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NUTRITIONAL  
ENDOCRINOLOGY

# Micronutrients: Vitamin E

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# Vitamin E Basics

- ✓ Vitamin E is a fat-soluble antioxidant
- ✓ The term describes a family of 8 antioxidants

- 4 tocopherols –

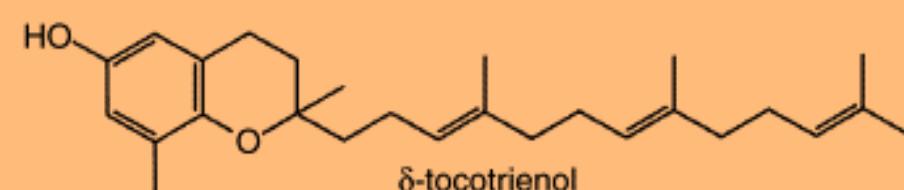
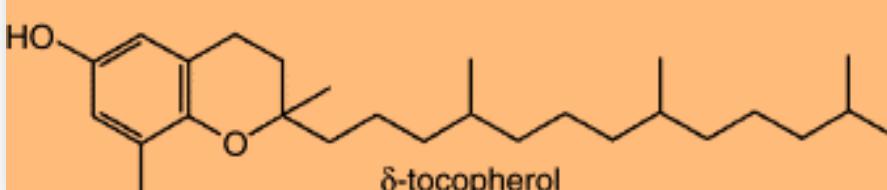
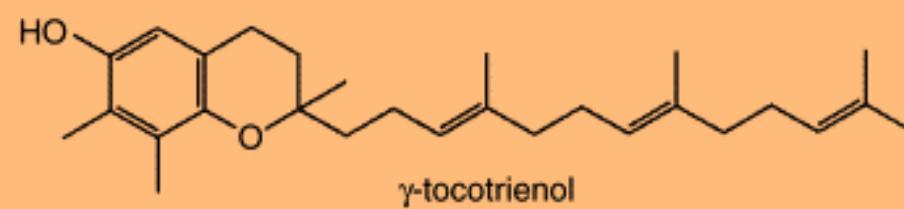
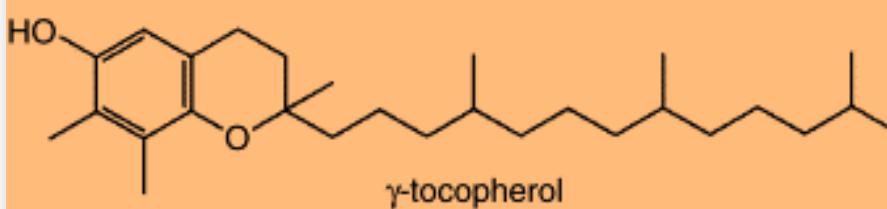
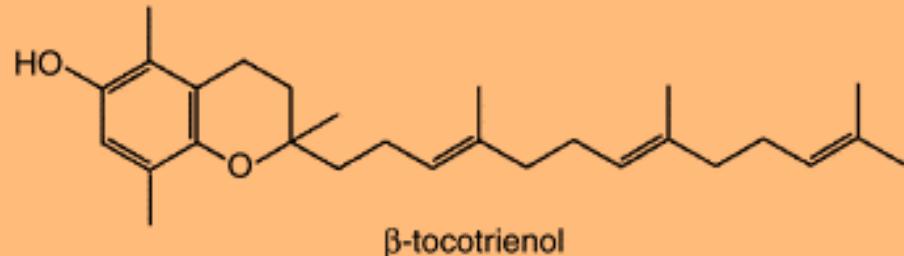
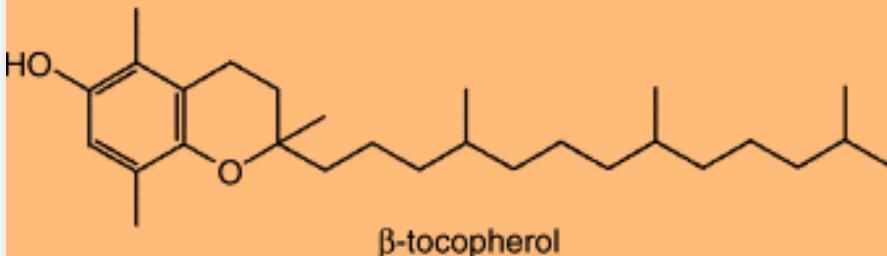
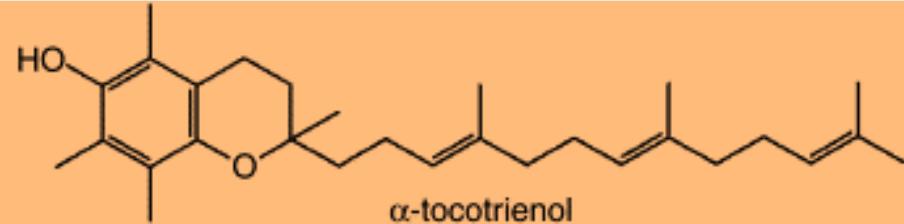
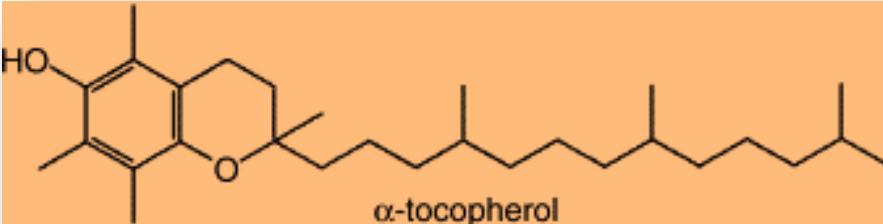
- α- alpha
- β- beta
- γ- gamma
- δ- delta

