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References of Consensus 4 on DHEA Therapy of Adrenal Androgen Deficiency in Adults

I) REPORTS WITH RESERVED OPINIONS ON DHEA TREATMENT

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2. Royal Academy of Medicine of Belgium « Utilisation de la dehydroépiandrosterone – DHEA – dans certaines « cures de jeunesse ». Académie Royale de Médecine de Belgique; séance du 23 mars 2002, communiqué de presse d'avril 2002
3. L'Ordre National des Médecins français; communiqué du 10 Avril 2001
4. Bulletin of the Conseil de l'Ordre des Médecins du Brabant d'expression française sur la DHEA de décembre 2002

II) “NO SIGNIFICANT EFFECT” OF DHEA ON MEMORY- STUDIES:

The studies were of short duration

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III) NEED FOR DHEA WITH ADVANCING AGE: There may be a need for DHEA with increasing age as senescence is associated with a decline of the adrenal-DHEA axis

Senescence is associated with a decline in adrenal androgen levels

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The anabolic/catabolic hormone balance becomes increasingly inadequate with senescence

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Senescence is associated with alterations of the circadian cycle of serum DHEA sulphate:

a reduced amplitude up to a disappearance of the circadian rhythm

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IV) BENEFICIAL EFFECTS OF DHEA ON MENTAL AND PHYSICAL HEALTH PARAMETERS, AND AGAINST THE DEVELOPMENT OF AGE-RELATED DISEASES

1) DHEA may improve psychic well-being

Lower quality of life and fatigue: the association with lower DHEA levels

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Lower quality of life and fatigue: the improvement with DHEA treatment

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Depression: the association with lower DHEA levels

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Depression: the improvement with DHEA treatment

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Anxiety: the association with lower DHEA levels

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Anxiety: the improvement with DHEA treatment

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Memory loss and Alzheimer's disease: the association with lower DHEA levels

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Memory loss: the improvement with DHEA treatment

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Sleep disorder: the improvement with DHEA treatment

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Loss of sexual drive, sensitivity and potency: the association with lower DHEA levels

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2) DHEA may partially protect against age-related diseases

Hypercholesterolemia: the association with lower DHEA levels

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Atherosclerosis: the association with lower DHEA levels

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Atherosclerosis: the improvement with DHEA treatment

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Arterial hypertension: the association with lower DHEA levels

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Cardiovascular disease: the association with lower DHEA levels

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Coronary heart disease and other cardiac diseases: the improvement with DHEA treatment

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Diabetes: the association with lower DHEA levels

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Rheumatism: the association with lower DHEA levels

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Rheumatism: the improvement with DHEA treatment

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Osteoporosis: the association with lower DHEA levels

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Osteoporosis: the improvement with DHEA treatment

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Infections and lower immunity: the association with low DHEA(s) levels

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Lower Immunity: the improvement with DHEA treatment

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Cancer: the association with lower DHEA levels

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Cancer: the improvement with DHEA treatment?

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Breast cancer: the improvement with DHEA in presence of estradiol in vitro and in vivo?

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3) DHEA may help to live longer

Longevity: the association with DHEA levels

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IV) DHEA TREATMENT OF DHEA DEFICIENCY

1) DHEA medications

Oral DHEA

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Sublingual/buccal DHEA

221. Wren BG, Day RO, McLachlan AJ, Williams KM. Pharmacokinetics of estradiol, progesterone, testosterone and dehydroepiandrosterone after transbuccal administration to postmenopausal women. *Climacteric.* 2003 Jun;6(2):104-11

Transdermal DHEA

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2) DHEA treatment may be justified for treatment in Addison's disease next to glucocorticoids and fludrocortisone

223. Lovas K, Loge JH, Husebye ES. Subjective health status in Norwegian patients with Addison's disease. *Clin Endocrinol (Oxf).* 2002 May;56(5):581-8 (*"Patients with Addison's disease under replacement therapy with cortisone acetate and fludrocortisone have reduced general health perception and vitality, and*

increased fatigue. Female patients reported reduced physical function, which might be due to adrenal androgen depletion. ... markedly reduced subjective health status and working ability in many others. Thus, there might be potential for further refinement of replacement therapy")

224. Devogelaer JP, Crabbe J, Nagant de Deuxchaisnes C. Bone mineral density in Addison's disease: evidence for an effect of adrenal androgens on bone mass. *Br Med J (Clin Res Ed)*. 1987 Mar 28;294(6575):798-800 ("indicates that adrenal androgens may be essential for the maintenance of bone mass in postmenopausal women with Addison's disease")

V) DHEA TREATMENT: SAFETY

DHEA treatment: relatively safe, minimal side effects

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1) Can DHEA treatment suppress the production of hormones by the adrenal glands?

