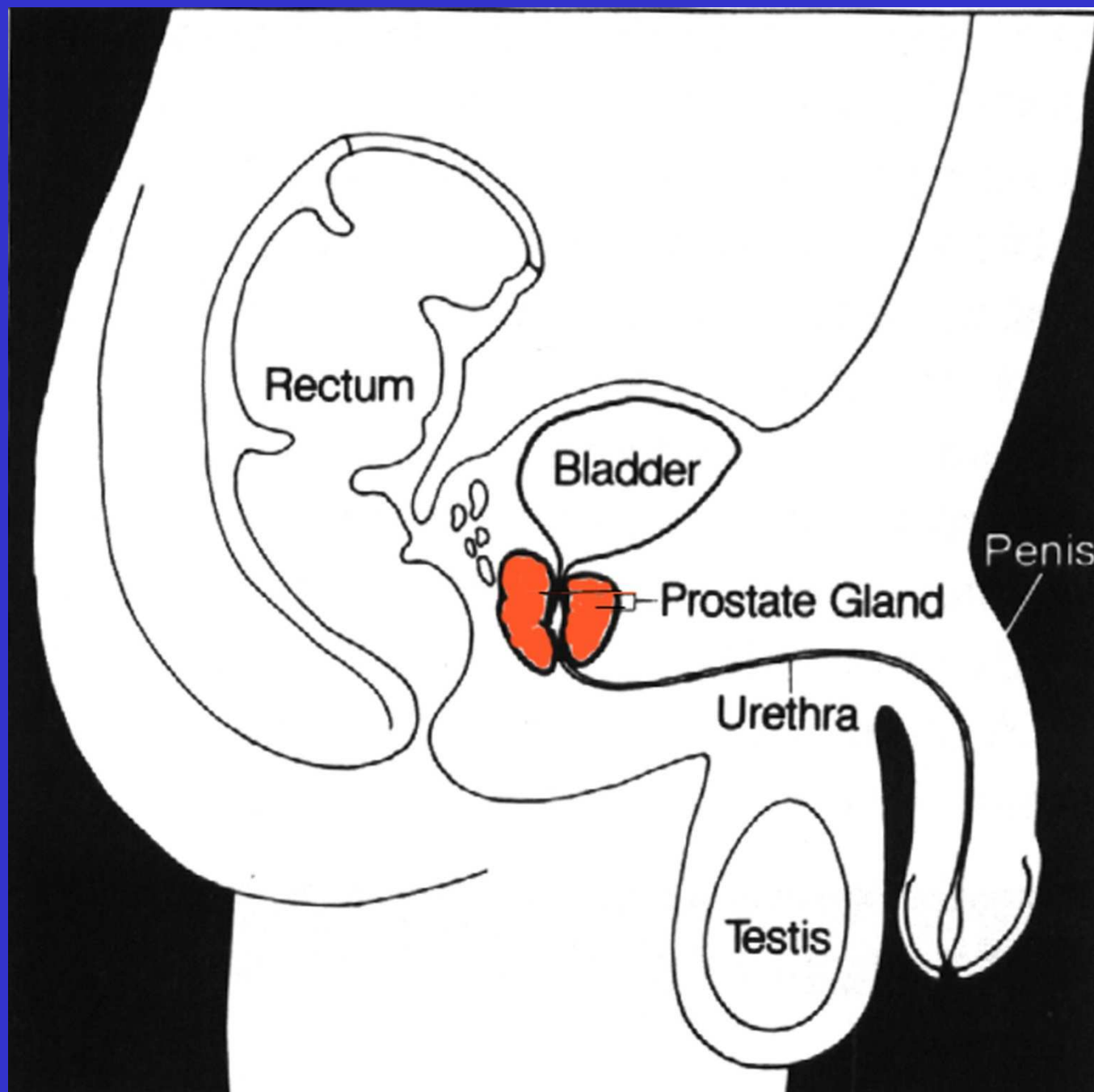


Phytotherapy & Prostate Cancer

Dr Andrew Yip
Specialist in Urology



The Prostate Gland

- Male sex gland
- Size of a walnut
- Helps control urine flow
- Produces fluid component of semen
- Produces Prostate Specific Antigen (PSA) and Acid Phosphatase

Prostate Cancer

Definition

- Relevance
 - Most common noncutaneous malignancy in men
- Incidence
 - Nearly 200,000 new cases per year in U.S.
- Mortality
 - 32,000 deaths in the United States each year
 - Second most common cause of cancer death in men²
- Morbidity
 - Single histologic disease
 - Ranges
 - From indolent, clinically irrelevant
 - To virulent, rapidly lethal phenotype.

Prostate - incidence

- 27 000 new cases per year in UK
- 10 000 deaths
- 8% of men will be diagnosed
- 3% will die from prostate cancer
- Latent cancer present in 25% of screened patients and 50% of post-mortem patients

International Patterns

- Lowest rates are observed in the Far East and on the Indian subcontinent
 - 2.9 per 100,000 men in China
- Highest rates occur in Western Europe, Australia, and North America
 - 107.8 and 185.4 per 100,000 white and black men in the United States
- Migration studies show that men of Asian heritage living in the U.S. are at lower risk than white Americans but greater risk than men of similar ancestries living in Asia

Prostate cancer risk factors:

- **Age:** The risk increases with age, but 25% of diagnoses are made under age 65.
- **Race:** African-Americans have a rate of incidence **double** that of Caucasian men
- **Family history of prostate cancer:** Men with a family history have two- to three-fold increase in the risk of prostate cancer
- **Diet:** A diet high in saturated animal fat can double the risk of developing prostate cancer.

