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The DHEA Debate

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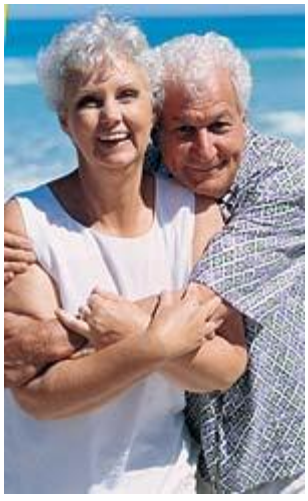
COVER STORY

A critical review of clinical and experimental data

x) **Naysayer:** That's just it. There doesn't seem to be any long-term studies to back up the anti-aging claims for DHEA.

Stephen Cherniske: You just haven't looked. When the National Institutes on Aging analyzed data from the Baltimore Longitudinal Study of Aging, they found a profound relationship between DHEA levels and survival.[38]

"Consistent with the beneficial effects of calorie restriction on aging and life span in other animals, men with lower temperature and insulin and those maintaining higher DHEA levels have greater survival than their respective counterparts."[39]



Likewise, studies of people aged 90 to 106 demonstrate that those who reach this remarkable milestone have higher-than-average DHEA levels. As you would expect, this was associated with a higher muscle-to-fat ratio and greater functional ability.[40,41]

The average adult replaces more than 300 billion cells each day. Anti-aging is accomplished in three ways: by providing optimal raw materials for this repair activity, reducing the damage that these cells are exposed to, and restoring and maintaining anabolic (repair) metabolism. As I mentioned, DHEA is the most comprehensive repair signal in human biochemistry, and it is time that we fully appreciate the influence it has on one's rate of aging. I am not the only scientist who believes that anti-aging is virtually impossible without paying careful attention to one's DHEA level. Here are the findings from a study on hormones and aging:

“The maintenance of a good physical functional ability and quality of life is related to serum testosterone, estrogen, and DHEA(S) concentrations.”[42]

Naysayer: But isn’t that the problem—that DHEA, because it is a cell proliferator, might accelerate nascent tumors?

Stephen Cherniske: Wrong! DHEA is a cell regulator. It induces apoptosis (cell death) in malignant and malfunctioning cells,[43-45] and controls hyperplasia (abnormal cell growth) in the smooth muscle of the lungs.[46] In numerous animal models, it has been shown to mimic the cell-regulating, anticancer benefits of calorie restriction.[36,47]

In thousands of animal studies, DHEA has been shown to prevent diabetes, obesity, infection, liver disease, and many types of cancer.[48] In humans, DHEA levels predict mortality in a number of disease states, including AIDS, sepsis, cancer, and heart disease.[49-52] And supplementation with DHEA has been shown—in controlled human studies—to increase muscle mass, improve bone density, combat stress and depression, enhance quality of life, restore immunity, protect the brain, improve memory, reduce the symptoms of systemic lupus erythematosus, and reduce risk for diabetes and cardiovascular disease.[3,4,22,53-61]

Naysayer: How can you be sure that DHEA won’t cause cancer?

Stephen Cherniske: There are no data to suggest that. In fact, all the evidence is to the contrary. Dr. Marian Laderoute, a pathologist at the Canadian Bureau of Infectious Diseases, reminds us that cancer is associated with low DHEA levels. She and others point out that the specific mutations required for carcinogenesis can be traced to a failure of immunity and cell regulation that takes place as a consequence of falling levels of DHEA.[62]

Clearly, cancer does not take place due to high levels of DHEA. If that were the case, young people would get cancer, when in fact it is remarkably rare in the young. Declining immunity must be a factor, but we also do not see an increased incidence of cancer among young patients on immunosuppressive therapy (for example, organ transplant recipients). Cancer incidence, it turns out, is tied to numerous aspects of aging, including impaired apoptosis, decreased immune surveillance and decreased number and activity of NK (natural killer) cells. DHEA has been shown to improve every one of these factors.[45,55,63,64]

Current research also shows that DHEA, like calorie restriction, reduces the inducible generation of nitric oxide, which is yet another way of reducing cancer risk.[65] On the gene level, DHEA’s anticancer activity includes a reduction in levels of the mutant gene p53.[66] Moreover, aging and cancer are associated with the dysregulation of cytokine production in which IL-6 dominates over IL-2. It is known that IL-2 has powerful anticancer activity, and IL-2 injection resently used in Europe with various stages of cancer. Since optimizing DHEA has been own to significantly increase IL-2 and normalize cytokine balance, maintaining optimal levels HEA appears to be an effective cancer-preventive strategy.