- 4 tocotrienols

- α- alpha
- β- beta
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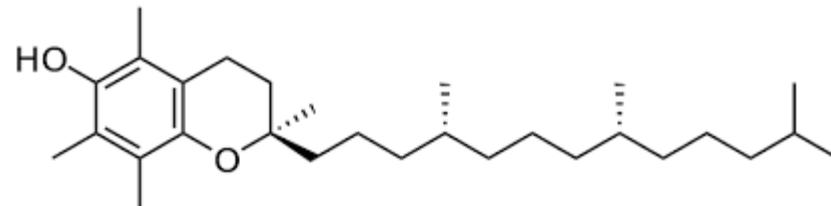


# Tocopherols and Tocotrienols



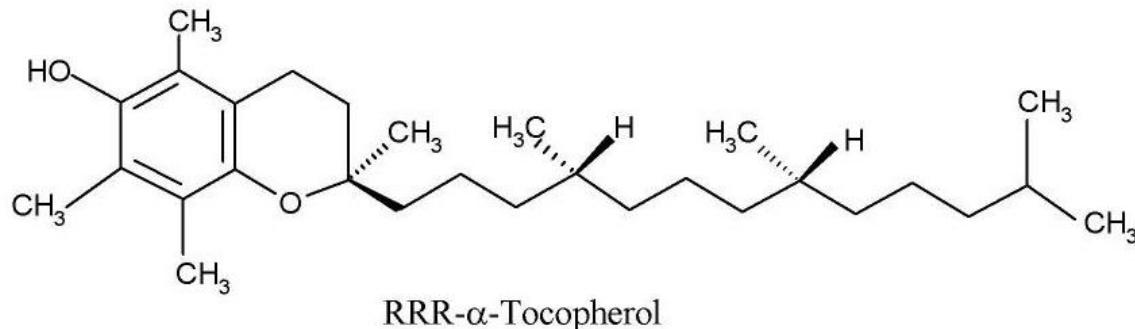
# $\alpha$ -Tocopherol

- ✓ Main function is as an anti-oxidant
- ✓ Intercepts free radicals and prevents lipid destruction
- ✓ Maintains integrity of cell membranes throughout the body
- ✓ Protects the fats in low-density lipoproteins (LDL) from oxidation
- ✓ Inhibits the activity of protein kinase C, a cell-signaling molecule
- ✓ Inhibits platelet aggregation to enhance vasodilation