Risk Factors

AGE	RISK
45 – 49 :	23 per 100,000
50 – 54 :	103 per 100,000
55 – 59 :	273 per 100,000
60 - 64 :	568 per 100,000
65 + :	1,000 per 100,000

Risk Factors

FAMILY HISTORY

2.4 times increased risk for men with a first-degree relative

(Spitz, et al, "Familial patterns of prostate cancer: A case-control analysis", J Urol, 1991, 146:1305-1307)

Nutrition & Prostate Cancer

- Improved nutrition may reduce the incidence of prostate cancer & also reduce the risk of prostate cancer progression.(J Urol. 2005 Sep;174(3):1065-9).
- “Scientific evidence suggests that differences in diet & lifestyle may account in large part for the variability of prostate cancer rates in different countries” (CaPCure).
 - Trends – Mortality rates are rising in some Asian countries, especially Japan & Singapore, which is thought to be due to Westernization

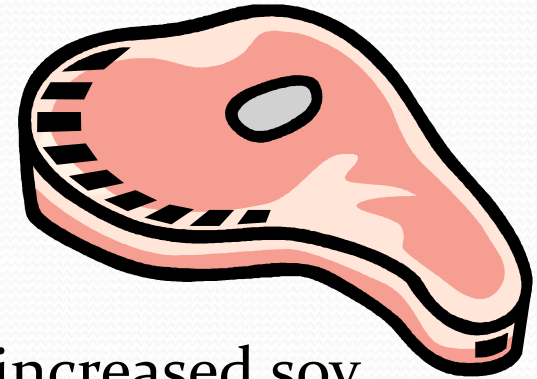
ACS. The Worldwide Cancer Burden. Atlanta: ACS; 2006

Risk Factors

DIET

- Eating red meat increases the risk of developing prostate cancer 2.64 times
- Red meat and dairy products are high in saturated fat rich in arachidonic acid (a fatty acid)
- Vegetable oil is rich in alpha linolenic acid (a fatty acid)
- By-products of these fats promote the growth and seriousness of prostate cancer
- Eating a diet high in fats also lowers the body's defenses

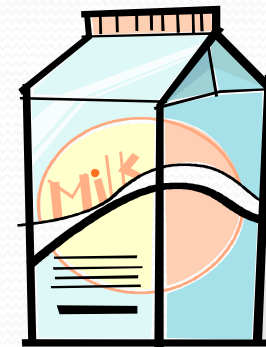
Diet – Protein



- Soy
 - Possible decrease in prostate risk with increased soy intake
- Red meat and processed meat
 - Consumption of red or processed meat has been associated with a higher risk of total or advanced prostate cancer in some cohort studies
- Fish
 - Some studies have shown protective effect of eating fish regularly, mostly attributed to omega-3 fatty acids

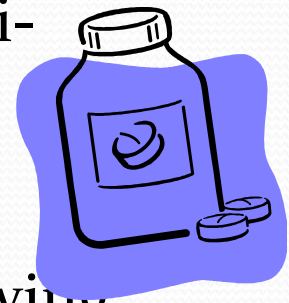
Diet – Other

- Association between fat consumption and prostate cancer has been observed in some studies
- Countries with greater per capita milk consumption have higher prostate cancer mortality rates
- No significant association between smoking and alcohol use has been observed



Other Factors

- Aspirin and Non-Steroidal Anti-Inflammatory Agents
 - Weak inverse association between regular anti-inflammatory use and prostates cancer
- Vasectomy
 - Some studies have shown increased risk following vasectomy
- Occupational and Environmental Exposures
 - Pesticide use
 - High electromagnetic field exposure
- STD Infection



Diagnosis

- ❑ digital rectal exam (DRE)
- ❑ PSA (prostate specific antigen) elevated in the majority of patients with CaP
- ❑ transrectal ultrasound (TRUS) —> size and local staging
- ❑ TRUS-guided needle biopsy
- ❑ incidental finding on TURP
- ❑ bone scan may be omitted in untreated CaP with PSA < 10 ng/ml
- ❑ lymphangiogram and CT scanning to assess metastases

Diagnosing Prostate Cancer

DETECTING PROSTATE CANCER

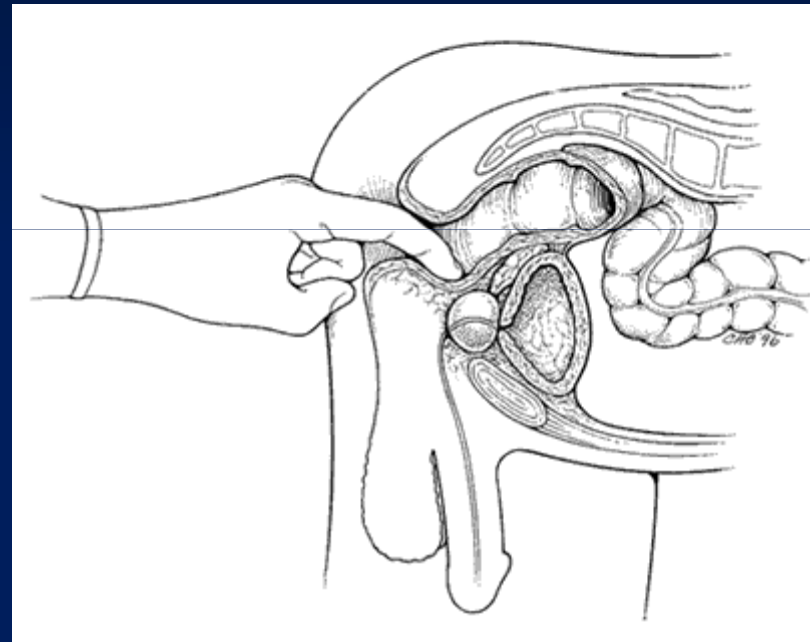
- PSA
- Kallikrein Tumor Markers
- Digital Rectal Exam
- Biopsy

STAGING PROSTATE CANCER

- The TNM staging system
- Histologic Grading: The Gleason Score
- Post-Surgical Evaluation
- Imaging Bone Metastases

DRE

- PSA can be falsely elevated
- DRE does not palpate entire prostate gland
- Abnormal: nodules, hard spots, soft spots, enlarged