A treatment with DHEA at physiological does not or poorly inhibit the hypothalamic-pituitary-adrenal axis

1. Stomati M, Monteleone P, Casarosa E, Quirici B, Puccetti S, Bernardi F, Genazzani AD, Rovati L, Luisi M, Genazzani AR. Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause. *Gynecol Endocrinol* 2000 Oct;14(5):342-63
2. Meno-Tetang GM, Blum RA, Schwartz KE, Jusko WJ. Effects of oral prasterone (dehydroepiandrosterone) on single-dose pharmacokinetics of oral prednisone and cortisol suppression in normal women. *J Clin Pharmacol* 2001 Nov;41(11):1195-205
3. Barnhart KT, Freeman E, Grisso JA, Rader DJ, Sammel M, Kapoor S, Nestler JE. The effect of dehydroepiandrosterone supplementation to symptomatic perimenopausal women on serum endocrine profiles, lipid parameters, and health-related quality of life. *J Clin Endocrinol Metab* 1999 Nov;84(11):3896-902 (*intake of 50 mg/day of DHEA reduces serum cortisol by 13.2 % less*)

2) Can DHEA increase the risk of PROSTATE CANCER?

Fear: DHEA could promote or aggravate hormone dependent cancers, because of its transformation into sex hormones. The effect could be more important in treatment of long duration or at high doses.

Facts: In humans, studies show no significant effect of DHEA on prostate cancer. In most animal studies a protective effect of DHEA on prostate cancer is observed. The more the DHEA dose is increased, the more potent DHEA's anti-cancer effect is.

Arguments against DHEA use

1. Algarte-Genin M, Cussenot O, Costa P. Prevention of prostate cancer by androgens: experimental paradox or clinical reality. *Eur Urol*. 2004 Sep;46(3):285-94

Studies that show that DHEA may protect the human prostate against cancer

Lower serum DHEA and DHEA sulfate levels have been found in men with prostate cancer

2. Comstock GW, Gordon GB, Hsing AW. The relationship of serum dehydroepiandrosterone and its sulfate to subsequent cancer of the prostate. *Cancer Epidemiol Biomarkers Prev*. 1993 May-Jun;2(3):219-21
3. Stahl F, Schnorr D, Pilz C, Dorner G. Dehydroepiandrosterone (DHEA) levels in patients with prostatic cancer, heart diseases and under surgery stress. *Exp Clin Endocrinol*. 1992;99(2):68-70

Lower prostate tissue levels of DHEA and androstenedione are found in recurrent prostate cancer compared to the levels in benign prostate hypertrophy

4. Mohler JL, Gregory CW, Ford OH 3rd, Kim D, Weaver CM, Petrusz P, Wilson EM, French FS. The androgen axis in recurrent prostate cancer. *Clin Cancer Res*. 2004 Jan 15;10(2):440-8

The serum DHEA sulfate is inversely related with the serum PSA: a high DHEAs is related to a low PSA

5. Ponholzer A, Plas E, Schatzl G, Jungwirth A, Madersbacher S; Austrian Society of Urology. Association of DHEA-S and estradiol serum levels to symptoms of aging men. *Aging Male*. 2002 Dec;5(4):233-8

With age, the serum DHEA sulfate progressively declines, while the incidence of human prostate cancer gradually and almost exponentially increases

6. Labrie F, Luu-The V, Belanger A, Lin SX, Simard J, Pelletier G, Labrie C. Is dehydroepiandrosterone a hormone? *J Endocrinol*. 2005 Nov;187(2):169-96
7. Data from the Surveillance, Epidemiology, and End Results (SEER) Program Staff. Section III: Incidence. In: *Cancer statistics review 1973-1986*. Bethesda, MD: NIH;1989;III.45

DHEA treatment reduces the development of transplants of human prostate cancer in animals

8. van Weerden WM, van Kreuningen A, Elissen NM, de Jong FH, van Steenbrugge GJ, Schroder FH. Effect of adrenal androgens on the transplantable human prostate tumor. *Endocrinology*. 1992; 131(6): 2909-13

DHEA treatment inhibits prostate cancer promoted by testosterone and estradiol in rats

9. Christov KT, Moon RC, Lantvit DD, Boone CW, Kelloff GJ, Steele VE, Lubet RA, Pezzuto JM. Prostate intraepithelial neoplasia in Noble rats, a potential intermediate endpoint for chemoprevention studies. *Eur J Cancer*. 2004 Jun;40(9):1404-11