# RRR- $\alpha$ -tocopherol

- ✓ The isomeric form of  $\alpha$ -tocopherol found in foods is RRR- $\alpha$ -tocopherol (also referred to as "natural" or d- $\alpha$ -tocopherol).
- ✓ Synthetic  $\alpha$ -tocopherol, which is labeled all-rac- or dl- $\alpha$ -tocopherol, has only one-half the biological activity of RRR- $\alpha$ -tocopherol.
- ✓ Often vitamin E-fortified foods contain synthetic  $\alpha$ -tocopherol, and the amounts are given as a percentage of the daily value of 30 IU.



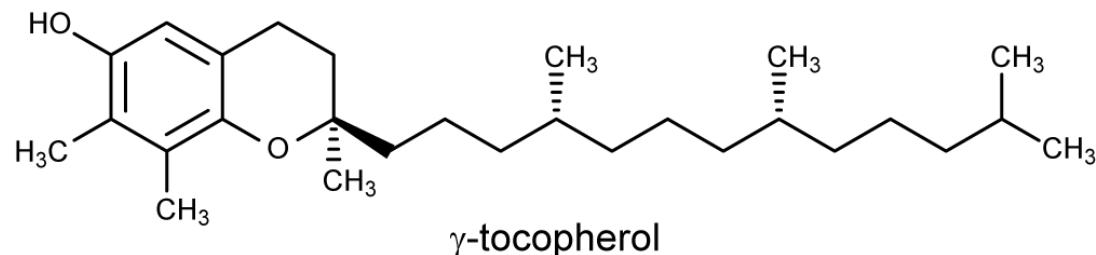
# $\gamma$ -Tocopherol

✓ Gamma tocopherol is the most common form of vitamin E in the American diet.

✓ Blood levels are 10 times lower than  $\alpha$ -tocopherol.

✓  $\alpha$ -Tocopherol is preferentially retained in the body by the action of the  $\alpha$ -tocopherol transfer protein (a-TTP) in the liver, which preferentially incorporates  $\alpha$ -tocopherol into lipoproteins that are circulated in the blood.

➤ Delivers  $\alpha$ -tocopherol to different tissues in the body



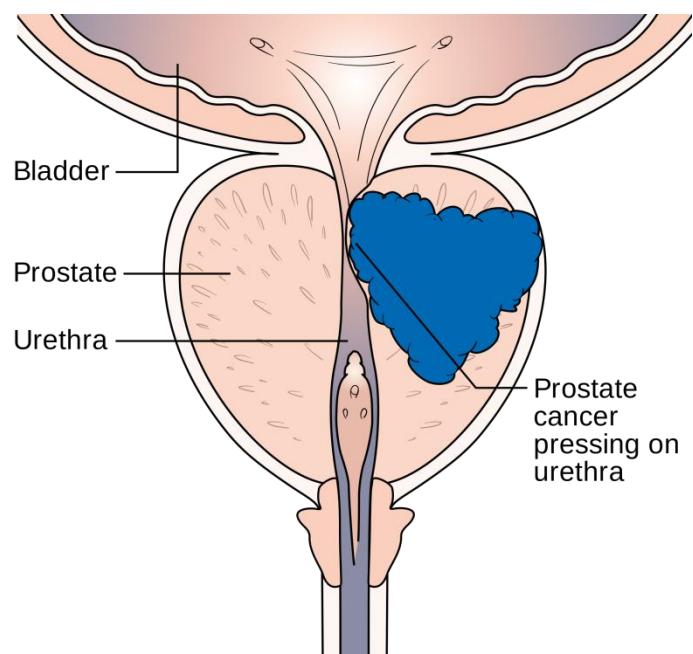
# $\gamma$ -Tocopherol vs $\alpha$ -Tocopherol

- ✓ Forms of vitamin E other than  $\alpha$ -tocopherol are actively metabolized.
- ✓ Because  $\gamma$ -tocopherol is initially absorbed in the same manner as  $\alpha$ -tocopherol, small amounts of  $\gamma$ -tocopherol are detectable in blood and tissue.
- ✓ Breakdown products of tocopherols, known as metabolites, can be detected in urine. More  $\gamma$ -tocopherol metabolites are excreted in urine than  $\alpha$ -tocopherol metabolites, suggesting less  $\gamma$ -tocopherol is needed for use by the body.