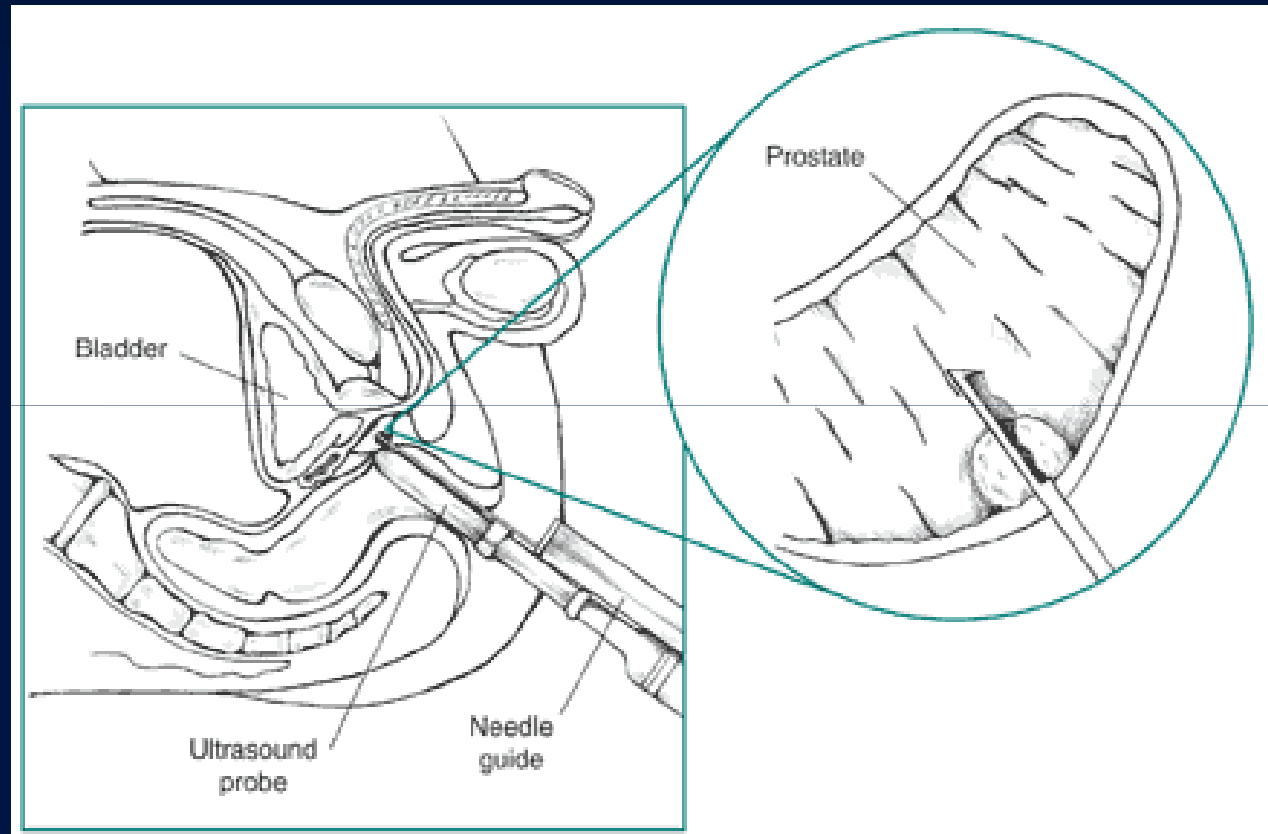


Prostate Specific Antigen

- Protein released by prostate into ejaculate
- Some leaks into blood – more in cancer
- Normal range 0-4 ng/ml
- PSA 4-10 = 25% chance of cancer
- PSA>50 = >50% chance metastatic cancer
- Next step is prostate needle biopsy

Biopsy (TRUSP)

- Hypoechoic shows abnormal area needing biopsy



Treatment options for prostate cancer

- Observation alone.
- Radical prostatectomy.
- Radiation therapy.
- Hormonal treatment.

Recommended treatments

Low risk – active surveillance (ie regular PSA monitoring and treat if PSA rises)

Medium risk – surgery or radiotherapy

High risk – radiotherapy usually with neoadjuvant hormone therapy

Surgery in few selected patients

Nutrition & Prostate Cancer

- Prostate Cancer Lifestyle Trial
 - 2 year follow up
- GEMINAL pilot study
- Related research

Ornish, et al., J Urol. 2005 Sep;174(3):1065-70

Frattaroli, et al. Urology 2008 Jul 2 (epub)

Carmody, et al. Urology 2008 Apr 7 (epub)

Ornish, et al., Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8369-74)

Prostate Cancer Lifestyle Trial (PCLT)

- Randomized controlled trial
 - 93 men (non-smoking) with biopsy proven prostate cancer
 - PSA 4 to 10 ng/ml, Gleason scores <7, opting for active surveillance
 - Randomized into intervention (low-fat, vegan diet, w/soy and antioxidants, omega-3 fatty acid, moderate aerobic exercise, stress management, and group support) or control (usual care)
- Results:
 - After 1 year, PSA ↓ 4% in the intervention group & ↑ 6% in the control group.
 - The growth of LNCaP prostate cancer cells was inhibited almost 8 times more by serum from the experimental than from the control group.
- Conclusion:
 - Intensive changes in diet and lifestyle may affect the progression of early stage prostate cancer and improve quality of life.
 - Further studies and longer term follow-up are warranted

PCLT - Two year follow up

- 13/49 (27%) control patients, 2/43 (5%) intervention patients underwent conventional treatment
- 3/10 (30%) of the treated control patients, 0/2 (0%) of the treated experimental patients had a PSA level of ≥ 10 ng/mL
- No differences in other clinical events
- Intervention group had significant decreases in total cholesterol and LDL
- 95% adherence



GEMINAL Study

- **Gene Expression Modulation by Intervention with Nutrition & Lifestyle Study**
 - Single arm, pilot study - 30 men, active surveillance, biopsy at baseline and after 3 mos intensive lifestyle change
 - Gene expression in > 500 genes was affected:
 - Significant modulation of biological processes that have critical roles in tumorigenesis.
 - Total PSA did not significantly change, % free PSA, CV risk factors, & some measures of QoL improved.

A very-low-fat vegan diet increases intake of protective dietary factors and decreases intake of pathogenic dietary factors.