DHEA treatment reduces the frequency and severity of carcinogen (MNU, N-methyl-N-nitrosurea)-induced prostate cancer from -33 to -60 %, whatever the moment of administration of the carcinogen (one week before, or 20 or 40 weeks after)

10. Rao KV, Johnson WD, Bosland MC, Lubet RA, Steele VE, Kelloff GJ, McCormick DL. Chemoprevention of rat prostate carcinogenesis by early and delayed administration of dehydroepiandrosterone. *Cancer Res*. 1999;59(13):3084-9
11. McCormick DL, Rao KV. Chemoprevention of hormone-dependent prostate cancer in the Wistar-Unilever rat. *Eur Urol*. 1999;35(5-6):464-7

DHEA treatment of rats predisposed to develop endocrine testicular Leydig cell tumors inhibits tumor development

12. Rao MS, Subbarao V, Yeldandi AV, Reddy JK. Inhibition of spontaneous testicular Leydig cell tumor development in F-344 rats by dehydroepiandrosterone. *Cancer Lett*. 1992 ;65(2):123-6.

No effect of DHEA on the prostate: Studies that show that the effect of DHEA on human prostate cancer is neutral

Healthy men have a level of DHEA (sulfate) equal to that of men with benign prostate hyperplasia or prostate cancer, even adjusted to age

13. Schatzl G, Reiter WJ, Thurridl T, Waldmuller J, Roden M, Soregi S, Madersbacher S. Endocrine patterns in patients with benign and malignant prostatic diseases. *Prostate*. 2000 Aug;44(3):219-24
14. Bartsch W, Kozak I, Gorenflos P, Becker H, Voigt KD. Concentrations of 3 β -hydroxy androgens in epithelium and stroma of benign hyperplastic and normal human prostate. *Prostate*. 1986;8(1):3-10
15. Comstock GW, Gordon GB, Hsing AW. The relationship of serum dehydroepiandrosterone and its sulfate to subsequent cancer of the prostate. *Cancer Epidemiol Biomarkers Prev*. 1993;2(3):219-21
16. Stahl F, Schnorr D, Pilz C, Dorner G. Dehydroepiandrosterone (DHEA) levels in patients with prostatic cancer, heart diseases and under surgery stress. *Exp Clin Endocrinol*. 1992;99(2):68-70
17. Oesterling JE, Epstein JI, Walsh PC. The inability of adrenal androgens to stimulate the adult human prostate: an autopsy evaluation of men with hypogonadotropic hypogonadism and panhypopituitarism. *J Urol*. 1986;136(5):1030-4

The level of DHEA in the prostate is 6-7 times that in the plasma, but the level in benign hypertrophic prostates does not differ from that in normal prostates

18. Bartsch W, Kozak I, Gorenflos P, Becker H, Voigt KD. Concentrations of 3 β -hydroxy androgens in epithelium and stroma of benign hyperplastic and normal human prostate. *Prostate*. 1986;8(1):3-10

The serum DHEA sulfate level does not influence the PSA, no significant association

19. Schatzl G, Reiter WJ, Thurridl T, Waldmuller J, Roden M, Soregi S, Madersbacher S. Endocrine patterns in patients with benign and malignant prostatic diseases. *Prostate*. 2000 Aug;44(3):219-24
20. Schatzl G, Brossner C, Schmid S, Kugler W, Roehrich M, Treu T, Szalay A, Djavan B, Schmidbauer CP, Soregi S, Madersbacher S. Endocrine status in elderly men with lower urinary tract symptoms: correlation of age, hormonal status, and lower urinary tract function. The Prostate Study Group of the Austrian Society of Urology. *Urology*. 2000;55(3):397-402

The prostate of men with normal adrenal glands but with no testicular function throughout life (hypogonadotropic hypogonadism or prepubertal castration) is at autopsy atrophic, while that of men with normal adrenal glands and normal testes is enlarged and shows some degree of benign prostatic hyperplasia

21. Oesterling JE, Epstein JI, Walsh PC. The inability of adrenal androgens to stimulate the adult human prostate: an autopsy evaluation of men with hypogonadotropic hypogonadism and panhypopituitarism. *J Urol*. 1986 Nov;136(5):1030-4

DHEA treatment does not increase PSA, nor at a physiologic (50 mg/day; Reiter et al.), nor at a supraphysiologic dose (100 mg/day; Wallace et al., Sun et al.)