# $\gamma$ -Tocopherol and Metabolites

- ✓ Limited research in the test tube and in animals indicates that  $\gamma$ -tocopherol or its metabolites may play a role in protecting the body from free radical-induced damage.
- ✓ In one study, increased levels of plasma  $\gamma$ -tocopherol were associated with a significantly reduced risk of developing prostate cancer.
- ✓ Increased levels of plasma  $\alpha$ -tocopherol and toenail selenium were protective against prostate cancer development only when  $\gamma$ -tocopherol levels were also high.



# Deficiency of Vitamin E

- ✓ Neurological symptoms, including impaired balance and coordination (ataxia)
- ✓ Injury to the sensory nerves (peripheral neuropathy)
- ✓ Muscle weakness (myopathy)
- ✓ Damage to the retina of the eye (pigmented retinopathy)



*Observed in individuals with severe malnutrition, genetic defects affecting the  $\alpha$ -tocopherol transfer protein, and fat malabsorption syndromes*

# Nervous System and E Deficiency

- ✓ The developing nervous system appears to be especially vulnerable to vitamin E deficiency.
  - Children with severe vitamin E deficiency at birth rapidly develop neurological symptoms if not treated with vitamin E.
  - Individuals who develop malabsorption of vitamin E in adulthood may not develop neurological symptoms for 10-20 years.
- ✓ Symptomatic vitamin E deficiency in healthy individuals who consume diets low in vitamin E has never been reported.



# Recommended Dietary Allowance

- ✓ The RDA for vitamin E was previously 8 mg/day for women and 10 mg/day for men.
- ✓ The RDA was revised by the Food and Nutrition Board of the Institute of Medicine in 2000.
- ✓ This new recommendation was based largely on the results of studies done in the 1950s in men fed vitamin E deficient diets.



# Recommended Daily Allowance

Life Stage	Age	Males		Females	
		mg/day	IU/day	mg/day	IU/day
Infants (AI)	0-6 months	4	6	4	6
Infants (AI)	7-12 months	5	7.5	5	7.5
Children	1-3 years	6	9	6	9
Children	4-8 years	7	10.5	7.5	10.5
Children	9-13 years	11	16.5	11	16.5
Adolescents	14-18 years	15	22.5	15	22.5
Adults	19 years and older	15	22.5	15	22.5
Pregnancy	all ages	-	-	15	22.5
Breast-feeding	all ages	-	-	19	28.5

Source: <http://ods.od.nih.gov/factsheets/VitaminE-Consumer/>



## World's Healthiest Foods ranked as quality sources of vitamin E

Food	Serving Size	Cals	Amount (mg (ATE))	DRI/DV (%)	Nutrient Density	World's Healthiest Foods Rating
<a href="#"><u>Sunflower Seeds</u></a>	0.25 cup	204.4	12.31	82.07	7.2	excellent
<a href="#"><u>Spinach</u></a>	1 cup	41.4	3.74	24.93	10.8	excellent
<a href="#"><u>Swiss Chard</u></a>	1 cup	35.0	3.31	22.07	11.3	excellent
<a href="#"><u>Turnip Greens</u></a>	1 cup	28.8	2.71	18.07	11.3	excellent
<a href="#"><u>Asparagus</u></a>	1 cup	39.6	2.70	18.00	8.2	excellent
<a href="#"><u>Mustard Greens</u></a>	1 cup	36.4	2.49	16.60	8.2	excellent
<a href="#"><u>Chili Peppers</u></a>	2 tsp	15.2	2.06	13.73	16.2	excellent
<a href="#"><u>Almonds</u></a>	0.25 cup	132.2	6.03	40.20	5.5	very good
<a href="#"><u>Broccoli</u></a>	1 cup	54.6	2.26	15.07	5.0	very good
<a href="#"><u>Bell Peppers</u></a>	1 cup	28.5	1.45	9.67	6.1	very good
<a href="#"><u>Kale</u></a>	1 cup	36.4	1.11	7.40	3.7	very good
<a href="#"><u>Cayenne Pepper</u></a>	2 tsp	11.4	1.07	7.13	11.2	very good
<a href="#"><u>Tomatoes</u></a>	1 cup	32.4	0.97	6.47	3.6	very good