- Meat Based

- High in cholesterol
- High in saturated fats
- High in oxidants
- Low in antioxidants
- Pro-inflammatory
- Low in fiber
- High in pathogenic substances

- Plant Based

- No cholesterol
- Low saturated fats
- Low in oxidants
- High in antioxidants
- Anti-inflammatory
- High in fiber
- High in protective substances

Insulin & Cancer

- A Western lifestyle -- characterized by low physical activity, & high dietary intake, animal protein, saturated fats, trans fats, & rapidly digestible carbohydrates -- is associated with ↑ risks of many cancers.
 - May be mediated by alterations in the metabolism of insulin and insulin-like growth factors (IGFs).
- Elevated serum insulin & IGF-I levels as well as insulin resistance appear to lead to both the development & promotion of cancer.

Limit Simple Carbohydrates

- Sources: candy, cookies, pastries, & white refined breads, pastas, crackers, alcohol, etc.
 - Also includes added sugars to beverages &/or processed foods.
- High sugar foods are usually highly processed & refined, low in nutrient value, & low in fiber.
- These foods appear to ↑ serum insulin & serum IGF-1 levels & contribute to insulin resistance.
- A recent animal study found that diet-induced hyperinsulinemia was associated with accelerated growth of prostate cancer.

Venkateswaran V, et al., J Natl Cancer Inst. 2007 Dec 5;99(23):1793-800

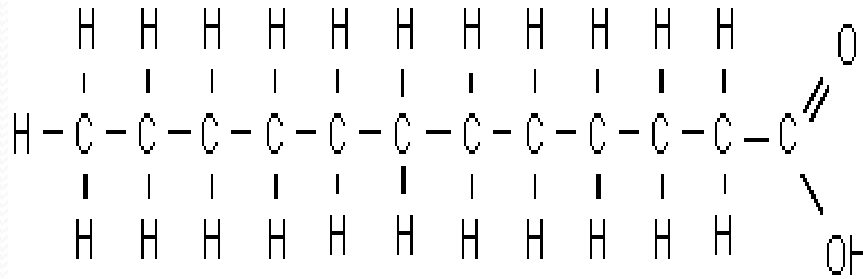
High-Fiber Diet

- A diet rich in natural fiber obtained from fruits, vegetables, legumes, & whole grains may reduce cancer risk &/or prevent prostate cancer progression.
- Fiber binds to toxic compounds & carcinogens, which are then later eliminated by the body.
 - Additionally, fiber ↓ circulating hormone levels.
- Men taking flaxseed daily had the slowest rate of tumor growth compared to a low fat diet alone or no intervention Demark-Wahnefried, et al. *J Clin Oncology*, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 1510

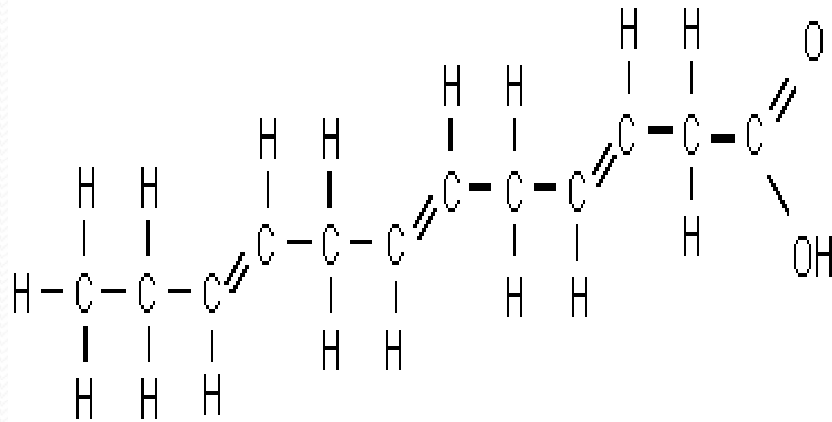
Low Fat Diet

- $\uparrow \text{ fat } \rightarrow \uparrow \text{ testosterone } \rightarrow \uparrow \text{ cancer }$
- A comprehensive review reported that 20 of 30 studies found positive, although not all statistically significant, associations between dietary fat intake and prostate cancer risk.
- Aim for ~20% of your total calories from fat, with less than 8% of total calories from saturated fat.
- The type of fat may be of greater importance than total fat.