Indeed, animal studies have supported this idea for over 25 years, where DHEA administration has reduced the risk of cancer of the liver, adrenals, pancreas, breast, lung, thyroid, colon, skin, and lymphatic tissue.[67-75]

In all, there is compelling genomic, biochemical, and biological evidence supporting the ability of DHEA to reduce cancer risk. But perhaps you have data from human trials showing that DHEA somehow stimulates cancer growth.

Naysayer: DHEA has been shown to cause liver cancer in mice.

Stephen Cherniske: Yes, there is a study in which mice were given a massive dose of DHEA—the human equivalent of 10,000 mg per day. And even then, this dose had to be administered continuously for at least 18 months (the human equivalent of 76 years) before they could induce cancer in these poor animals.[76]

Do you really think that this is relevant, considering that studies using a lower dose (the human equivalent of 2,000 mg per day) did not produce cancer,[77] and more than 50 rodent studies show that DHEA reduces cancer risk? Importantly, DHEA administration has reduced cancer risk in every conceivable model, whether the cancers were spontaneous or induced by a virus or carcinogenic chemical.[78]

Naysayer: Well, there are other studies . . .

Stephen Cherniske: Yes, the study at the University of Oregon where DHEA was fed to trout—an organism that does not even produce DHEA naturally.[79] Such data would be useful only if there were indications that the same thing might occur in humans. But in a review of more than 5,500 studies published on DHEA, not one has shown that DHEA stimulates cancer growth. In fact, DHEA has been used successfully in the treatment of cancer.[80]

Look at the recent research conducted by the National Cancer Institute. They created a reliable animal model for the study of breast cancer and found that DHEA administration significantly reduced both the incidence and multiplicity of tumors.[81] Here's the quote that appeared in the Journal of Nutrition (p. 2408S):

"Whenever it has been tested in a model of carcinogenesis and tumor induction, DHEA has preventative effects."[82]

Another animal study from 2001, also conducted by the National Cancer Institute, showed that DHEA administration reduced breast cancer incidence by 30% and multiplicity by 50%.[83] The following year, NCI published a mode-of-action study explaining how DHEA helps to limit cancer growth.[84]

DHEA has even shown powerful anti-cancer activity in mice selectively bred to be highly susceptible to cancer.[85] Researchers have also found the specific genes that confer this advantage (including p53, DHEA ST, and p21) are upregulated by oral administration of DHEA.[86,87]

DHEA may also be effective in reducing risk for colon cancer. Scientists in Japan exposed mice to a chemical that induces abnormal cellular proliferation in the colon. After this exposure, some of the mice were fed DHEA. At the end of the experiment, the DHEA-supplemented mice had a significant decrease in precancerous lesions compared to controls.[88]

In another animal study, small doses of DHEA were shown to significantly prevent breast cancer. DHEA treatment resulted in a marked reduction in tumor incidence and a whopping 92% reduction in tumor size compared to controls.[89]

Naysayer: But these are animal studies. They don't prove that DHEA prevents breast cancer in human beings.

Stephen Cherniske: Agreed. But they certainly disprove your "sky-is-falling" diatribe that DHEA might cause breast cancer. There isn't any evidence whatsoever that DHEA increases risk for breast cancer. In fact, a study published in the prestigious journal The Lancet showed a remarkable correlation between breast cancer and low DHEA levels.

In this longitudinal study, researchers measured DHEA metabolites in 5,000 women, and then followed these subjects for nine years for breast cancer. DHEA levels were significantly lower in cases (women who were subsequently diagnosed with breast cancer) compared to matched controls, leading the researchers to conclude that women with low DHEA levels are at increased risk for breast cancer.[90]

So the breast cancer scare is a red herring. You also claim that DHEA might cause prostate cancer, when all the evidence is to the contrary.

Naysayer: I disagree. DHEA can be converted to testosterone.

Stephen Cherniske: So? Human studies show that there is no correlation between DHEA or testosterone and prostate cancer.[91-95] In- vitro studies show that DHEA actually inhibits prostate cancer,[96] and even giving massive amounts of DHEA to animals does not induce abnormal growth in the prostate. A study published in the journal Cancer Research states:

"No effect on the development of prostate cancer precursor lesions was observed when ce were treated with DHEA."[83]

aysayer: But I've read in dozens of articles that DHEA might cause prostate cancer. All of se articles can't be wrong.