22. Reiter WJ, Pycha A, Schatzl G, Pokorny A, Gruber DM, Huber JC, Marberger M. Dehydroepiandrosterone in the treatment of erectile dysfunction: a prospective, double-blind, randomized, placebo-controlled study. *Urology*. 1999;53(3):590-4; discussion 594-5
23. Wallace MB, Lim J, Cutler A, Bucci L. Effects of dehydroepiandrosterone vs androstenedione supplementation in men. *Med Sci Sports Exerc*. 1999 Dec;31(12):1788-92
24. Sun Y, Mao M, Sun L, Feng Y, Yang J, Shen P. Treatment of osteoporosis in men using dehydroepiandrosterone sulfate. *Chin Med J (Engl)*. 2002 Mar;115(3):402-4

DHEA treatment at physiologic dose (50 mg/day) does not increase the prostate volume, nor the urinary residual volume

25. Reiter WJ, Pycha A, Schatzl G, Pokorny A, Gruber DM, Huber JC, Marberger M. Dehydroepiandrosterone in the treatment of erectile dysfunction: a prospective, double-blind, randomized, placebo-controlled study. *Urology*. 1999;53(3):590-4

DHEA treatment in vitro has no influence on the growth of prostate stromal cells

26. Le H, Arnold JT, McFann KK, Blackman MR. Dihydrotestosterone and testosterone, but not DHEA or estradiol, differentially modulate IGF-I, IGFBP-2 and IGFBP-3 gene and protein expression in primary cultures of human prostatic stromal cells. *Am J Physiol Endocrinol Metab*. 2005 published online Dec 20

Arguments against DHEA use

DHEA administered to castrated rats stimulated the development of an implanted prostate cancer. (*critic: but to obtain an adverse effect rats must first be castrated. Castrated rats have a lower risk of implanted prostate cancer development. DHEA administration normalized the risk of prostate cancer and brought it up to the level of non castrated rats, not above*)

27. Schiller CD, Schneider MR, Hartmann H, Graf AH, Klocker H, Bartsch G. Growth-stimulating effect of adrenal androgens on the R3327 Dunning prostatic carcinoma. *Urol Res* 1991;19(1):7-13

Anecdotal report

71. Jones JA, Nguyen A, Straub M, Leidich RB, Veech RL, Wolf S. Use of DHEA in a patient with advanced prostate cancer: a case report and review. *Urology*. 1997 Nov;50(5):784-8

3) Can DHEA increase the risk of BREAST CANCER?

Fear: DHEA could promote or aggravate hormone dependent cancers such as breast cancer, because of its transformation into sex hormones. The effect could be more important in treatment of long duration or at high doses.

Facts: In premenopausal women high levels of DHEA are associated with a low risk of breast cancer. Two studies in HRT untreated postmenopausal women show the opposite, namely that a high level of DHEA sulfate is associated with an increased risk of breast cancer. This confirms the finding that DHEA inhibits the proliferation of breast cancer cells in vitro in the presence of oestradiol, but stimulates it in the absence of estradiol. Postmenopausal women should therefore get female hormone replacement when they receive corrective DHEA therapy.

In the majority of animal studies a protective effect of DHEA on breast cancer is observed. The higher the dose of DHEA, the greater the anti-cancer effect.

Arguments FOR DHEA use: *DHEA may protect premenopausal women and HRT treated postmenopausal women against breast cancer*

HUMAN STUDIES

Studies with associations between low levels of DHEA sulfate and an increased risk of breast cancer

1. Rose DP, Stauber P, Thiel A, Crowley JJ, Milbrath JR. Plasma DHEAs, Androstenedione and cortisol, and urinary free cortisol excretion in breast cancer. *Eur J Cancer*. 1977; 13: 43-7
2. Gomes P, Cassanas G, Halberg F, Hermida R, Robel P, Baulieu EE, Lakatua D, Haus E. Taux sanguin de la DHEA-S et risque de cancer du sein. *C R Acad Sci III*. 1988;306(7):261-4
3. Brownsey B, Cameron EH, Griffiths K, Gleave EN, Forrest AP, Campbell H. Plasma dehydroepiandrosterone sulphate levels in patients with benign and malignant breast disease., *Eur J Cancer*. 1972;8(1):131-7
4. Wang DY, Bulbrook RD, Herian M, Hayward JL. Studies on the sulphate esters of dehydroepiandrosterone and androsterone in the blood of women with breast cancer. *Eur J Cancer*. 1974;10(8):477-82

Studies with associations between low urinary levels of DHEA metabolites and an increased risk of breast cancer

