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Nutritional Medicine in Male and Female Reproductive Health Issues

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Male Reproductive Health Issues

(many similar aspects of nutrition involvement are seen in Female Health Issues section)

- Aging and Andropause

- Prostate Health Issues:
  - Benign Prostatic Hyperplasia (BPH)
  - Prostate Cancer Prevention
  - Adjunctive Nutritional Management in Prostate Cancer

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Age-Related Hormonal Changes In Men

1. Testosterone – declines 1% each year after age 40 (muscle, abdom fat, bone mass, libido)

2. Growth Hormone – (20 yrs = 500 mcg per day, 200 mcg at 40 yrs old and only 25 mcg at 80 yrs old - IGF-1 below 275 ng/mL – muscle, immune, abdom fat, bone mass, skin)

3. Melatonin – (immune, sleep quality, libido, memory) 0.5-3mg

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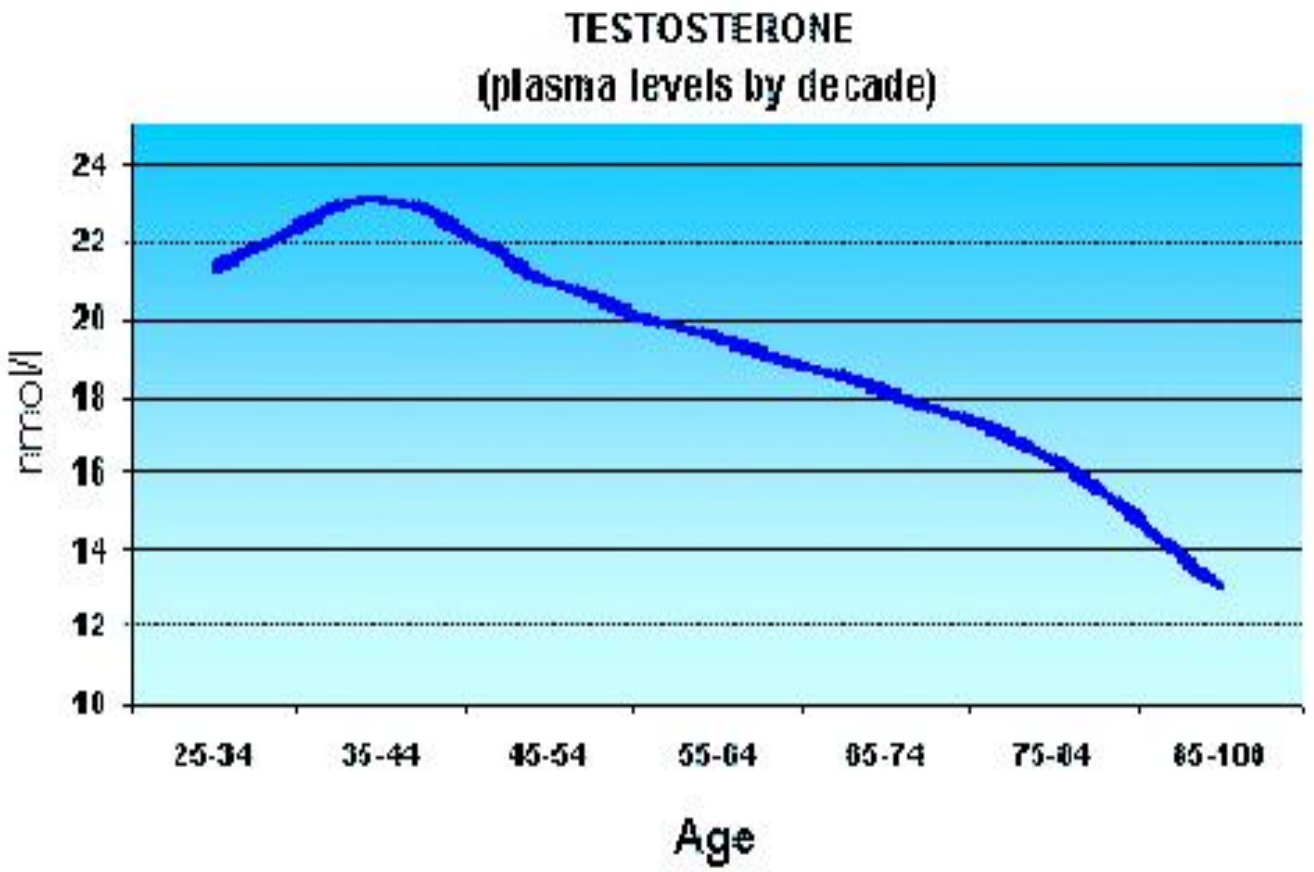
Age-Related Decline In Testosterone: 1% decline annually after 40



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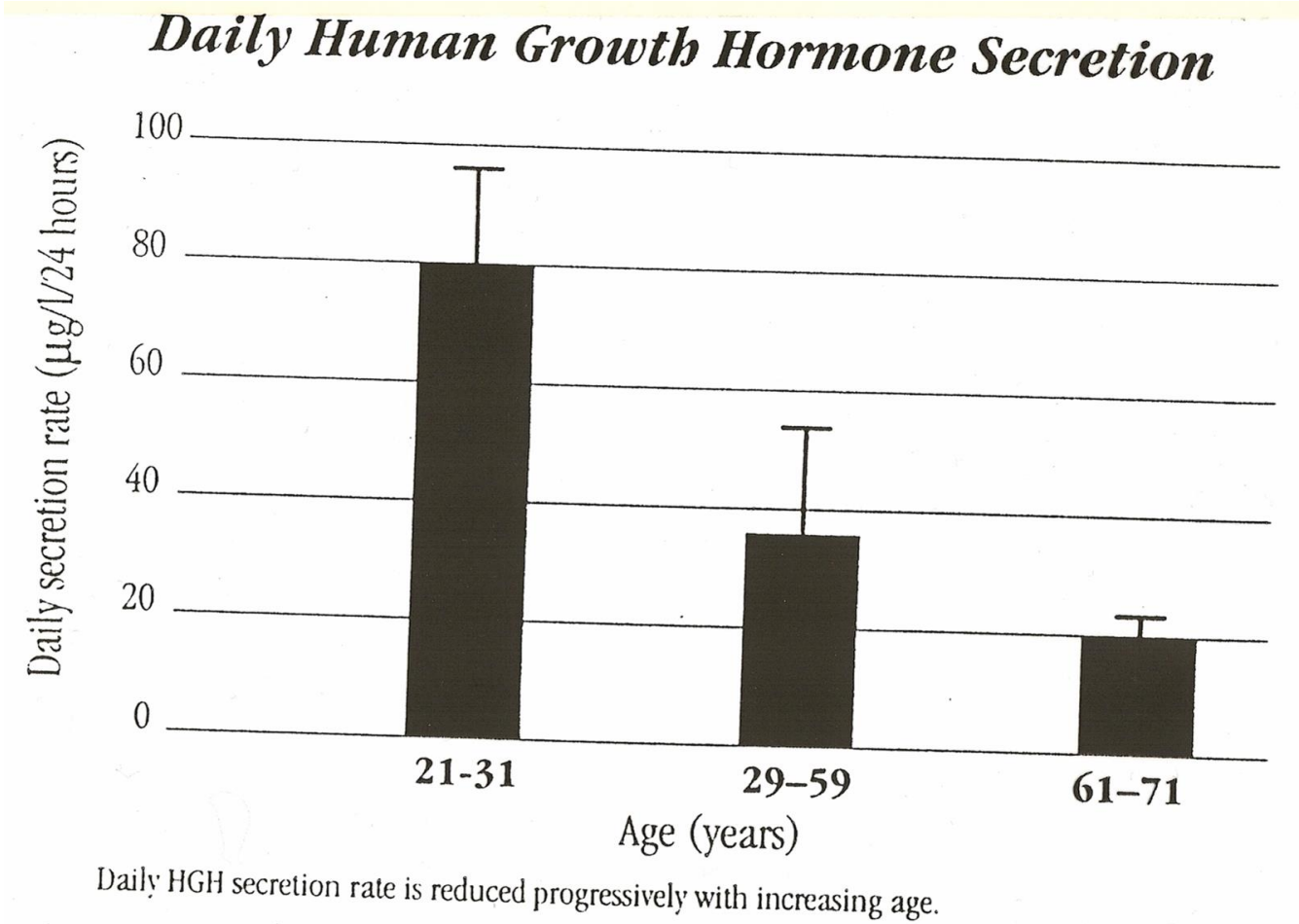
Oral GH Secretagogues Can Return IGF-1 To Age 35 Levels – 275 ng/mL



Daily HGH secretion rate is reduced progressively with increasing age.