# RDA Study

- ✓ In a test-tube analysis, hydrogen peroxide was added to blood samples and hemolysis was used to indicate vitamin E deficiency.
- ✓ Because hemolysis has also been reported in children with severe vitamin E deficiency, this analysis was considered to be a clinically relevant test of vitamin E status.
- ✓ Latest RDA for vitamin E is based on the prevention of deficiency symptoms rather than on health promotion and prevention of chronic disease.



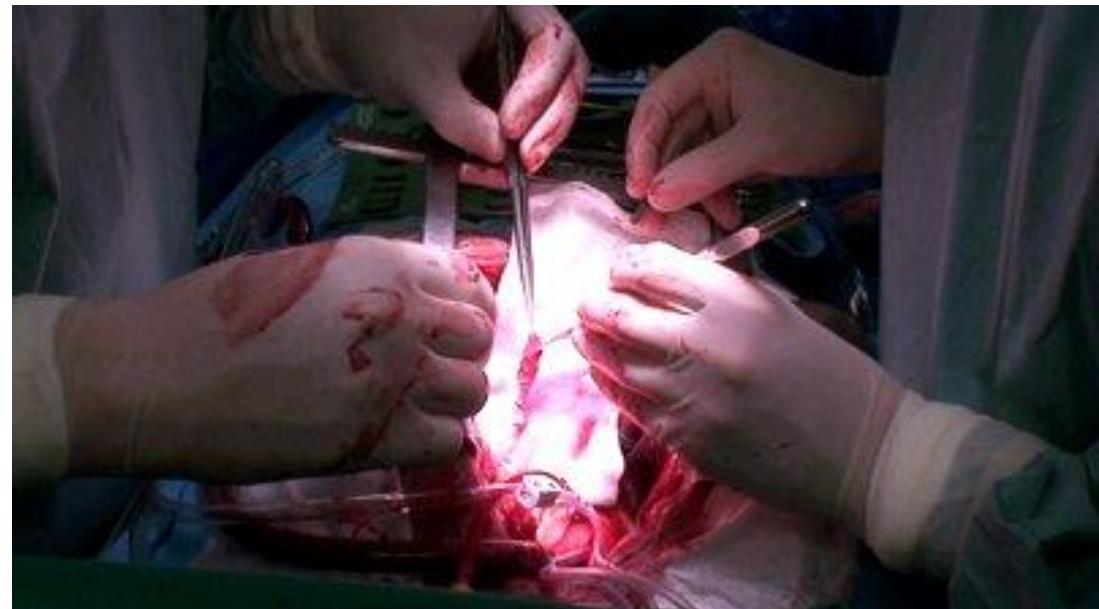
# Cardiovascular Disease

- ✓ Results of at least five large observational studies suggest that increased vitamin E consumption is associated with decreased risk of myocardial infarction or death from heart disease in both men and women.
- ✓ Each study was a prospective study that measured vitamin E consumption in presumably healthy people and followed them for a number of years to determine how many were diagnosed with or died as a result of heart disease.



# Bypass and Vitamin E

- ✓ Small observational study of men
- ✓ History of coronary artery bypass surgery
- ✓ Those who took at least 100 IU of supplemental  $\alpha$ -tocopherol (67 mg of RRR- $\alpha$ -tocopherol) daily had a reduction in the progression of coronary artery atherosclerosis measured by angiography compared to those who took less than 100 IU/day of  $\alpha$ -tocopherol.