5. Cameron EH, Griffiths K, Gleave E, Stewart HJ, Forrest AP, Campbell H. Benign and malignant breast disease in South Wales: a study of urinary steroids., *Br Med J*. 1970;4(738):768-71
6. Bulbrook RD, Hayward JL, Spicer CC, Thomas BS. Abnormal excretion of urinary steroids by women with early breast cancer. *Lancet*. 1962; 1238-40
7. Tominaga T, Tei N, Kitamura M, Taguchi T, Kudo Y. Urinary excretion of steroids by Japanese women with breast cancer. *Gann* 1975 Jun;66(3):305-10
8. Hindy I, Prajda N, Tapolcsanyi L, Sellei C, Eckhardt S. Investigation of 17-ketosteroid excretion in mastopathia and premenopausal breast cancer. *Arch Geschwulstforsch* 1975;45(5):453-6

Studies with an association between low urinary levels of DHEA metabolites and aggravation/progression of breast cancer

9. Tominaga T, Tei N, Kitamura M, Taguchi T, Kudo Y. Urinary excretion of steroids by Japanese women with breast cancer. *Gann* 1975 Jun;66(3):305-10
10. Hindy I, Prajda N, Tapolcsanyi L, Sellei C, Eckhardt S. Investigation of 17-ketosteroid excretion in mastopathia and premenopausal breast cancer. *Arch Geschwulstforsch* 1975;45(5):453-6

Studies where the DHEA and DHEA sulfate levels are significantly lower inside the breast cancer tumours compared to healthy breast tissues of control patients

11. Thijssen JH, van Landeghem AA, Poortman J. Uptake and concentration of steroid hormones in mammary tissues. *Ann N Y Acad Sci*. 1986;464:106-16.

Studies where low levels of DHEA sulfate were found in female patients with advanced cancer (with metastases) compared to the level found in women with loco-regional cancer

12. Lissoni P, Rovelli F, Giani L, Mandala M, Meregalli S, Barni S, Confalonieri G, Bonfanti A. Dehydroepiandrosterone sulfate (DHEAS) secretion in early and advanced solid neoplasms: selective deficiency in metastatic disease. *Int J Biol Markers*. 1998;13(3):154-7

With age the level of DHEA sulfate gradually declines, while at the same time the incidence of breast cancer quickly increases, phenomena that plead against the implication of DHEA in the genesis of breast cancer, and rather for the implication of DHEA deficiency as a factor in favor of breast cancer

13. Labrie F, Luu-The V, Belanger A, Lin SX, Simard J, Pelletier G, Labrie C. Is dehydroepiandrosterone a hormone? *J Endocrinol*. 2005 Nov;187(2):169-96
14. Cutler SY, Young JL. Third National Cancer Survey: incidence data. Washington DC: National Cancer Institute Monograph; 1975; vol. 41

A low serum level of DHEA has been observed in other cancers in women: ovarian cancer, metastasized ovarian cancer, the adult type of acute T cell leukemia, metastasized cancer

15. Cuzick J, Bulstrode JC, Stratton I, Thomas BS, Bulbrook RD, Hayward JL. A prospective study of urinary androgen levels and ovarian cancer. *Int J Cancer* 1983 Dec 15;32(6):723-6
16. Heinonen PK, Koivula T, Pystynen P. Decreased serum level of dehydroepiandrosterone sulfate in postmenopausal women with ovarian cancer. *Gynecol Obstet Invest* 1987;23(4):271-4
17. Blaakaer J, Hogdall CK, Hording U, Bennett P, Toftager-Larsen K, Daugaard S, Bock J. Hormonal factors and prognosis in epithelial ovarian cancer: a multivariate analysis. *Eur J Obstet Gynecol Reprod Biol* 1993 Sep;51(1):21-7

18. Uozumi K, Uematsu T, Otsuka M, Nakano S, Takatsuka Y, Iwahashi M, Hanada S, Arima T. Serum dehydroepiandrosterone and DHEA-sulfate in patients with adult T-cell leukemia and human T-lymphotropic virus type I carriers. *Am J Hematol* 1996;53(3):165-8
19. Lissoni P, Rovelli F, Giani L, Mandala M, Meregalli S, Barni S, Confalonieri G, Bonfanti A. Dehydroepiandrosterone sulfate (DHEAS) secretion in early and advanced solid neoplasms: selective deficiency in metastatic disease. *Int J Biol Markers*. 1998;13(3):154-7

ANIMAL STUDIES :

DHEA potently reduces the incidence and development of breast cancer in rats that keep their ovaries (The effect is proportional to the dose (the cancer incidence can be up to less than 10 % of normal mice not treated with DHEA!!)