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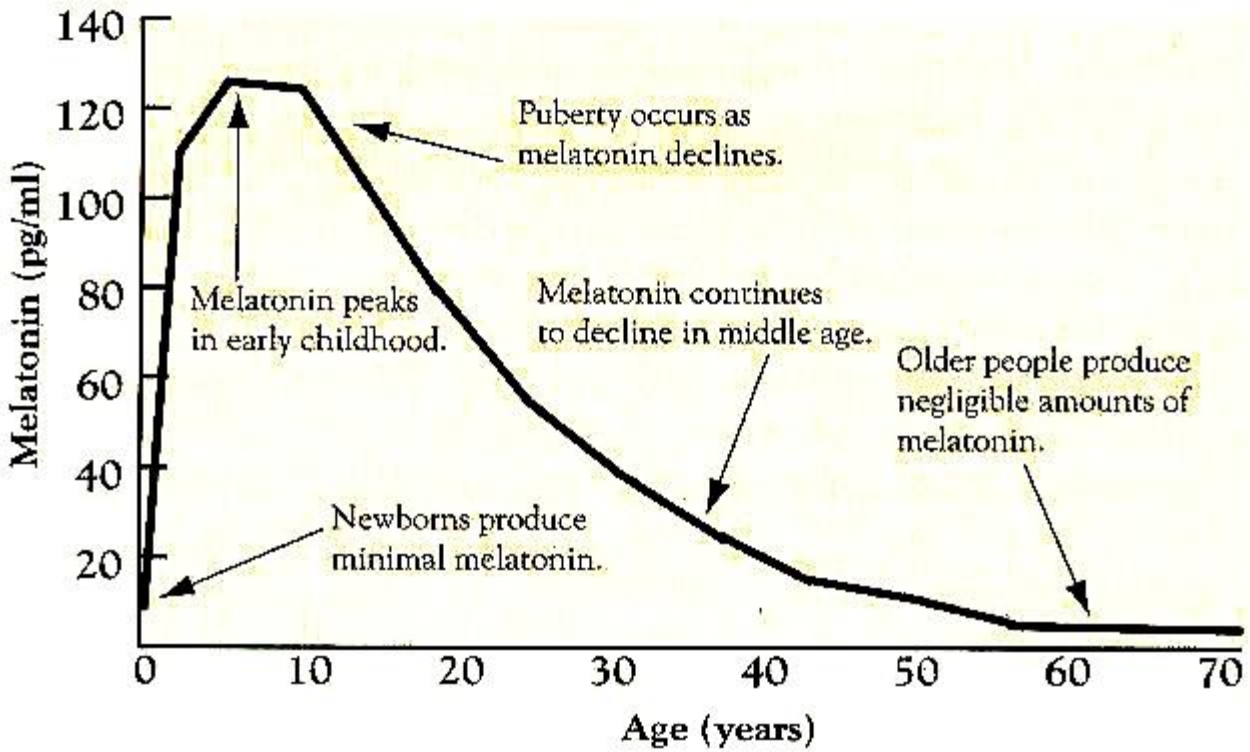
Age-Related Decline In Melatonin



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Symptoms and Signs of Andropause

1. Prostate enlargement
2. Erectile dysfunction and lower libido
3. Loss of lean Mass
4. Increased fat mass
5. Reduced bone mass
6. Loss of energy and cardiovascular decline

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- Many physicians prescribe **testosterone** replacement therapy, but this may hasten initiation, promotion and progression of **prostate cancer** – 2nd leading cancer death.

- Some physicians recommend **growth hormone** injections, but this can lead to diabetes, cardiovascular complications, and cancer

- Some physicians prescribe **DHEA,** but this can trigger prostate cancer promotion and progression

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Natural Strategies To Combat Andropause:

1. Low fat diet – atherosclerosis, erectile function
2. Endurance exercise – abdominal obesity, diabetes, erectile function
3. Resistance training – preserve lean mass, and metabolic rate, bone mass
4. Adequate protein for lean mass gains (.5-.6 gms/lb body weight)
5. Creatine Monohydrate (and maybe Branched-chain Amino Acids)
6. Strategies to Protect the Prostate Gland – more details to follow
7. Natural Sexual Performance Supplements – more details to follow

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Natural Supplements and Sexual Dysfunction (SD)

1. Muira Puama (Brazilian plant)

*European explorers brought it to Europe

*Aphrodisiac and nerve stimulant

Dosage:

*1000-1500 mg per day (single intervention)

*Listed in British Pharmacopoeia (for impotence)

*Male Study – Inst of Sexology – excellent results (libido, freq of intercourse, correction of ED

*Herbal Vx helped women with low libido

2. Tribulus Terrestris (punture vine)

- Used in Europe and Asia
- Increases testosterone (?) – unlikely as SD effect is quite immediate
- Increases nitric oxide (vasodilation)
- Protodioscin and other saponins (active ingredients)

- **Dosage:** 750-1500 mg per day (st grade of 40-45% saponins)

- Angina studies (improve ECG)

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*No side effects noted or drug-nutrient interact

*Saponins also lower cholesterol (block cholesterol absorb and increase cholesterol excretion via bile

*Anti-inflammation (COX-2 inhibitor), no damage to intestinal tract

*Contains beta-sitosterol – blocks DHT production

*Also increased female libido (hormonal changes and clitoral sensitivity)

3. Damiana (Mexico, Central America and Caribbean)

*Shown to increase sensitivity of sex organs via mild irritant effect

*Mild GI- upset on occasion

Dosage: 200-300 mg per day, usually with other herbs

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4. Epimedium (Horny Goat Weed)

*Often prescribed by Chinese doctors as libido enhancer for men and women

*Chinese farmers noted grazing goats increased copulation behavior

*May reduce cortisol in stressed individuals to enhance libido, but other mechanisms likely such as altering neurotransmitters (dopamine, serotonin)

Epimedium Dosage – 100 mg, three times per day (std to 10% icariin flavonoids)

No side effects noted at recommended dosage

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5. Avena Sativa (Wild Oat)

Seeds and stem used for supplementation

*Contains many constituents (e.g. saponins, flavonoids, alkaloids)

*Increases tactile sensation, increasing pleasure

*Men – 22% increase in sensation, Women – 15% increase in genital sensation and 29% increase in frequency of orgasm

Dosage: 130 mg per day

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More Dangerous Herbs

1. Yohimbe – contains alkaloid that increased vasodilation via effects on nervous system

Side Effects:

Anxiety, panic attacks, hallucinations, hypertension, tachycardia, dizziness, HA, skin flush, aggravate kidney and psychological problems

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More Dangerous Herbs

FDA – classified as unsafe herb, should only be taken under supervision

OTC Yohimbe is missing yohimbine alkaloid, which must be present as 6% extract to be effective in ED (34-43% success rate)

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More Dangerous Herbs

2. Ginkgo Biloba Extract

- High success rate with ED, due to vasodilation and anti-coagulant effects (atherosclerosis and diabetics)
- Dosage – 60-80 mg, three times per day
- Risk of bleeding disorder (prothrombin time)
- Increased risk with other anti-coagulant drugs
- Std to 24% flavone glycosides & 6% terpenes

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More Dangerous Herbs

3. Ginseng
   Increases sperm count and motility
   Increases free testosterone, DHT, FSH, LH
   May increase nitric oxide

Study – 1800 mg per day (3 months) improved male libido and improved ED)

Side Effects:

1.May interfere with antidepressant and mood drugs causing mania
2.Can reduce effects of anti-coagulant drugs
3. Dangerous to combine with Digitalis

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More Dangerous Herbs

4. Cordyceps – mushroom that grows on caterpillar at high altitudes

Sex enhancement qualities (Venix – GBE, L-Arg and Cordyceps) –34% improvement ED

Side Effects:

1. Acts as anti-coagulant and may increase bleeding

2. May interfere with mood drugs

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More Dangerous Herbs

5. L-Arginine – at high dosages can be converted into nitric oxide

2800 mg per day, 2 weeks – improved ED and performance (also 1670 mg per day study)

Side Effects:

1. Anti-coagulant – may increase bleeding

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Example of Anti-Aging Sexual-Enhancement Supplement

– for men and women

3-capsules contain:

1.Tribulis Terrestris – 1500 mg
2. Muira Puama – 375 mg
3. Epimedium – 15 mg
4. Damiana – 37.5 mg
5. Avena Sativa – 30 mg
6. Maca root – 375 mg

Also consider natural agents providing L-dopa (Mucana pruriens) and THC oil

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Prostate Gland

Aging, Enlargement And Risk Of, And Adjunctive Management Of Prostate Cancer

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-Prostate Aging: Enlargement and Cancer

- BPH affects 50-60% of men 40-59 yrs, and 90% of men by age 80
- A number of factors combine to increase DHT levels in male prostate cells
- DHT increases cell division rate leading to enlargement and increased cancer risk