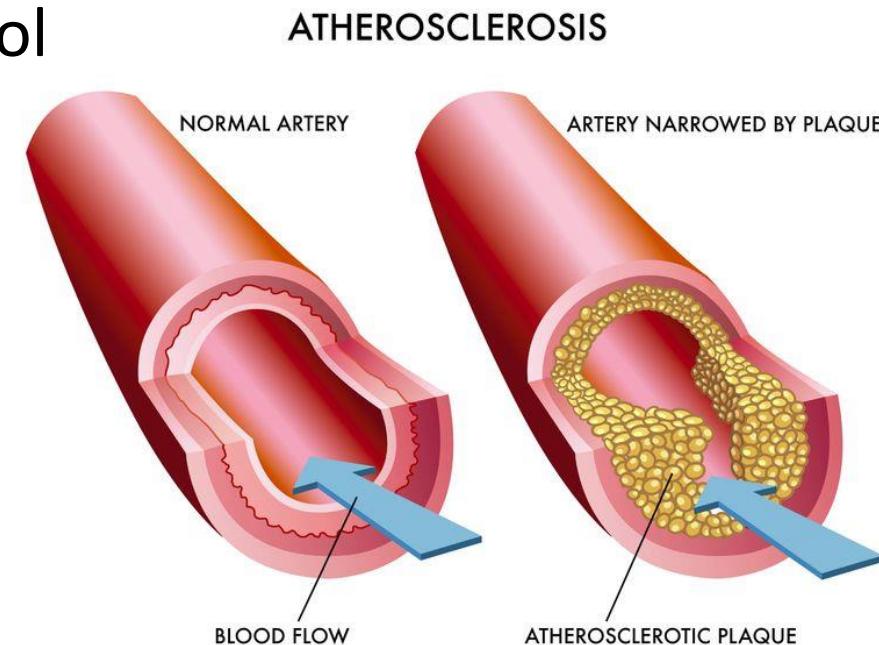
# Cardiovascular Disease Studies

- ✓ In two of the studies, individuals who consumed more than 7 mg/day of  $\alpha$ -tocopherol in food were only approximately 35% as likely to die from heart disease as those who consumed less than 3-5 mg/day of  $\alpha$ -tocopherol.
- ✓ Two other large studies observed a significantly reduced risk of heart disease only in women and men who consumed at least 100 IU of supplemental RRR- $\alpha$ -tocopherol (67 mg of RRR- $\alpha$ -tocopherol) daily.



# Atherosclerosis

- ✓ Several studies have observed plasma or red blood cell levels of  $\alpha$ -tocopherol to be inversely associated with severity of carotid atherosclerosis, detected using ultrasonography.
- ✓ A randomized, placebo-controlled, intervention trial in 39,876 women participating in the Women's Health Study found that supplementation with 600 IU of RRR- $\alpha$ -tocopherol (400 mg of RRR- $\alpha$ -tocopherol) every other day for ten years had no effect on the incidence of myocardial infarction and stroke, but the vitamin E intervention decreased cardiovascular-related deaths by 24%.



# More Studies

- ✓ Analysis of data from the Women's Health Study also showed that women receiving the vitamin E intervention experienced a 21% reduction in risk of venous thromboembolism.
- ✓ A large randomized control trial conducted in healthy middle-aged men (trial name: PHS II) observed that supplementation with 400 IU of synthetic  $\alpha$ -tocopherol every other day for eight years had no significant effect on the risk of major cardiovascular events.



# Cataracts and Vitamin E

- ✓ Cataracts formed by protein oxidation in the lens of the eye may be prevented by  $\alpha$ -tocopherol.
- ✓ Mixed results of observational studies: some report increased vitamin E intake protects against cataract development, while others report no association.



