性素受體使青少年長出鬍鬚，所以雄性素受體在不同部位會有不同功能。

Emory大學泌尿腫瘤中心主任Peter Nieh醫師表示，醫師一直都知道在身體不同部位、不同時間使用荷爾蒙治療會有不同結果。

Nieh醫師向WebMD表示，我們希望發現可以不會造成任何傷害的方法，問題是，總會有附帶的傷害。

Chang博士的團隊指出，在細胞培育研究中，雄性素受體的相反效果，也進行喪失前列腺上皮細胞雄性素受體老鼠的前列腺癌傾向研究；這些老鼠有比較多的侵犯性癌症，顯然是因為牠們失去雄性

素抑制癌症的能力。

研究者也點出從前列腺癌男性移除前列腺的研究，轉移前列腺癌的雄性素受體比早期前列腺癌或正常前列腺細胞顯著減少。

Nieh醫師指出，需要進行人類研究，以證實荷爾蒙治療的癌症促進效應，解釋何以在最初成功之後，為什麼治療經常失敗；他同時表示，即使荷爾蒙治療會促進癌症，對一些病患來說，其抑制效果更重要。

Nieh醫師表示，對於每個末期前列腺癌連續以荷爾蒙治療的觀念已經有60年，骨骼轉移和擴散疾病的患者可能有比較多的前列腺基質，刺激產生雄性素，所以他們對於荷爾蒙治療抑制效果的反應比促進癌症的效應佳。

但是**Chang**博士的團隊進行的老鼠研究認為，荷爾蒙治療對於疾病早期的基質細胞會有更強烈的效果。

Nieh醫師提出，間歇性的荷爾蒙治療臨床試驗、病患某段時間停止療程，此觀念在於減少治療的副作用而延伸抗癌效果。

他表示，動物研究認為，藉由間歇性荷爾蒙治療，可以在癌症的抑制與刺激效果之間取得平衡，連續荷爾蒙治療可能會失去抑制效果而只留下癌症促進效應；我們無法在四至五年內知道，因為試驗才剛開始。

Messing醫師希望研究者未來可以找到使荷爾蒙治療更有特定性的方法，可以阻斷雄性素受體的癌症促進功能，還可促進其抑制癌症的效果。

Chang博士、**Messing**醫師等人在8月13日美國國家科學院院刊線上版發表研究發現。

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