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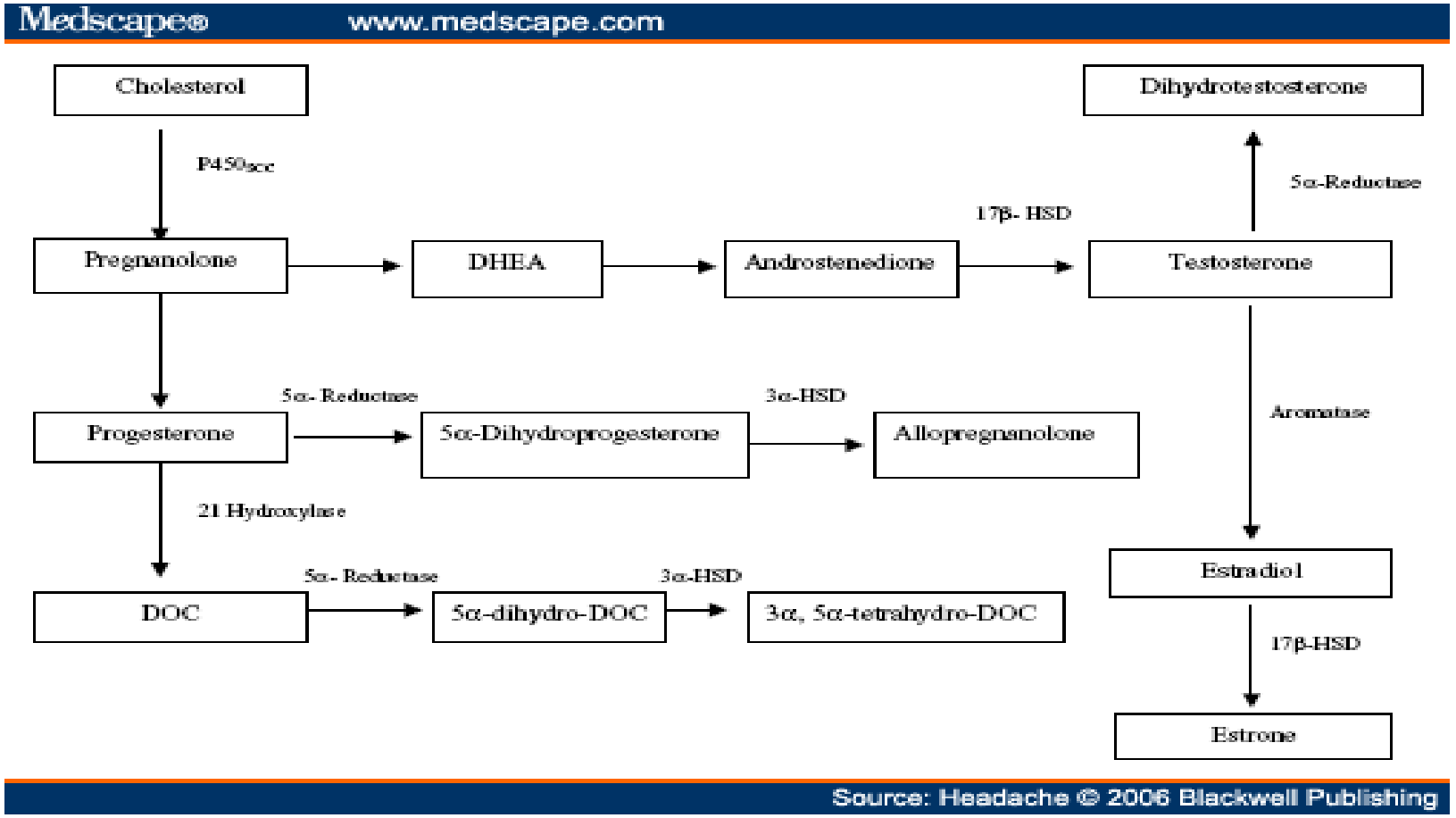
Steroid Synthesis Pathways (note DHT production)



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DHT and Prostate Cancer Link

- **Andropause: Hormonal Changes Affecting Prostate:**
  - Lower blood testosterone, but increased conversion to DHT in prostate
  - Rise in estrogen, prolactin, LH and FSH
  - Elevated estrogen decreases DHT breakdown

More Evidence:

- Prostate cancer is known to be hormone-dependent and rarely develops in **castrated men** (Cancer Research UK.org)
- Men who **lack DHT** (5 alpha-reductase absent) do not develop prostate cancer
- **Eunichs** - (castrated boys who provide lifelong servant-like or servile tasks to the hierarchy in cultural or religious practices) - do not develop prostate cancer

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DHT: Enlargement and Cancer Risk

- DHT:
  - Increases prostate cell division
  - Increases spread of prostate cancer
  - Increases oxidative stress to prostate cells

  - Hypercholesterolemia and hyperlipidaemia have been associated with an increased risk of prostate cancer (stimulate production of testosterone ?)

- Bravi, F., et al., Self-reported history of hypercholesterolaemia and gallstones and the risk of prostate cancer. Ann Oncol, 2006.
- Kaye, J.A. and H. Jick, Statin use and cancer risk in the General Practice Research Database. Br J Cancer, 2004. 90(3): p. 635-7

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Prostate Enlargement (BPH)

Prostate Anatomy and Functions:

- The prostate gland makes and stores **seminal fluid.**
- Located in the pelvis, under the urinary bladder and in front of the rectum.
- The prostate surrounds part of the urethra
- Thus, prostate enlargement can impair urine stream, produce frequent urination with incomplete voiding of the bladder, and produce ejaculation problems and pain

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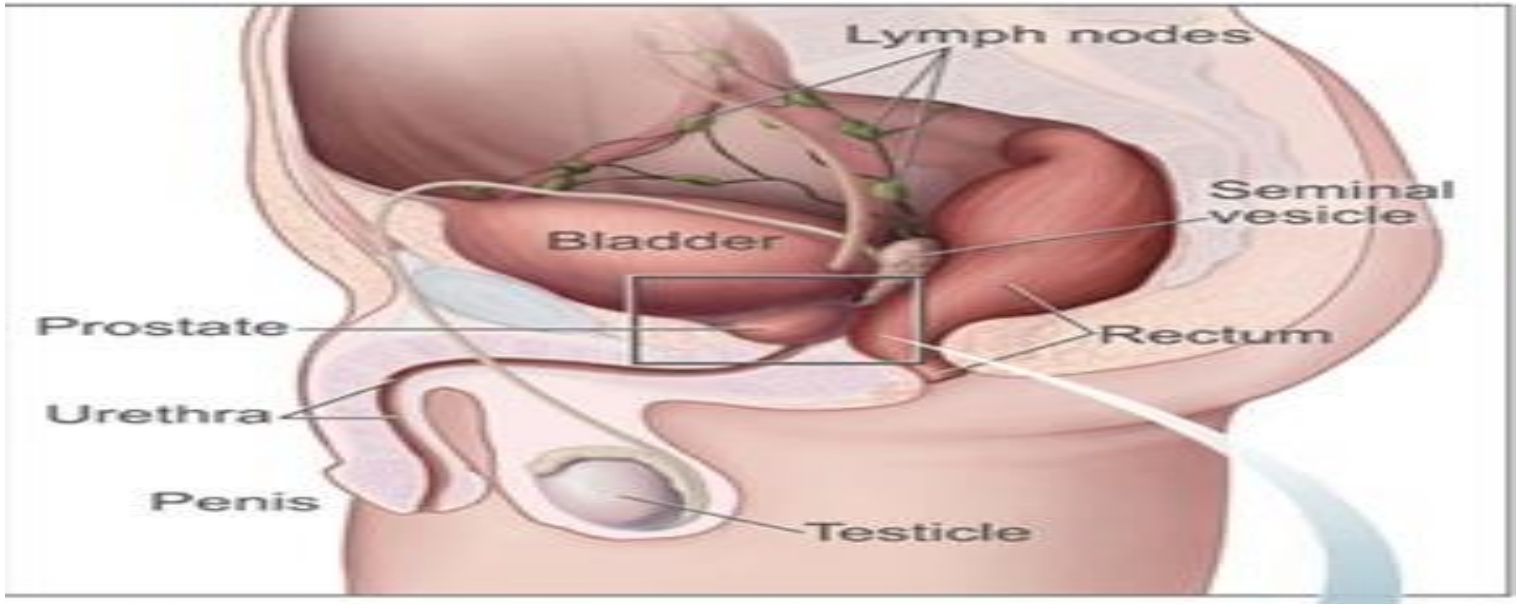
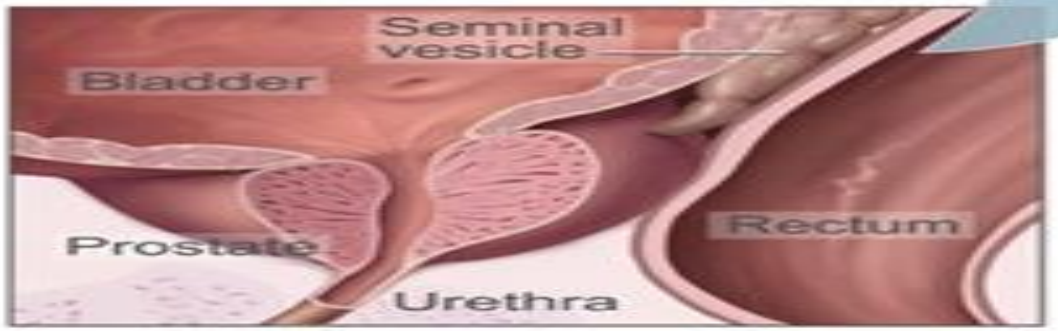
Prostate and Urine Stream



This shows the prostate and nearby organs.