Types of Free Fatty Acids



Saturated Fatty Acid



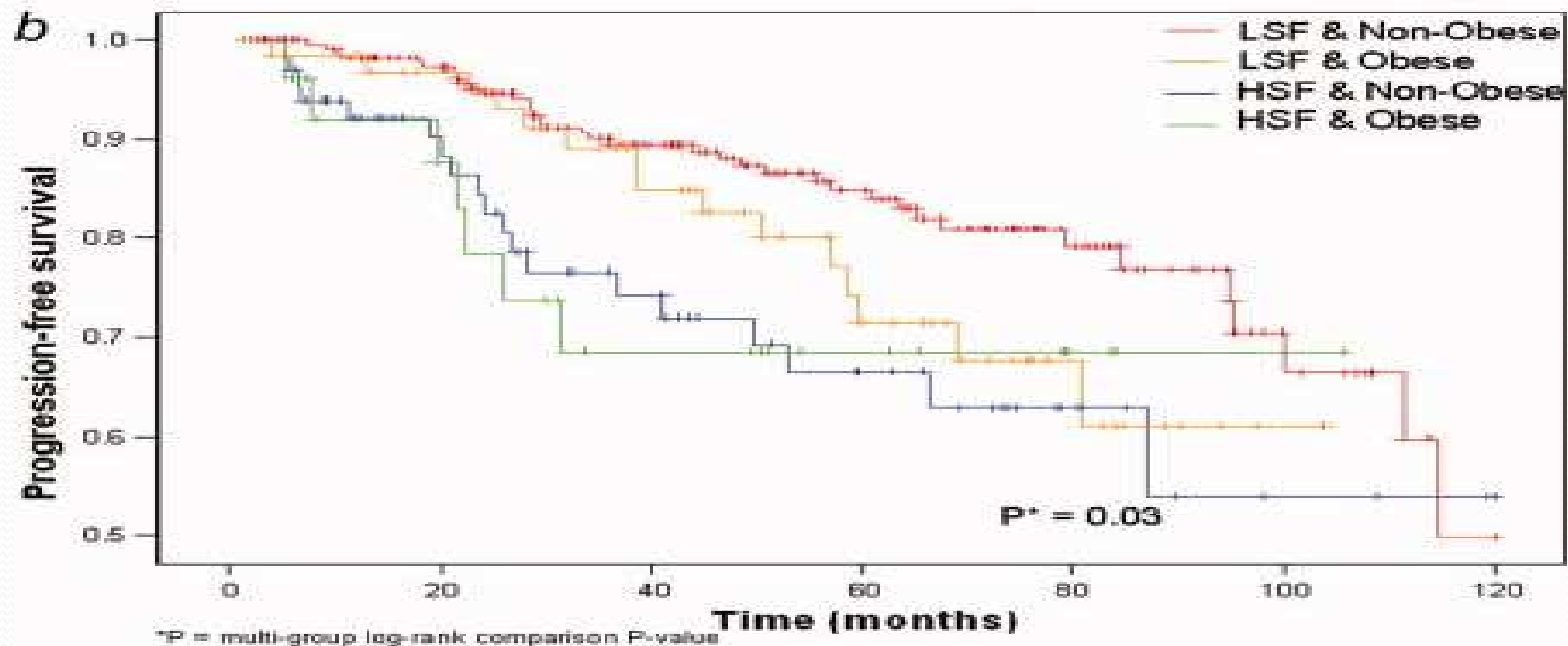
Unsaturated Fatty Acid

- **Saturated**
 - Fatty acids are *saturated* with hydrogen molecules
 - Semi-solid or solid at room temperature
- **Monounsaturated (omega-9)**
 - Fatty acid contains one double bond
 - Liquid at room temperature
- **Polyunsaturated (omega-6 & omega-3)**
 - Fatty acid contains 2 or more double bonds
 - Liquid at room temperature
- **Hydrogenated**
 - Industrial hardening of edible oils to make products hard at room temperature

Saturated Fats

- Many studies indicate a positive association between saturated fat intake from meat & dairy products & prostate cancer.
 - Intakes of red meat and dairy products appear to also be related to increased risk of metastatic prostate cancer.
- Limit use of meats, dairy products, butter, mayonnaise, & baked goods due to high saturated fat & total fat content.

Saturated fat intake predicts biochemical failure after prostatectomy.



c

Saturated Fat	BMI	Mean time to progression (months)
Low	Non-obese	45.9
Low	Obese	41.5
High	Non-obese	29.4
High	Obese	19.2

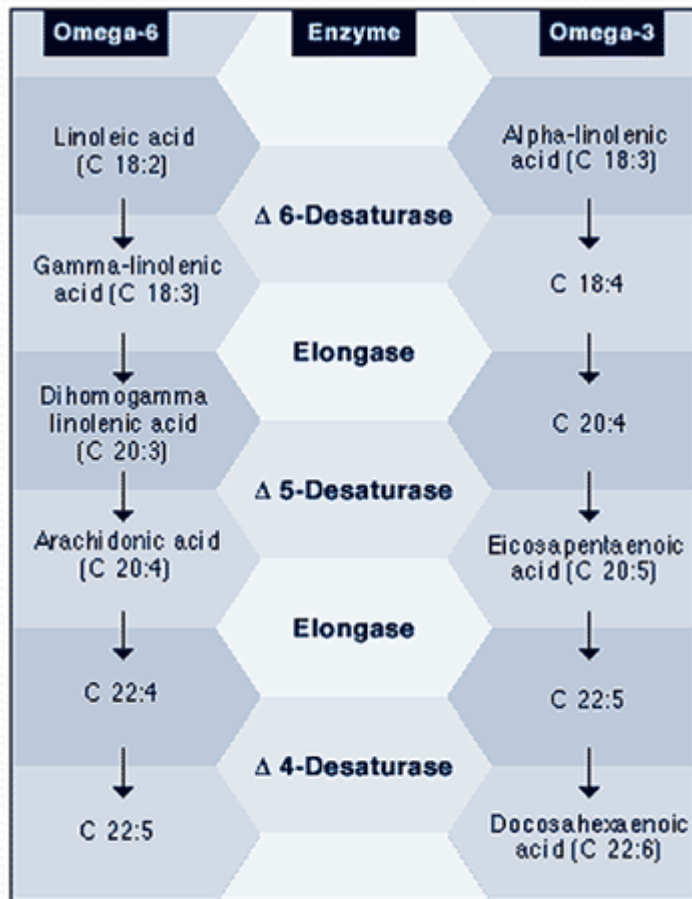
Strom SS, et al., Int J Cancer. 2008 Jun 1;122(11):2581-5

Omega-9 Fatty Acids



- Offer cardio-protective benefits, may offer cancer protection.
- Results suggest a neutral relationship between these fats & prostate cancer
- Good sources: olives, extra-virgin olive oil, canola oil, avocados, & almonds.
- Use these oils only in moderation.

Essential Fatty Acids (EFAs)



- Balance of omega-6 to omega-3 oils is critical to proper prostaglandin metabolism.
- Most American diets contain excessive omega-6 fats.
- Consuming a diet rich in omega-3 acids can restore the balance between the two fatty acids & can possibly reverse these disease processes.

EFA Sources



- Omega-3 Dietary Sources:
 - Include cold-water fish (i.e., salmon, trout, sardines, herring, sablefish), flaxseed, chia seeds, hemp seeds, walnuts, & pumpkin seeds.
- Omega-6 Dietary Sources:
 - Include meats (especially grain-fed), butter, whole milk, egg yolks, sunflower oil, safflower oil, cottonseed oil, corn oil, & processed foods made with these oils.