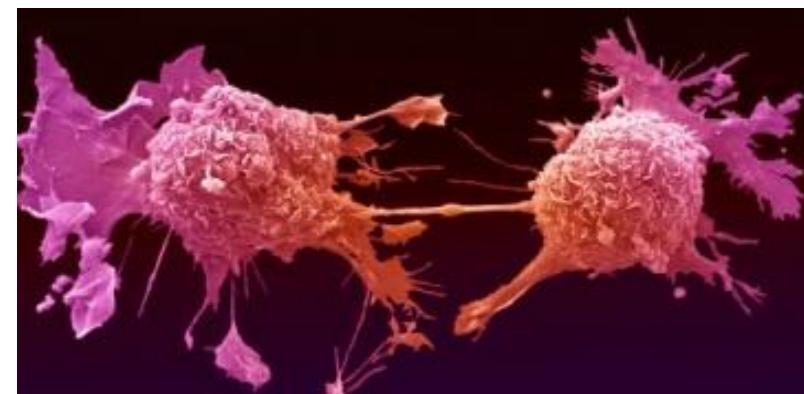
# Immune Function and Vitamin E

- ✓  $\alpha$ -Tocopherol has been shown to enhance specific aspects of the immune response that appear to decline as people age.
- ✓ A randomized, placebo-controlled trial in elderly nursing home residents reported that daily supplementation with 200 IU of synthetic  $\alpha$ -tocopherol (equivalent to 90 mg of RRR- $\alpha$ -tocopherol) for one year significantly lowered the risk of upper respiratory tract infections, especially the common cold, but had no effect on lung infections.



# Cancer and Vitamin E

- ✓ Many types of cancer are thought to result from oxidative damage to DNA caused by free radicals.
- ✓ The ability of  $\alpha$ -tocopherol to neutralize free radicals has made it the subject of a number of cancer prevention studies.
- ✓ Several large prospective studies have failed to find significant associations between  $\alpha$ -tocopherol intake and the incidence of lung or breast cancer.



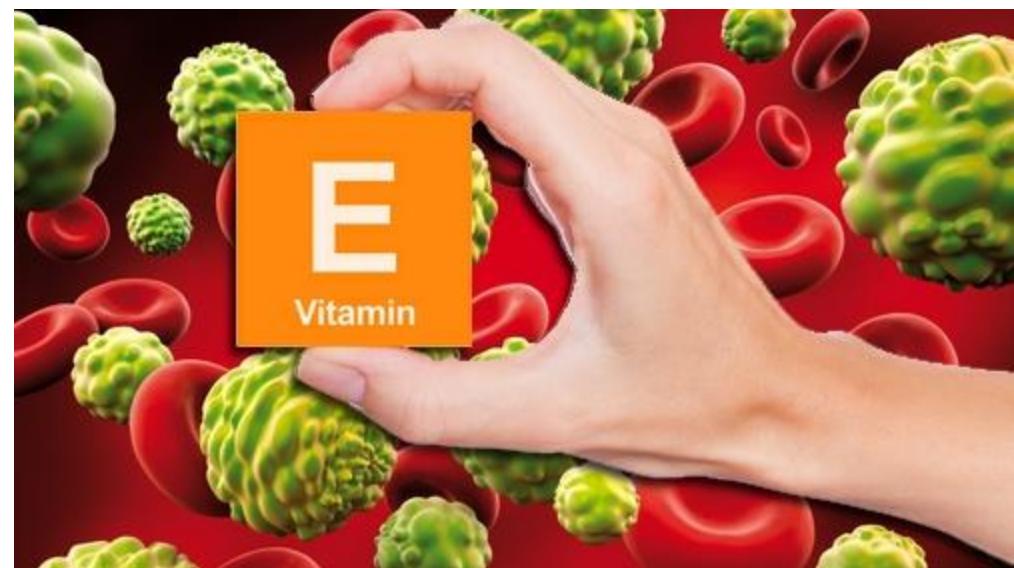
# Vitamin E and Prostate Cancer

- ✓ The effect of vitamin E supplementation on prostate cancer risk has received particular attention in randomized control trials.
- ✓ A placebo-controlled intervention (trial name: ATBC) reported a 34% reduction in the incidence of prostate cancer in smokers given daily supplements of 50 mg of synthetic  $\alpha$ -tocopherol (equivalent to 25 mg of RRR- $\alpha$ -tocopherol) daily.