This shows the inside of the prostate, urethra, rectum, and bladder.

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Additional Prostate Facts

- The prostate contains many small glands, which make about twenty percent of the fluid constituting semen.

- **In prostate cancer the cells of these prostate glands mutate into cancer cells**

- The prostate glands under influence of androgens, to work properly – but can also be overstimulated.

- Androgens include testosterone, which is made in the testes; dehydroepiandrosterone, made in the adrenal glands; and dihydrotestosterone, which is converted from testosterone within the prostate itself. (5 alpha –reductase enzyme)

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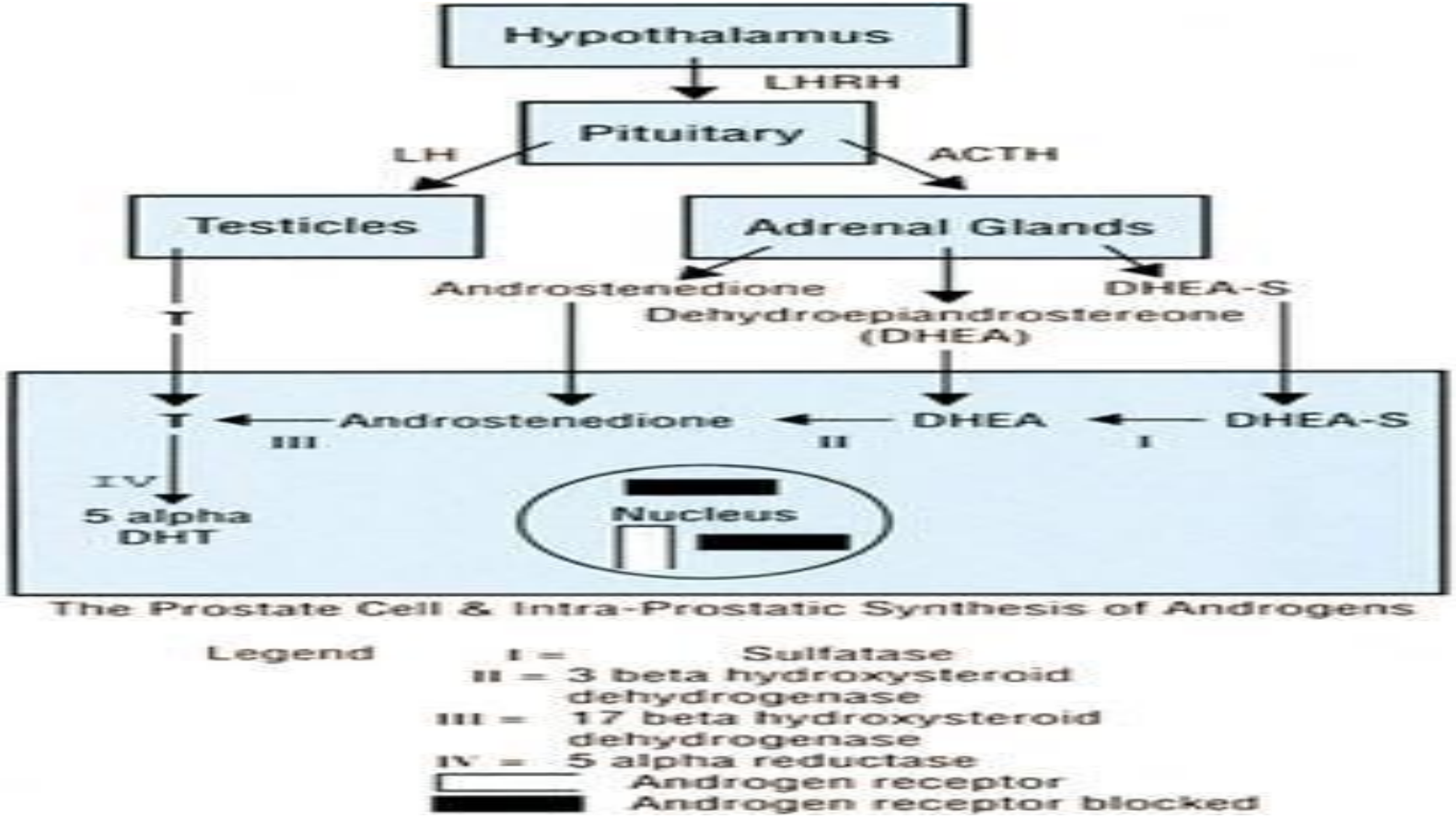
The Prostate Converts DHEA, Androstenedione and Testosterone Into Dihydrotestosterone: Over stimulation by androgens appears to increase risk of BPH and cancer



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Reversing BPH With Natural Supplements

- 1. Saw Palmetto
  - 160 mg, twice per day-std 85-90% FA & Sterols
  - As effective as Proscar, possibly better
  - Fewer side effects (erectile dysfunction)
  - Action: inhibits 5-alpha-reductase enzyme, androgen blockade, estrogen blockade (phytoestrogen), anti-inflamm (PG-2)
  - Berries only 1% FA and Sterols

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Reversing BPH

- 2. Pygeum Africanum (bark of tree)
  - 100-200 mg-std to 12-14% triterpenes
  - Action: decreases blood levels of LH, prolactin, which increase uptake of testosterone by prostate, reduces prostate synthesis of cholesterol (statin drugs shown to reduce BPH)

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Reversing BPH

- 3. Beta-sitosterol
  - Dosage: 65 mg, twice per day, or 20 mg, three times per day
  - Action: inhibits 5-alpha-reductase enzyme, blocks estrone synthesis in fat cells, apoptosis of prostate cancer cells (via signal transduction caspase 8 and 9 pathways)