Stephen Cherniske: Sure they can. Journalists are not scientists. If they believe their source to be accurate, they print the information without checking the medical literature. Then the story is repeated and, as you know, if an error is repeated enough, it appears to be true. If journalists were willing or able to carefully research this topic, they'd find an animal study reported in the European Journal of Urology that concludes:

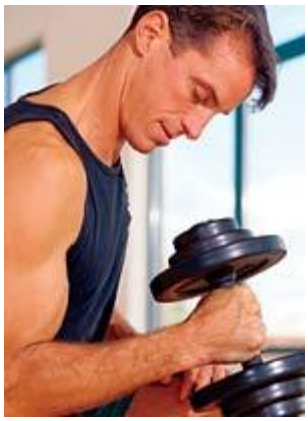
"DHEA and 9-cis-retinoic acid are the most active [cancer-preventive] agents identified to date. DHEA inhibits prostate cancer induction both when chronic administration is begun prior to carcinogen exposure, and when administration is delayed until preneoplastic pros-tate lesions are present."[97]

Notice that DHEA administration inhibited prostate cancer when given prior to carcinogen exposure, and was effective even after the initial stages of prostate cancer.

Naysayer: But again, that's an animal study.

Stephen Cherniske: And animal studies are routinely used to establish safety and efficacy, especially when there is no evidence that DHEA might cause or accelerate abnormal prostate growth in humans.

Naysayer: There must be evidence.



Stephen Cherniske: No, there's only inference, speculation. Look, if DHEA caused abnormal prostate growth, high levels of DHEA would be associated with high PSA scores. In fact, low DHEA levels are associated with elevated PSA in men, and the converse is also true: men with higher DHEA levels have lower PSA scores.[98]

Naysayer: Still, DHEA supplements might raise PSA levels.

Stephen Cherniske: That does not occur. In study after study, supplementation with DHEA—even at high doses—has been shown to have no negative effect on PSA levels.[99,100] In private communication, many clinicians have told me that they have observed a gradual decline in PSA levels in patients taking DHEA. Consistent with this are recent findings that prostate cancer patients have higher serum levels of immunosuppressive glucocorticoids[95] (DHEA counters that) and that DHEA metabolites can inhibit PSA expression by interrupting androgen binding to the prostate androgen receptor.[101] These provide yet more evidence that DHEA may actually reduce prostate cancer risk.

Naysayer: Well, if there is no danger, and DHEA might even help prevent prostate disease, why are there no human trials with DHEA and prostate health?

Stephen Cherniske: Actually, the Division of Cancer Prevention at the National Cancer Institute is planning to study DHEA supplementation as a way to prevent prostate cancer in men.[102] DHEA has already been used successfully in the treatment of erectile

dysfunction.[103,104] Here are the findings from a study that reviewed the effects of DHEA on common age-related ailments:

"Low concentrations of DHEA are associated with immunosenescence, physical frailty, decline in muscle mass, increased mortality, loss of sleep, diminished feelings of well-being and impaired ability to cope, and occur in several common diseases (including cancer, atherosclerosis, hypertension, diabetes, osteoporosis and Alzheimer's disease."[105]

Naysayer: Still, DHEA stimulates IGF-1, and that promotes cancer.

Stephen Cherniske: First of all, the widely cited association between IGF-1 and prostate cancer has been debunked.[106,107] That said, the concern for tumor acceleration does make sense because IGF has angiogenic activity that would favor tumor growth. But IGF-1 has only been shown to accelerate tumor growth in test tubes. Test tubes and petri dishes do not have immune systems, which are upregulated by IGF-1. In fact, the preponderance of the evidence shows that IGF-1 does not promote cancer in any living organism, whether animal or human. Even direct injection of IGF-1 does not promote tumor growth in animals.[108] In Europe, IGF-1 is routinely given to cancer patients to help them gain weight.

Aside from this, it is important to note that increases in IGF-1 after DHEA supplementation are significant but modest, and there are no published studies in which DHEA administration caused IGF-1 to rise above the normal range. Moreover, scores of published studies demonstrate the essential role that IGF-1 plays in the repair and regeneration of the brain, skeleton, and cardiovascular and immune systems.[109-112] Conversely, low IGF-1 levels have been associated with dementia, atherosclerosis, osteoporosis, and sarcopenia,[54,113] and a study in the journal Gerontology shows that men who maintain youthful levels of IGF-1 do not experience the decline in testosterone or muscle mass, or the accumulation of fat, that has been considered an inevitable consequence of aging.[114]