20. Li S, Yan X, Belanger A, Labrie F. Prevention by dehydroepiandrosterone of the development of mammary carcinoma induced by 7,12-dimethylbenz(a)anthracene (DMBA) in the rat. *Breast Cancer Res Treat*. 1994;29(2):203-17.
21. Lubet RA, Gordon GB, Prough RA, Lei XD, You M, Wang Y, Grubbs CJ, Steele VE, Kelloff GJ, Thomas CF, Moon RD. Modulation of methylnitrosourea-induced breast cancer in Sprague Dawley rats by dehydroepiandrosterone: dose-dependent inhibition, effects of limited exposure, effects on peroxisomal enzymes, and lack of effects on levels of Ha-Ras mutations. *Cancer Res* 1998;58(5):921-6
22. Luo S, Labrie C, Belanger A, Labrie F. Effect of dehydroepiandrosterone on bone mass, serum lipids, and dimethylbenz(a)anthracene-induced mammary carcinoma in the rat. *Endocrinology* 1997 Aug;138(8):3387-94
23. Luo S, Sourla A, Labrie C, Belanger A, Labrie F. Combined effects of dehydroepiandrosterone and EM-800 on bone mass, serum lipids, and the development of dimethylbenz(A)anthracene-induced mammary carcinoma in the rat. *Endocrinology* 1997;138(10):4435-44
24. Ratko TA, Detrisac CJ, Mehta RG, Kelloff GJ, Moon RC. Inhibition of rat mammary gland chemical carcinogenesis by dietary dehydroepiandrosterone or a fluorinated analogue of dehydroepiandrosterone. *Cancer Res*. 1991;51(2):481-6
25. McCormick DL, Rao KV, Johnson WD, Bowman-Gram TA, Steele VE, Lubet RA, Kelloff GJ. "Exceptional chemopreventive activity of low-dose dehydroepiandrosterone in the rat mammary gland." *Cancer Res*. 1996 Apr 15;56(8):1724-6.
26. Gatto V, Aragno M, Gallo M, Tamagno E, Martini A, Di Monaco M, Brignardello E, Boccuzzi G. Dehydroepiandrosterone inhibits the growth of DMBA-induced rat mammary carcinoma via the androgen receptor. *Oncol Rep*. 1998 Jan-Feb;5(1):241-3
27. Boccuzzi G, Aragno M, Brignardello E, Tamagno E, Conti G, Di Monaco M, Racca S, Danni O, Di Carlo F. Opposite effects of dehydroepiandrosterone on the growth of 7,12-dimethylbenz(a)anthracene-induced rat mammary carcinomas. *Anticancer Res*. 1992 Sep-Oct;12(5):1479-83
28. Spinola PG, Marchetti B, Labrie F. Adrenal steroids stimulate growth and progesterone receptor levels in rat uterus and DMBA-induced mammary tumors. *Breast Cancer Res Treat*. 1986;8(3):241-8

DHEA reduces the incidence and development of breast cancer in mice that keep their ovaries

29. Green JE, Shibata MA, Shibata E, Moon RC, Anver MR, Kelloff G, Lubet R. 2-difluoromethylornithine and dehydroepiandrosterone inhibit mammary tumor progression but not mammary or prostate tumor initiation in C3(1)/SV40 T/t-antigen transgenic mice. *Cancer Res*. 2001 Oct 15;61(20):7449-55

The levels of DHEA that protect rodents against breast cancer are the same than the physiological levels found in premenopausal women

30. Li S, Yan X, Belanger A, Labrie F. Prevention by dehydroepiandrosterone of the development of mammary carcinoma induced by 7,12-dimethylbenz(a)anthracene (DMBA) in the rat. *Breast Cancer Res Treat*. 1994;29(2):203-17

DHEA protection is possible on condition that the ovaries remain

31. Boccuzzi G, Aragno M, Brignardello E, Tamagno E, Conti G, Di Monaco M, Racca S, Danni O, Di Carlo F. Opposite effects of dehydroepiandrosterone on the growth of 7,12-dimethylbenz(a)anthracene-induced rat mammary carcinomas. *Anticancer Res* 1992 Sep-Oct;12(5):1479-83
32. Spinola PG, Marchetti B, Labrie F. Adrenal steroids stimulate growth and progesterone receptor levels in rat uterus and DMBA-induced mammary tumors. *Breast Cancer Res Treat*. 1986;8(3):241-8

DHEA treatment may facilitate the development of breast cancer induced by carcinogens at the condition that the ovaries are previously removed, and thus major estrogen deficiency is created. These data should incite MD's not to prescribe DHEA to postmenopausal women without addition of female hormone replacement.