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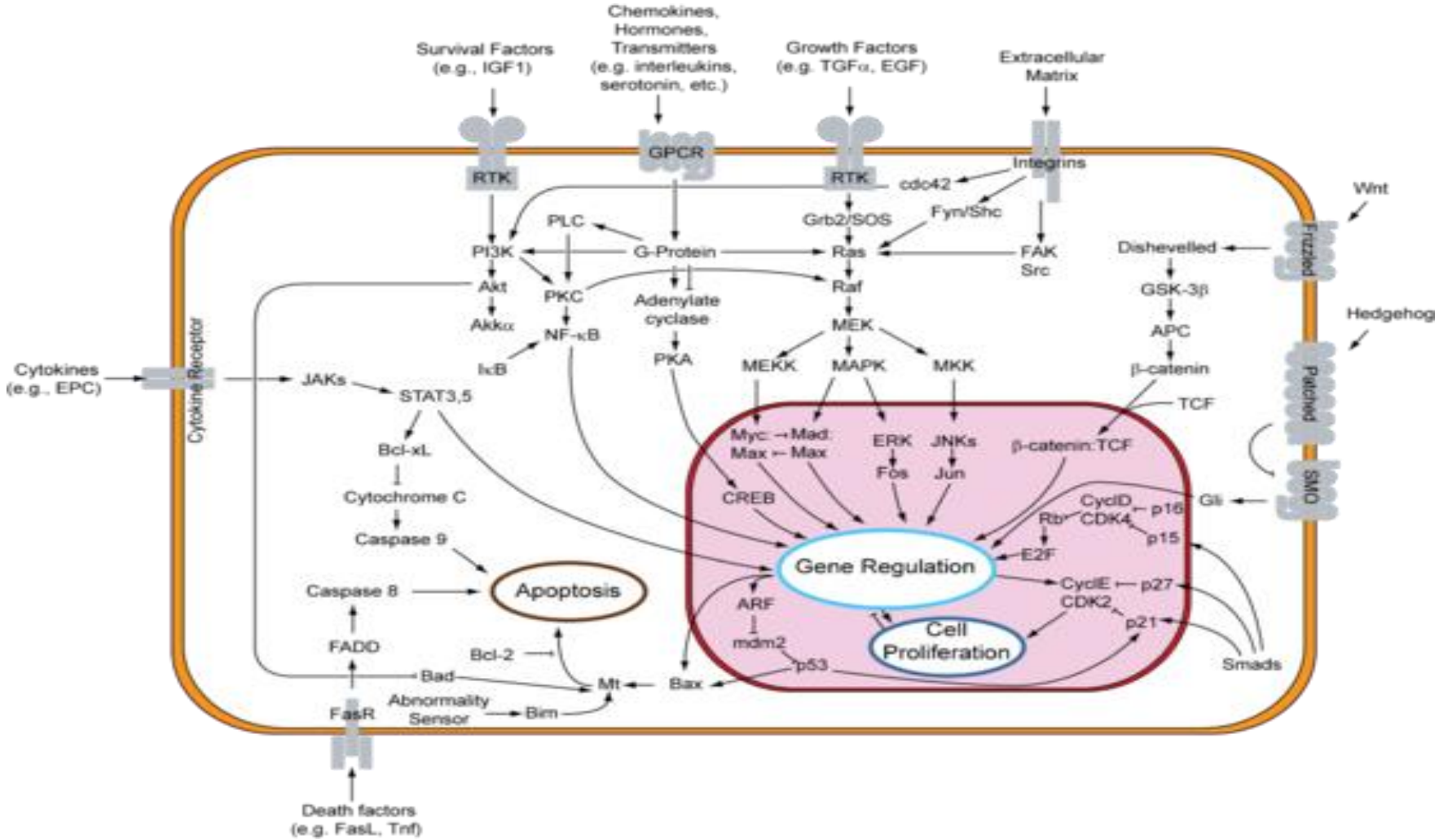
Caspase 8 9 Apoptosis Pathways



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Reversing BPH

- 4. Soy Isoflavones
  - 25-75 mg per day associated with decreased prostate cancer and enlargement
  - Actions: inhibits 5-alpha-reductase enzyme, apoptosis of prostate cancer cells, inhibit proliferative enzymes, increase SHBG, inhibits estrone synthesis in fat cells, antioxidant, anti-angiogenisis, androgen and estrogen blockade

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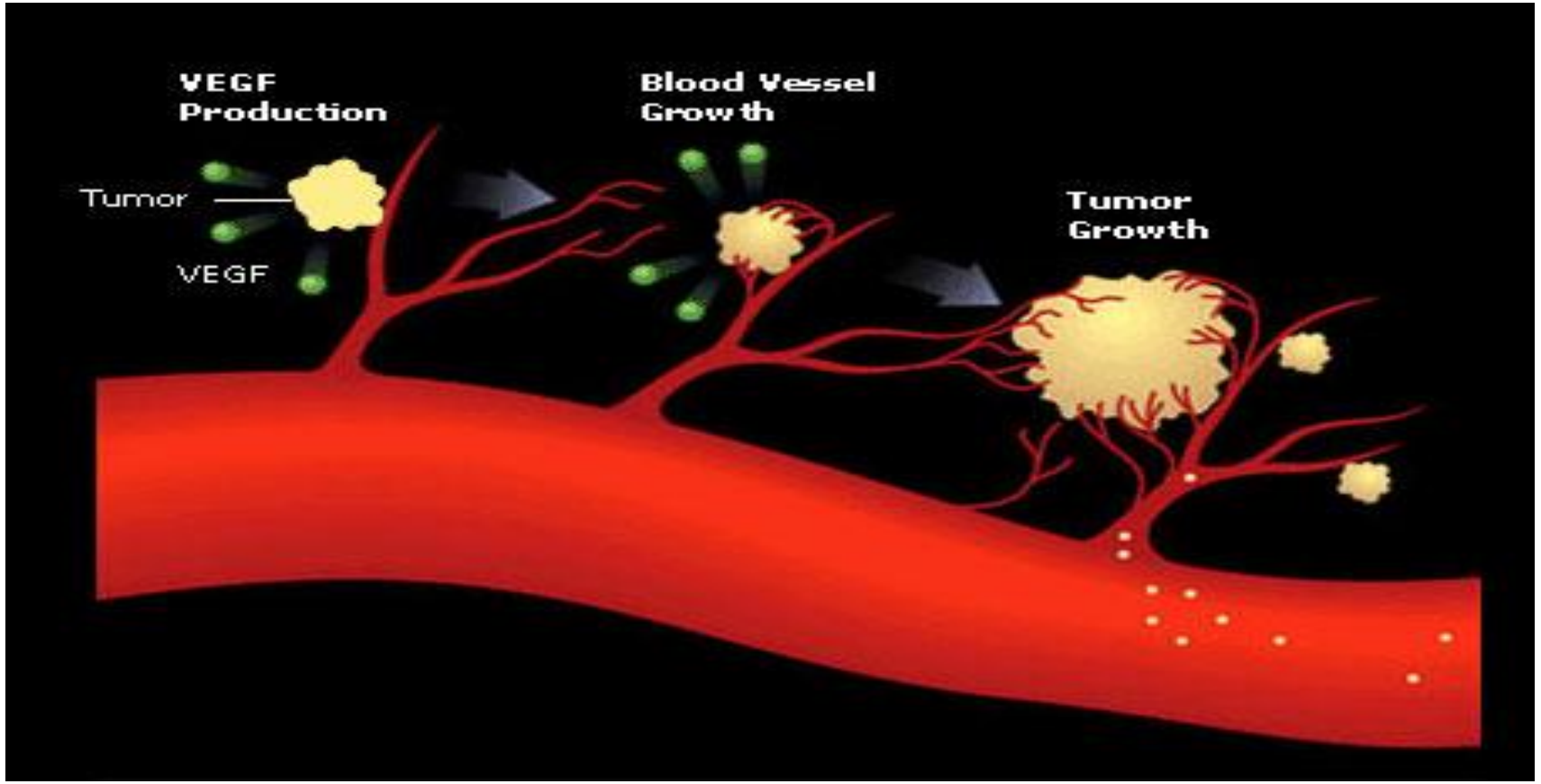
Anti-angiogenesis (VEGF)



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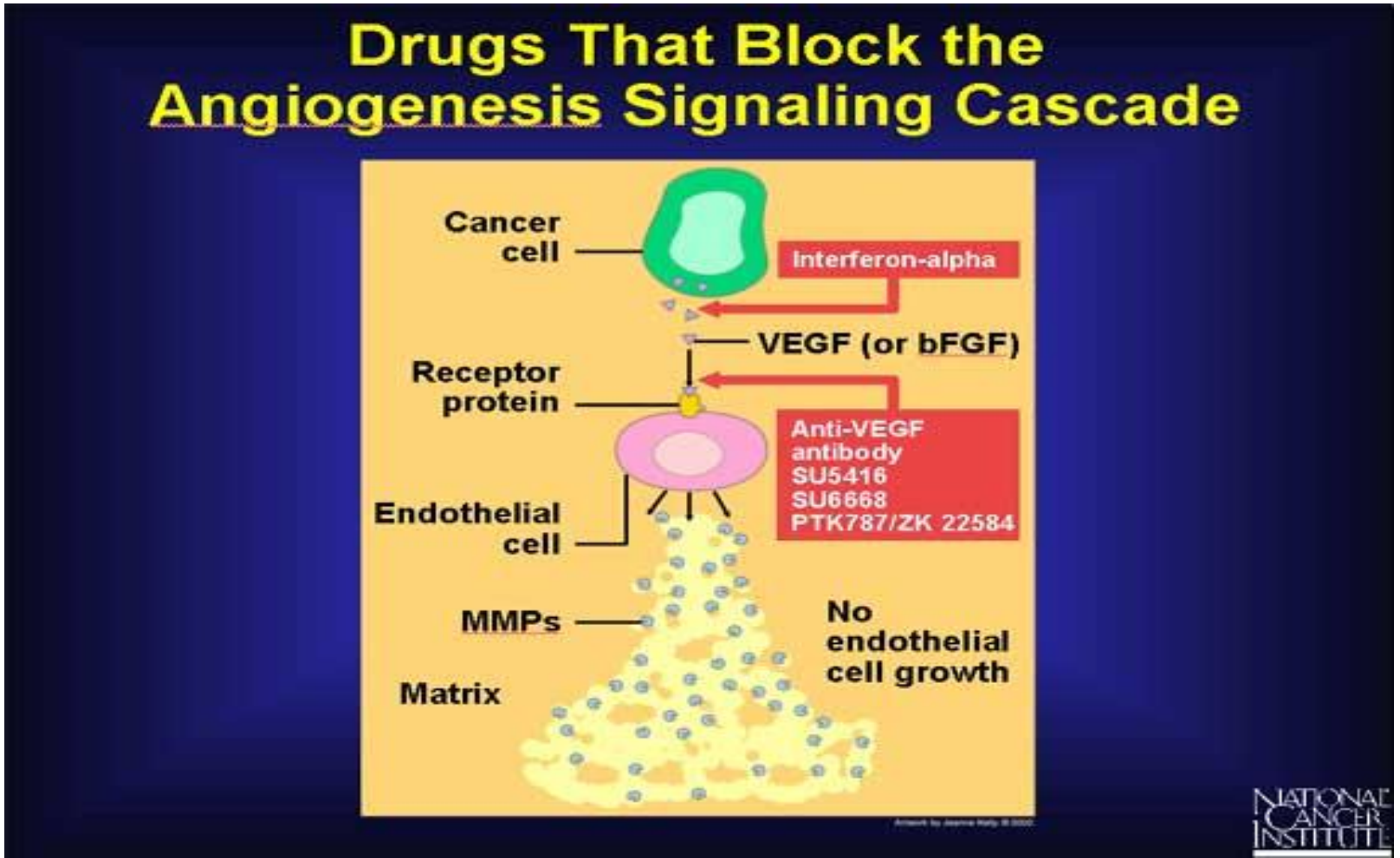
Avastin and Related Drugs