Omega 3 Fatty Acids & Prostate CA

- Studies show omega-3 fatty acids reduce risk of prostate cancer.
 - Men who consumed cold-water fish 3-4x/week had a reduced risk of prostate cancer.
 - Consuming fish two or more times a week was associated with a reduction in prostate cancer progression.
 - Omega-3 fatty acids may prevent androgen-deprived prostate cancer cells from starting to grow again following androgen deprivation therapy by stopping the androgen-receptor gene from functioning.
- www.AICR.org
- Increase Omega-3 food sources: cold-water fish (i.e., salmon, herring, sardines, trout, sablefish), flaxseeds, walnuts, chia seeds, hemp seeds & pumpkin seeds.

Omega 6 Fatty Acids & Prostate CA

- Essential fats, but high amounts of omega-6 may stimulate growth of prostate cancer cells

Ritch, CR, et al., J Urol. 2007 Jan;177(1):97-101

- Diets high in omega-6 fatty acids have been associated with an increased risk of bone metastasis from prostate cancers

- A recent study found that arachidonic acid modulates the crosstalk between prostate carcinoma and bone stromal cells.

Angelucci A, et al., Endocr Relat Cancer. 2008 Mar;15(1):91-100.

- Limit Omega-6 food sources: meats, butter, egg yolk, whole milk, corn oil, safflower oil, sunflower oil, cottonseed oil.

Healthy Fat Recommendations

- Keep saturated fats to 8% total kcals from fat.
 - Limit fatty meats, whole milk dairy products, cheese, mayonnaise, butter, & baked goods.
- Avoid hydrogenated oils
- Aim for 1:1 to 4:1 omega-6:omega-3
 - Increase sources of omega-3's daily
 - Flaxseed, fish, walnuts, pumpkin seeds
 - EPA/DHA supplement if appropriate
 - Decrease Omega-6 dietary sources:
 - Meats (especially grain-fed), butter, whole milk, egg yolks, sunflower oil, safflower oil, cottonseed oil, corn oil
 - Limit processed foods
 - Inquire about type of oil used at restaurants
 - Use olive oil, avocado, almond, macadamia nut or canola oil in moderation (omega-9 fatty acids)

High Calcium Diets & Prostate CA

- Meta-analysis of cohort data showed:
 - 27% ↑ risk for prostate cancer per 1000mg/day
 - 32% ↑ risk for advanced or aggressive prostate cancer per 1000mg/day
- High calcium down regulates the formation of vitamin D₃ from vitamin D, thereby increasing cell proliferation in the prostate.
- Prostate cancer tumors in rats treated with vitamin D₃ were significantly smaller and presented fewer lung metastases.
- Recommended to consume adequate (800-1200 mg daily), calcium, but to avoid high calcium intakes (>1500 mg daily).

Body Weight & Physical Activity

- Higher body mass & physical inactivity may contribute to prostate cancer risk.
 - A cohort study reported obese men to have a 20% increased risk of dying from prostate cancer & those men who were severely obese had a 34% elevated risk.
- A UCSF study of over 2,000 men found that men who maintained a healthy body weight had a lower risk of recurrence.
 - Obese men ↑ recurrence by 30%
 - Very obese men ↑ recurrence by 69%

Diet – Fruits and Vegetables

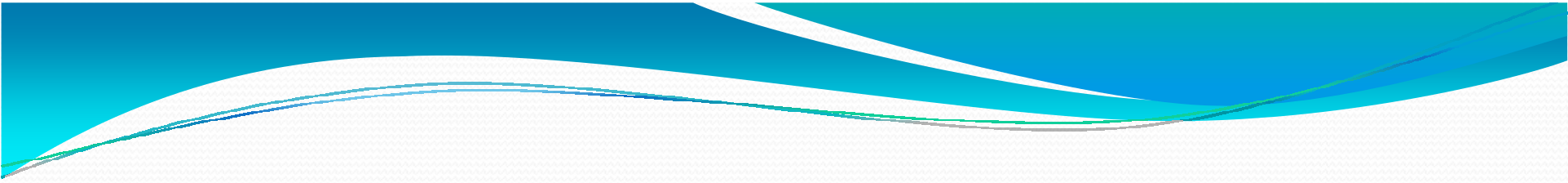
- Some studies have shown decreased risk of prostate cancer with increased intake of vegetables, but these findings are inconsistent
- Tomatoes
 - Overall data indicate that the intake of tomatoes (associated with higher circulating concentrations of lycopene) is associated with lower risk of prostate cancer
- Brassica or Cruciferous vegetables (Broccoli, etc.)
 - Small number of studies suggest inverse association between eating brassica vegetables and prostate cancer





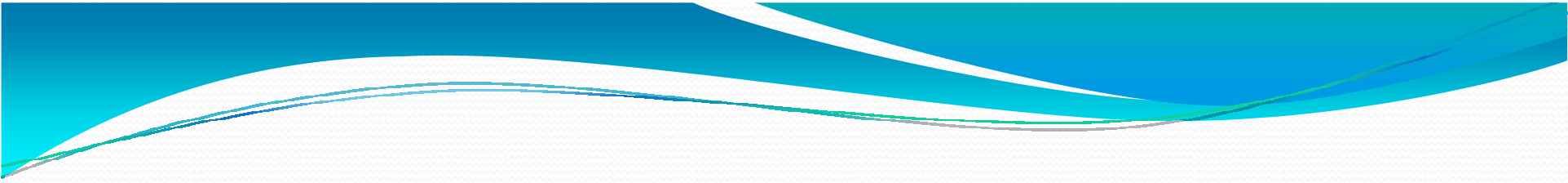
Phytotherapy for Prostate Cancer

- 1. improve immune system
- 2. minimize morbidity with conventional therapy
- 3. palliative care



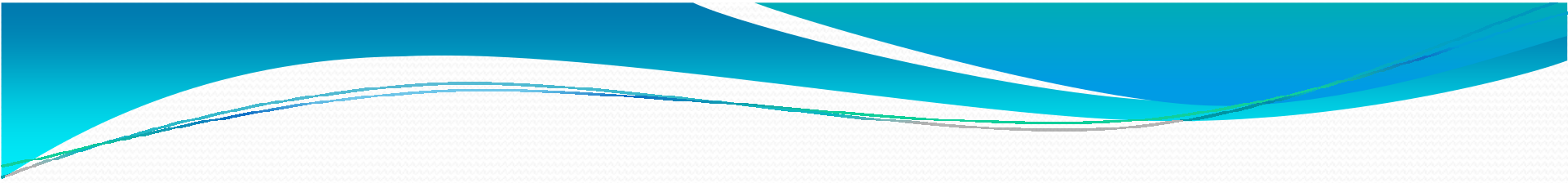
Phytochemicals 植物化學劑

- Not nutrients
- Modulating cancer cell growth
- Chemopreventive agents for cancer
- From vegetable & fruits
 - Phytoestrogens
 - Carotenoids (lycopene)
 - Polyphenols