33. Boccuzzi G, Aragno M, Brignardello E, Tamagno E, Conti G, Di Monaco M, Racca S, Danni O, Di Carlo F. Opposite effects of dehydroepiandrosterone on the growth of 7,12-dimethylbenz(a)anthracene-induced rat mammary carcinomas. *Anticancer Res.* 1992 Sep-Oct;12(5):1479-83
34. Spinola PG, Marchetti B, Labrie F. Adrenal steroids stimulate growth and progesterone receptor levels in rat uterus and DMBA-induced mammary tumors. *Breast Cancer Res Treat.* 1986;8(3):241-8
35. Inano H, Ishii-Ohba H, Suzuki K, Yamanouchi H, Onoda M, Wakabayashi. Chemoprevention by dietary dehydroepiandrosterone against promotion/progression phase of radiation-induced mammary tumorigenesis in rats. *J Steroid Biochem Mol Biol.* 1995 Jul;54(1-2):47-53

DHEA treatment protects animals from breast cancer caused by intensive radiation

36. Schwartz AG. Inhibition of spontaneous breast cancer formation in female C3H(Avy/a) mice by long-term treatment with dehydroepiandrosterone. *Cancer Res.* 1979;39(3):1129-32.

DHEA treatment significantly prevents spontaneous breast cancer development in mice predisposed to breast cancer

37. Couillard S, Labrie C, Belanger A, Candas B, Pouliot F, Labrie F. Effect of dehydroepiandrosterone and the antiestrogen EM-800 on growth of human ZR-75-1 breast cancer xenografts. *J Natl Cancer Inst* 1998 May 20;90(10):772-8
38. Labrie F, Luu-The V, Labrie C, Simard J. DHEA and its transformation into androgens and estrogens in peripheral target tissues: intracrinology. *Front Neuroendocrinol* 2001 Jul;22(3):185-212 (*Labrie, one of the top-researchers in DHEA suggests after several years of research in animals and humans that DHEA is free of breast and uterin cancer risk*)

DHEA treatment can significantly inhibit the development of human breast cancer transplants in mice

39. Pashko LL, Schwartz AG, Abou-Gharbia M, Swern D. Inhibition of DNA synthesis in mouse epidermis and breast epithelium by dehydroepiandrosterone and related steroids. *Carcinogenesis* 1981;2(8):717-21

DHEA treatment can be beneficial for many other cancers, in animals: uterin, prostate, testicular, pancreas, thyroid, liver (at low doses)

40. Rao AR. Inhibitory action of dehydroepiandrosterone on methylcholanthrene-induced carcinogenesis in the uterine cervix of mouse. *Cancer Lett* 1989 Apr;45(1):1-5
41. van Weerden WM, van Kreuningen A, Elissen NM, de Jong FH, van Steenbrugge GJ, Schroder FH. Effect of adrenal androgens on the transplantable human prostate tumor. *Endocrinology.* 1992; 131(6): 2909-13
42. Christov KT, Moon RC, Lantvit DD, Boone CW, Kelloff GJ, Steele VE, Lubet RA, Pezzuto JM. Prostate intraepithelial neoplasia in Noble rats, a potential intermediate endpoint for chemoprevention studies. *Eur J Cancer.* 2004 Jun;40(9):1404-11
43. Rao KV, Johnson WD, Bosland MC, Lubet RA, Steele VE, Kelloff GJ, McCormick DL. Chemoprevention of rat prostate carcinogenesis by early and delayed administration of dehydroepiandrosterone. *Cancer Res.* 1999;59(13):3084-9
44. McCormick DL, Rao KV. Chemoprevention of hormone-dependent prostate cancer in the Wistar-Unilever rat. *Eur Urol.* 1999;35(5-6):464-7
45. Rao MS, Subbarao V, Yeldandi AV, Reddy JK. Inhibition of spontaneous testicular Leydig cell tumor development in F-344 rats by dehydroepiandrosterone. *Cancer Lett.* 1992 ;65(2):123-6
46. Muscarella P, Boros LG, Fisher WE, Rink C, Melvin WS. Oral dehydroepiandrosterone inhibits the growth of human pancreatic cancer in nude mice. *J Surg Res.* 1998;79(2):154-7
47. Ghinea E, Dumitriu L, Stefanovici G, Pop A, Damian A, Handoca A, Stanciu R. Protein content and thyroid hormone release in vitro by differentiated thyroid cancer cells in the presence of estradiol, dehydroepiandrosterone, polypeptidic hormones and pesticides. *Endocrinologie.* 1988;26(3):165-71
48. Moore MA, Thamavit W, Tsuda H, Sato K, Ichihara A, Ito N. Modifying influence of dehydroepiandrosterone on the development of dihydroxy-di-n-propylnitrosamine-initiated lesions in the thyroid, lung and liver of F344 rats *Carcinogenesis* 1986 Feb;7(2):311-6
49. Garcea R, Daino L, Pascale R, Frassetto S, Cozzolino P, Ruggiu ME, Feo F. Inhibition by dehydroepiandrosterone of liver preneoplastic foci formation in rats after initiation-selection in experimental carcinogenesis. *Toxicol Pathol* 1987;15(2):164-9
50. Weber E, Moore MA, Bannasch P. Phenotypic modulation of hepatocarcinogenesis and reduction in N-nitrosomorpholine-induced hemangiosarcoma and adrenal lesion development in Sprague-Dawley rats by dehydroepiandrosterone. *Carcinogenesis* 1988 Jul;9(7):1191-5
51. Moore MA, Weber E, Thornton M, Bannasch. Sex-dependent, tissue-specific opposing effects of dehydroepiandrosterone on initiation and modulation stages of liver and lung carcinogenesis induced by dihydroxy-di-n-propylnitrosamine in F344 rats. *Carcinogenesis* 1988 Aug;9(8):1507-9