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Reversing BPH

- 5. Stinging Nettle (Urtica dioica)
  - Action: inhibits binding of DHT to cell nucleus
  - Dosage: 20-60 mg usually in prostate combo products

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Reversing BPH

- 6. Cernilton (rye grass pollen extract)
  - Contains hydroxamic acid and other bioactive agents, which reduce prostate inflammation
  - Hydroxamic acid shown to inhibit replication of prostate cancer cells
  - Dosage: 63 mg, twice per day

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Prostate Cancer

- BPH incidence is canary in the mine shaft (low incidence BPH in Asia compared to west)
- Rate of prostate CA is 80% higher in NA than Asia and some other countries
- However, 13-32% of men in all countries have prostatic neoplasm by ages 45-50

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Prostate Cancer

- Low-risk countries show up to 80% lower progression to significant disease
- One in 7 men in Canada develops prostate CA, and one in 27 men in Canada will die from it
- Prostate is second leading cause of CA death after lung CA in Canadian men

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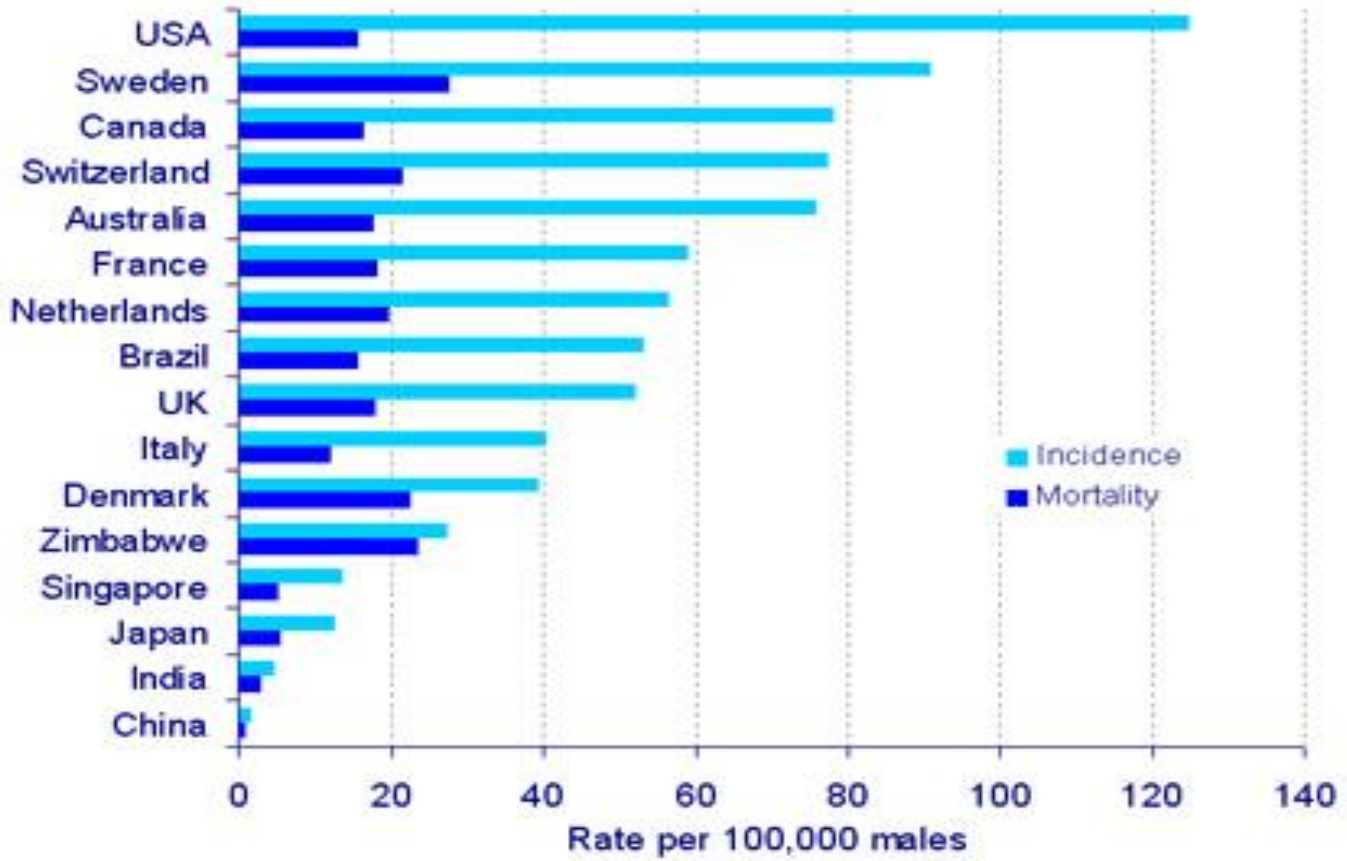
Prostate Cancer Stats Around the World



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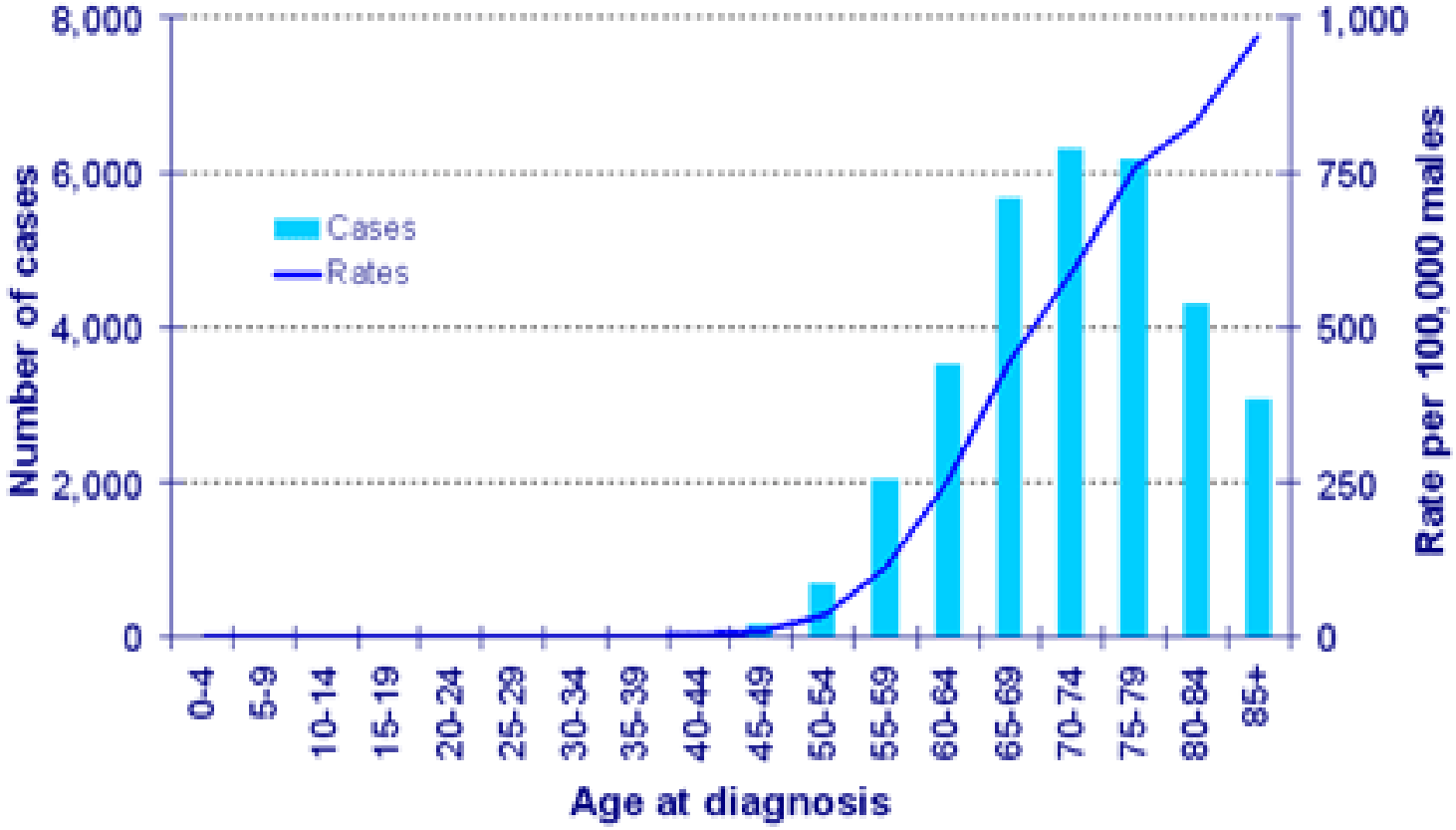
UK Prostate Cancer Rates