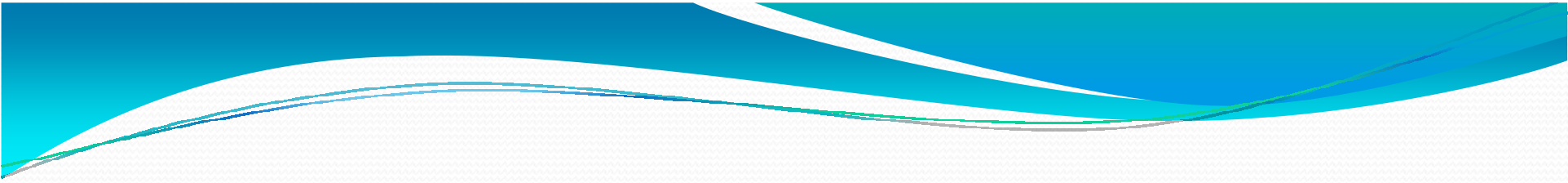
I. Phytoestrogens

- Naturally occurring phenolic plant compounds
 - Flavones (Quercetin)
 - Isoflavones (Genistein)
 - Coumestans
 - Lignans
- Soy products (beans & tofu)
- Legumes, whole grain – plant lignans
- ⇒ oestrogen-like activity



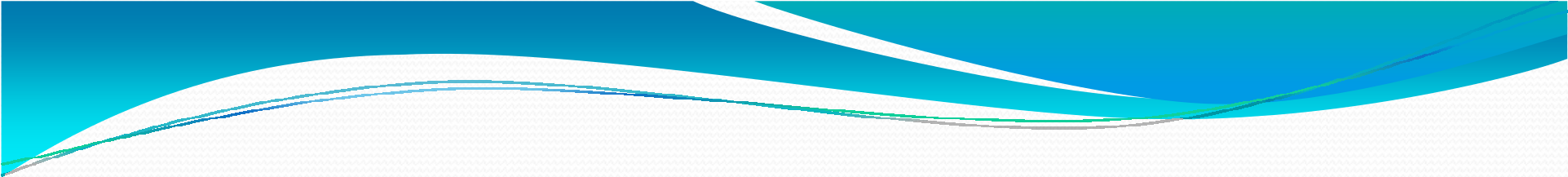
II. Carotenoids

- Lycopene – most potent antioxidant
 - Tomatoes
 - Pink grapefruit
 - Watermelon
- Highly concentrated in LDL & VLDL (lipophilic nature)
- High level in prostate



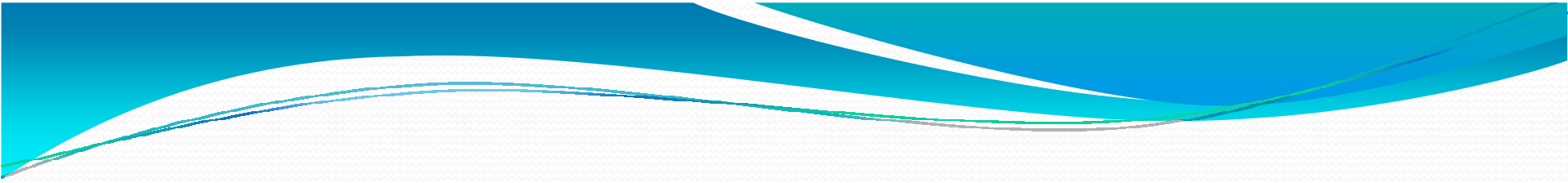
III. Polyphenols

- Curcumin
- Epigallocatechin-gallate
- Resveratrol



Curcumin

- Diferuloylmetnane
- A yellow pigment of Turmeric (*Curcuma longa*), a seasoning spice in India
- A natural anti-inflammatory agent



Green tea

Cancer preventive effects

Dried nonoxidized, unfermented leaves of *Camellia sinensis*

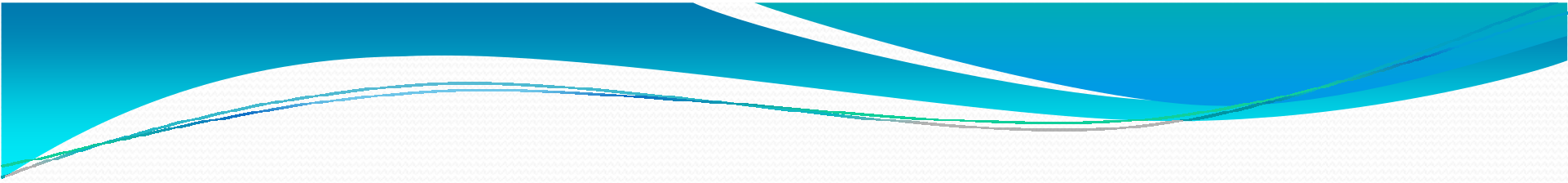
Contains a variety of polyphenolic compounds

epicatechin

epicatechin gallate

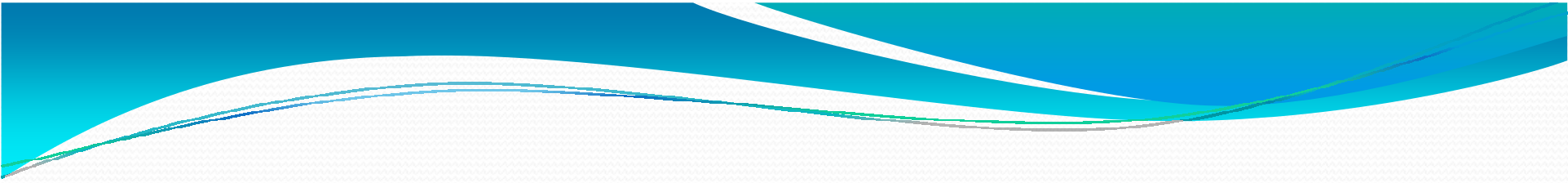
epigallocatechin

epigallocatechin-3-gallate



Resveratrol

- Skin of grapes
 - Peanuts
 - Berries
 - Anti carcinogenic
 - Anti oxidative
 - Cardioprotective
 - Phytoestrogenic
- ⇒ a potent chemopreventive agent for prostate cancer
- Grape juice or wine