52. Thornton M, Moore MA, Ito N. Modifying influence of dehydroepiandrosterone or butylated hydroxytoluene treatment on initiation and development stages of azaserine-induced acinar pancreatic preneoplastic lesions in the rat. *Carcinogenesis* 1989 Feb;10(2):407-10
53. Simile M, Pascale RM, De Miglio MR, Nufri A, Daino L, Seddaiu MA, Muroli MR, Rao KN, Feo F. Inhibition by dehydroepiandrosterone of growth and progression of persistent liver nodules in experimental rat liver carcinogenesis. *Int J Cancer* 1995 Jul 17;62(2):210-5

No effect of DHEA on the breast cancer risk in premenopausal women and HRT treated postmenopausal women

Studies with no significant association between DHEA levels and breast cancer

54. Zumoff B, Levin J, Rosenfeld RS, Markham M, Strain GW, Fukushima DK. Abnormal 24-hr mean plasma concentrations of dehydroisoandrosterone and dehydroisoandrosterone sulfate in women with primary operable breast cancer. *Cancer Res* 1981 Sep;41(9 Pt 1):3360-3
55. Read GF, Wilson DW, Campbell FC, Holliday HW, Blamey RW, Griffiths K. Salivary cortisol and dehydroepiandrosterone sulphate levels in postmenopausal women with primary breast cancer. *Eur J Cancer Clin Oncol* 1983 Apr;19(4):477-83

Studies with no significant associations between the urinary levels of DHEA metabolites and the risk of breast cancers

56. Juricskay S, Szabo I, Kett K. Urinary steroids at time of surgery in postmenopausal women with breast cancer. *Breast Cancer Res Treat.* 1997;44(1):83-9

Arguments contra DHEA use in untreated postmenopausal women: DHEA may increase the risk in postmenopausal women without HRT

Two studies with report of an association between high levels of DHEA and an increased risk of breast cancer in (HRT) untreated postmenopausal women

57. Zumoff B, Levin J, Rosenfeld RS, Markham M, Strain GW, Fukushima DK. Abnormal 24-hr mean plasma concentrations of dehydroisoandrosterone and dehydroisoandrosterone sulfate in women with primary operable breast cancer. *Cancer Res* 1981 Sep;41(9 Pt 1):3360-3
58. Gordon GB, Bush TL, Helzlsouer KJ, Miller SR, Comstock GW. Relationship of serum levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate to the risk of developing postmenopausal breast cancer. *Cancer Res* 1990 Jul 1;50(13):3859-62

Apparently, women need to have all their deficiencies corrected, including female hormones in order to benefit from the breast cancer protective actions of DHEA

59. Stoll BA. Dietary supplements of dehydroepiandrosterone in relation to breast cancer risk. *Eur J Clin Nutr.* 1999;53(10):771-5.

In vitro and in vivo studies where DHEA treatment inhibited the proliferation of breast cancer (cells) in presence of estradiol in vitro, but if estrogens are withdrawn (estrogen deficiency) DHEA stimulated the proliferation of the breast cancer cells

60. Boccuzzi G, Aragno M, Brignardello E, Tamagno E, Conti G, Di Monaco M, Racca S, Danni O, Di Carlo F. Opposite effects of dehydroepiandrosterone on the growth of 7,12-dimethylbenz(a)anthracene-induced rat mammary carcinomas. *Anticancer Res.* 1992 Sep-Oct;12(5):1479-83.
61. Boccuzzi G, Brignardello E, di Monaco M, Forte C, Leonardi L, Pizzini A. Influence of dehydroepiandrosterone and 5-en-androstene-3 beta, 17 beta-diol on the growth of MCF-7 human breast cancer cells induced by 17 beta-estradiol. *Anticancer Res.* 1992 May-Jun;12(3):799-803