Figure 4.1: Numbers of new cases and age-specific incidence rates, prostate cancer, UK 2002



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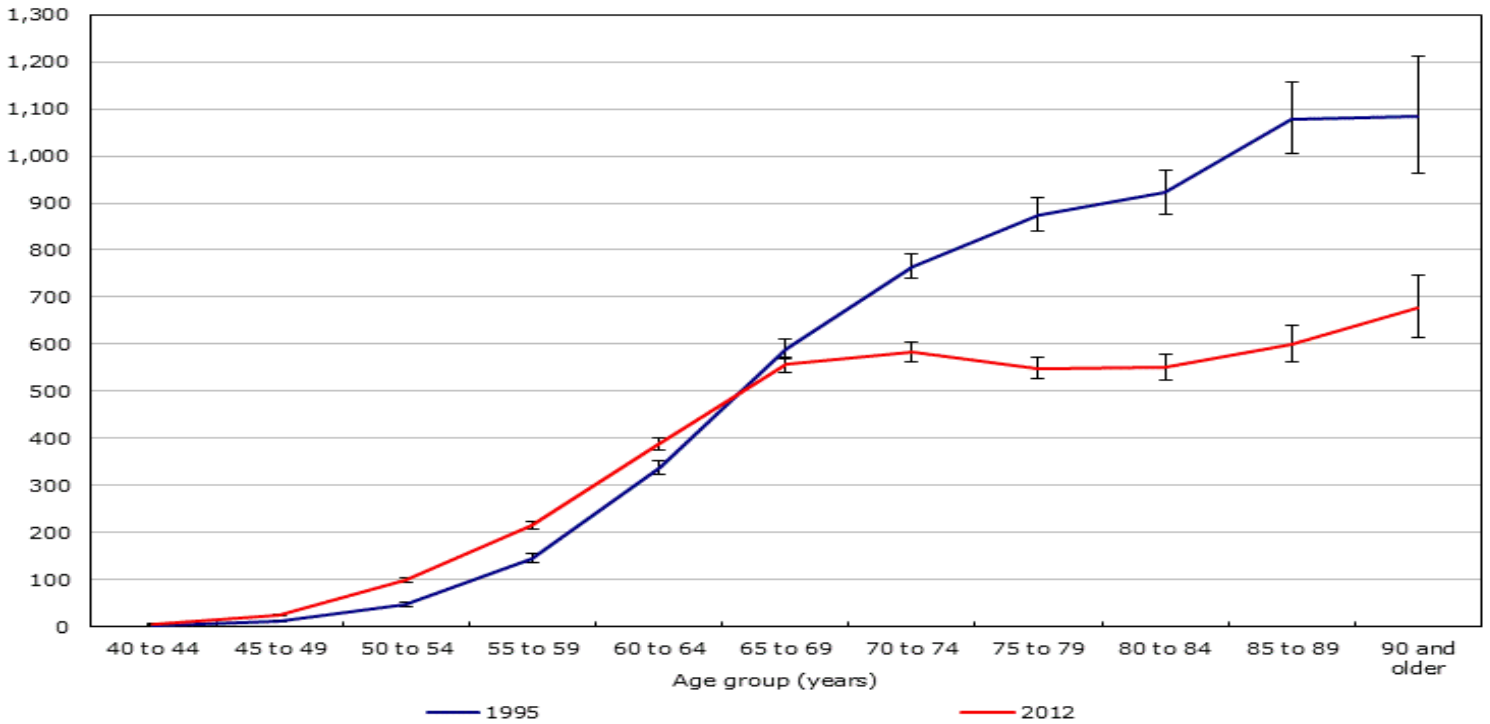
Canada Prostate Cancer Trends

Chart 4
Age-specific prostate cancer incidence rates, ages 40 and older, Canada, 2012 versus 1995
rate (per 100,000 men)



Note: 95% confidence intervals are denoted by vertical bars overlaid on the trend lines. They indicate the degree of variability in the estimates. Rates are based on counts that have been randomly rounded to a base of five.
Source: Statistics Canada, 1995 and 2012, Canadian Cancer Registry.

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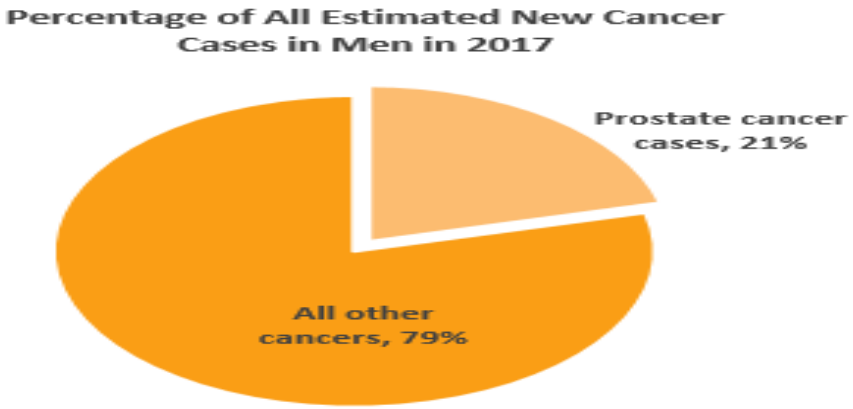
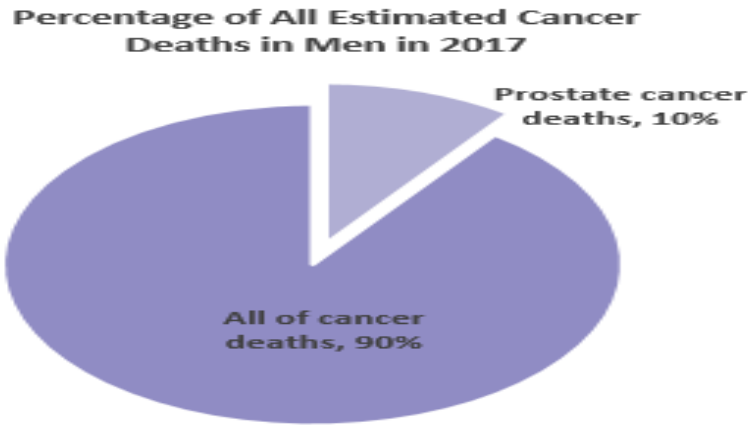
Canadian Prostate Cancer Incidence and Deaths