Resveratrol

- Inhibit platelet aggregation
- ↑ high-density lipoprotein
- Vasorelaxing effect on the aortal endothelium

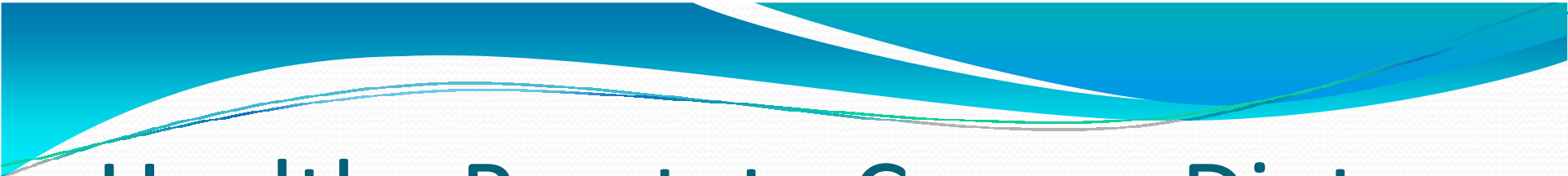
Molecular Targets of Phytochemicals

- Inhibition of tumour cell growth
- Inhibition of apoptosis
- Inhibition of PSA expression
- Suppression of DNA synthesis
- Inhibition of spontaneous mutagenesis



What can a healthy diet do for me?

- May help to inhibit prostate cancer growth
- Reduce risk of chronic diseases
- Enhance immune system
- Increase energy levels
- Facilitate recovery → ↓ toxicities of treatment



Healthy Prostate Cancer Diet

Plant-Based

- 8-10 COLORFUL fruit & vegetable servings daily
 - Eat 1 cup or more vegetables with at least 2 meals
- Beans/legumes, whole grains & other high fiber foods
 - 30-45 grams of fiber daily
 - 2 T ground flaxseed
- Limit meats & dairy
- Limit processed & refined foods → avoid WHITE

Fats

- Low in fat
- Healthy fats → cold-water fish, flaxseed, walnuts, soybeans, olive oil, avocados

Guidelines for a Healthy Diet

- Plant-based diet
 - Plethora of fruits & vegetables
 - High fiber – whole grains and beans/legumes
 - Limit processed & refined foods → avoid WHITE
 - Limit meats & dairy
- Low fat diet with emphasis on healthy fats
- Drink plenty of fluids
- Stop smoking if you smoke
- Limit alcohol consumption
- Be physically active to help achieve and maintain a healthy weight

Healthy Prostate Cancer Diet

Selenium (200 mcg) → Brazil nuts, seafood, enriched brewer's yeast, & grains

Lycopene (30 mg) from food → 6 ½ tbsp tomato paste, ¾ C tomato sauce, or 12 fl oz tomato juice

Vitamin E (50-200 IU)

- Natural form, high in gamma-tocopherol

Green Tea → 1-4 cups daily

Pomegranate → 1 oz concentrate, 8 oz juice

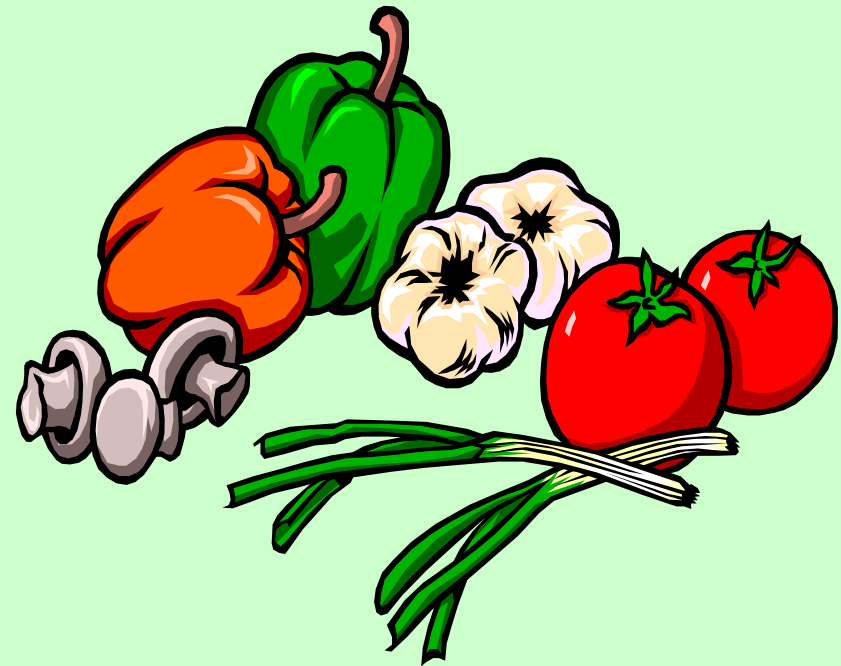
Vitamin D (1000 IU or more if needed)

- Consider serum 25-OH test

Regular physical activity to achieve or maintain a healthy body weight.

So what CAN I eat?

- A balanced diet rich in fruits and vegetables!
(5 servings/day)
- Lower your intake of red meat, processed and fried foods. Eat more plant-based food like soy protein.
- Watch portion sizes
(3 oz meat/serving)
- Eat foods with lycopene
(tomatoes, watermelon and red grapefruit) which may be associated with a decreased risk of prostate cancer



Thank you