# Using Vitamin E with Cancer

- ✓ Cancer cells proliferate rapidly and are resistant to death by apoptosis (programmed cell death).
- ✓ Cell culture studies indicate that the vitamin E ester,  $\alpha$ -tocopheryl succinate, can inhibit proliferation and induce apoptosis in a number of cancer cell lines.
- ✓ The ester form,  $\alpha$ -tocopheryl succinate, not  $\alpha$ -tocopherol, is required to effectively inhibit proliferation or induce cancer cell death.



# Diabetes and Vitamin E

- ✓ One study found urinary excretion of F2-isoprostanes, a biochemical marker of oxidative stress, was elevated in type 2 diabetic individuals.
- ✓ Supplementation with 600 mg of synthetic  $\alpha$ -tocopherol (equivalent to 300 mg of RRR- $\alpha$ -tocopherol) for 14 days reduced levels of the biomarker.



# Dementia and Alzheimer's

- ✓ The brain is particularly vulnerable to oxidative stress, and low vitamin E is considered a contributory factor in Alzheimer's disease.
- ✓ Low vitamin E has been found in cerebrospinal fluid of patients with Alzheimer's disease.
- ✓ A large placebo-controlled intervention trial in individuals with moderate neurological impairment found that supplementation with 2,000 IU of synthetic  $\alpha$ -tocopherol daily for two years (equivalent to 900 mg/day of RRR- $\alpha$ -tocopherol) significantly slowed progression of Alzheimer's dementia.



# Toxicity

- ✓ Few side effects have been noted in adults taking supplements of less than 2,000 mg of  $\alpha$ -tocopherol daily (RRR- or all-rac- $\alpha$ -tocopherol).
- ✓ Most studies of toxicity or side effects of  $\alpha$ -tocopherol supplementation have lasted only a few weeks to a few months.
- ✓ Side effects as a result of long-term  $\alpha$ -tocopherol supplementation have not been adequately studied.
- ✓ It's possible that excess vitamin E may increase the likelihood of hemorrhage in some individuals.



# Drug Interactions

- ✓ Use of vitamin E supplements may increase the risk of bleeding in individuals taking anticoagulant drugs, such as warfarin (Coumadin); antiplatelet drugs, such as clopidogrel (Plavix) and dipyridamole (Persantine); and non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, and others.
- ✓ Also, individuals on anticoagulant therapy (blood thinners) or individuals who are vitamin K deficient should not take  $\alpha$ -tocopherol supplements without close medical supervision because of the increased risk of hemorrhage.



# Food Sources

- ✓ Major sources of  $\alpha$ -tocopherol in the American diet include vegetable oils (olive, sunflower, and safflower oils), nuts, whole grains, and green leafy vegetables.
- ✓ All eight forms of vitamin E ( $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocopherols and tocotrienols) occur naturally in foods but in varying amounts.



# Supplements: $\alpha$ -Tocopherol

- ✓ In the US, the average intake of  $\alpha$ -tocopherol from food (including enriched and fortified sources) for individuals 2 years and older is 6.9 mg/day; this level is well below the RDA of 15 mg/day of RRR- $\alpha$ -tocopherol.
- ✓ Many scientists believe it is difficult for an individual to consume more than 15 mg/day of  $\alpha$ -tocopherol from food alone without increasing fat intake above recommended levels.



# $\alpha$ -Tocopheryl succinate and $\alpha$ -tocopheryl acetate ( $\alpha$ -tocopheryl esters)

- ✓  $\alpha$ -Tocopherol supplements are available in the ester forms:  $\alpha$ -tocopheryl succinate and  $\alpha$ -tocopheryl acetate.
- ✓ Tocopherol esters are more resistant to oxidation during storage than unesterified tocopherols.
- ✓ When taken orally, the succinate or acetate moiety is removed from  $\alpha$ -tocopherol in the intestine.



# $\gamma$ -Tocopherol Supplements

- ✓  $\gamma$ -Tocopherol supplements and mixed tocopherol supplements are also commercially available.
- ✓ The amounts of  $\alpha$ - and  $\gamma$ -tocopherol in mixed tocopherol supplements vary, so it is important to read the label to determine the amount of each tocopherol present in supplements.