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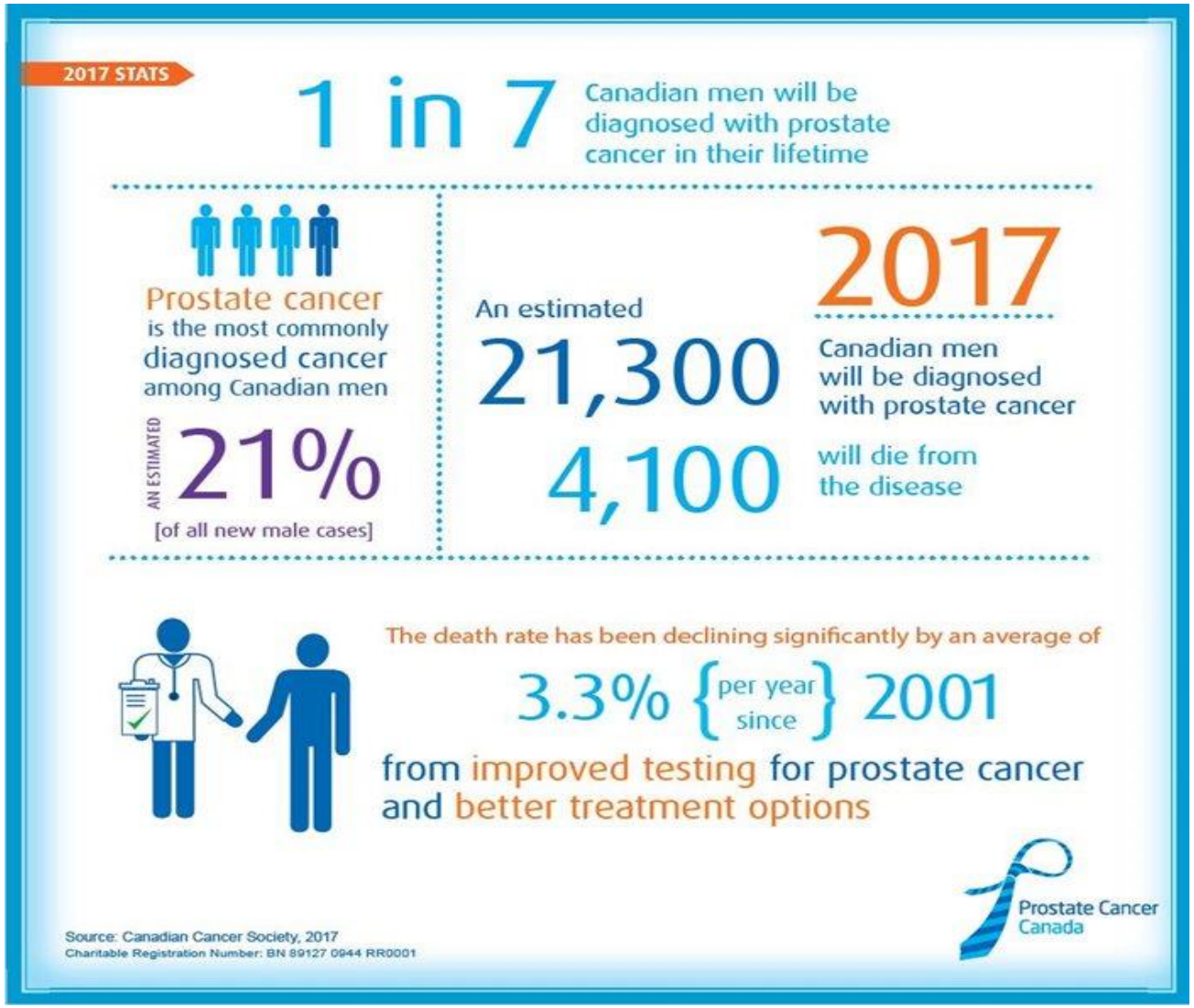
Prostate Cancer Canada



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Age Group: 50-69yrs (both sexes)

- Prostate Cancer – 18% of all newly diagnosed cancers
- Breast Cancer – 14% of all newly diagnosed cancers
- Lung Cancer – 14% of all newly diagnosed cancers
- Colorectal Cancer – 12% of all newly diagnosed cancers

Total = 58% of all newly diagnosed cancers involve cancer types in which their development is known to be highly influenced by diet and lifestyle, and where early detection is available

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Prostate CA is Adenocarcinoma

- Prostate cancer is classified as an adenocarcinoma, or glandular cancer, that **begins when normal semen-secreting prostate gland cells mutate into cancer cells.**

- The region of prostate gland where the adenocarcinoma is **most common is the peripheral zone**.

- Initially, small clumps of cancer cells remain confined to otherwise normal prostate glands, a condition known as carcinoma in situ or prostatic intraepithelial neoplasia (PIN). Although there is no proof that PIN is a cancer precursor, it is closely associated with cancer.

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- Over time these cancer cells begin to multiply and spread to the surrounding prostate tissue (the stroma) forming a tumor.

- Eventually, the tumor may grow large enough to invade nearby organs such as **the seminal vesicles** or **the rectum**, or the tumor cells may develop the ability to travel in the bloodstream **and lymphatic** system.

- Prostate cancer is considered a malignant tumor because it is a mass of cells which can metastasize, **most commonly to bones** (**often vertebrae)**, lymph nodes, **rectum, and bladder.**

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Genetic Risk Factors For Prostate Cancer:

- Studies of twins in Scandinavia suggest that up to forty percent of prostate cancer risk can be explained by inherited factors **(up to 40% in cases under 45 years of age – closer to 25% of total cancer cases).**

- However, no single gene is responsible for prostate cancer; many different genes have been implicated. Two genes (*BRCA1* and *BRCA2)* that are important risk factors for ovarian cancer and breast cancer in women have also been implicated in prostate cancer.

- The BRCA1 and BRCA2 are tumor suppressor genes involved in DNA repair, DNA stabilization, inhibiting uncontrolled cellular replication, helping to induce apoptosis of damaged, infected or cancerous cells.

(Lichtenstein, P; Holm NV; Verkasalo PK; Iliadou A; Kaprio J; Koskenvuo M; Pukkala E; Skytthe A; Hemminki K (July 13 2000). "Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland". *N Engl J Med* **343** (2): 78–85).

(Struewing, JP; Hartge P; Wacholder S; Baker SM; Berlin M; McAdams M; Timmerman MM; Brody LC; Tucker MA (May 15 1997). "The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews". *N Engl J Med* **336** (20): 1401–8.).

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Genetic Risk Factors – Continued

Having a brother or father with prostate cancer doubles risk (a brother is a stronger risk indicator)

- Having a mother with breast cancer may increase risk (BRCA1 and 2 mutations)

- Blacks have a higher incidence prostate cancer incidence than caucasians (possibly related to vit D levels or vit D polymorphism)

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Prostate Cancer Screening - PSA

- The 2007 National Comprehensive Cancer Network (NCCN) guideline recommends *offering* a **baseline** PSA test and DRE at ages 40 and 45 and **annual** PSA testing and DRE beginning at age 50 through age 80, along with information on the risks and benefits of screening.

- However, annual PSA testing and DRE should begin at age 40 for African-American men, men with a family history of prostate cancer, and men with a PSA ≥ 0.6 ng/mL at age 40 or PSA > 0.6 ng/mL at age 45

- Biopsy is **recommended** if DRE is positive or PSA ≥ 4 ng/mL, and biopsy **considered** if PSA > 2.5 ng/mL or PSA velocity ≥ 0.35 ng/mL/year when PSA ≤ 2.5 ng/mL.

- Some U.S. radiation oncologists and medical oncologists who specialize in treating prostate cancer recommend obtaining a baseline PSA in all men at age 35 or beginning annual PSA testing in high risk men at age 35.

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- However, PSA test may lead to over diagnosis, with additional testing and treatment. Follow-up tests, such as prostate biopsy, may **cause pain, bleeding and infection (or encourage spread of existing cancer).**

- Prostate cancer **treatments** may cause **urinary incontinence and erectile dysfunction**, which affect quality of life. (radiation/ surgery – localized disease; castration and testosterone ablation Rx in metastatic disease)

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- In most cases prostate cancer is **slow growing** and the person usually dies from other causes.

- Therefore, essential that risks and benefits of diagnostic procedures and treatment be carefully considered before PSA screening. (But prostate cancer is the second leading cause of cancer death in men after lung cancer)

- Since no firm evidence or general agreement that benefits of PSA screening outweigh the harms, major scientific and medical organizations recommend that clinicians use a process of shared decision-making that includes discussing with patients the risks of prostate cancer, the potential benefits and harms of screening, and involving the patients in decision

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Prostate Specific Antigen

- The PSA test measures blood level of prostate-specific antigen, an enzyme produced by the prostate. Specifically, PSA is a serine protease that helps liquify gelatinous semen after ejaculation, allowing spermatozoa to more easily navigate through the uterine cervix.

- PSA levels can change for many reasons other than cancer. Two common causes of high PSA levels are **enlargement** of the prostate (benign prostatic hypertrophy (BPH)) and **infection** in the prostate (prostatitis). It can also be raised for 24 hours after **ejaculation** and several days after catheterization of the urethra.

- Measuring the amount of PSA which is free or bound may provide additional screening information, but questions regarding usefulness limit their widespread use

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- Although the DRE only evaluates the back of the prostate, 85% of prostate cancers arise there. Prostate cancer which can be felt on DRE is generally more advanced.

- The use of DRE has never been shown to prevent prostate cancer deaths when used as the only screening test. (by the time you can feel it, its likely too late)

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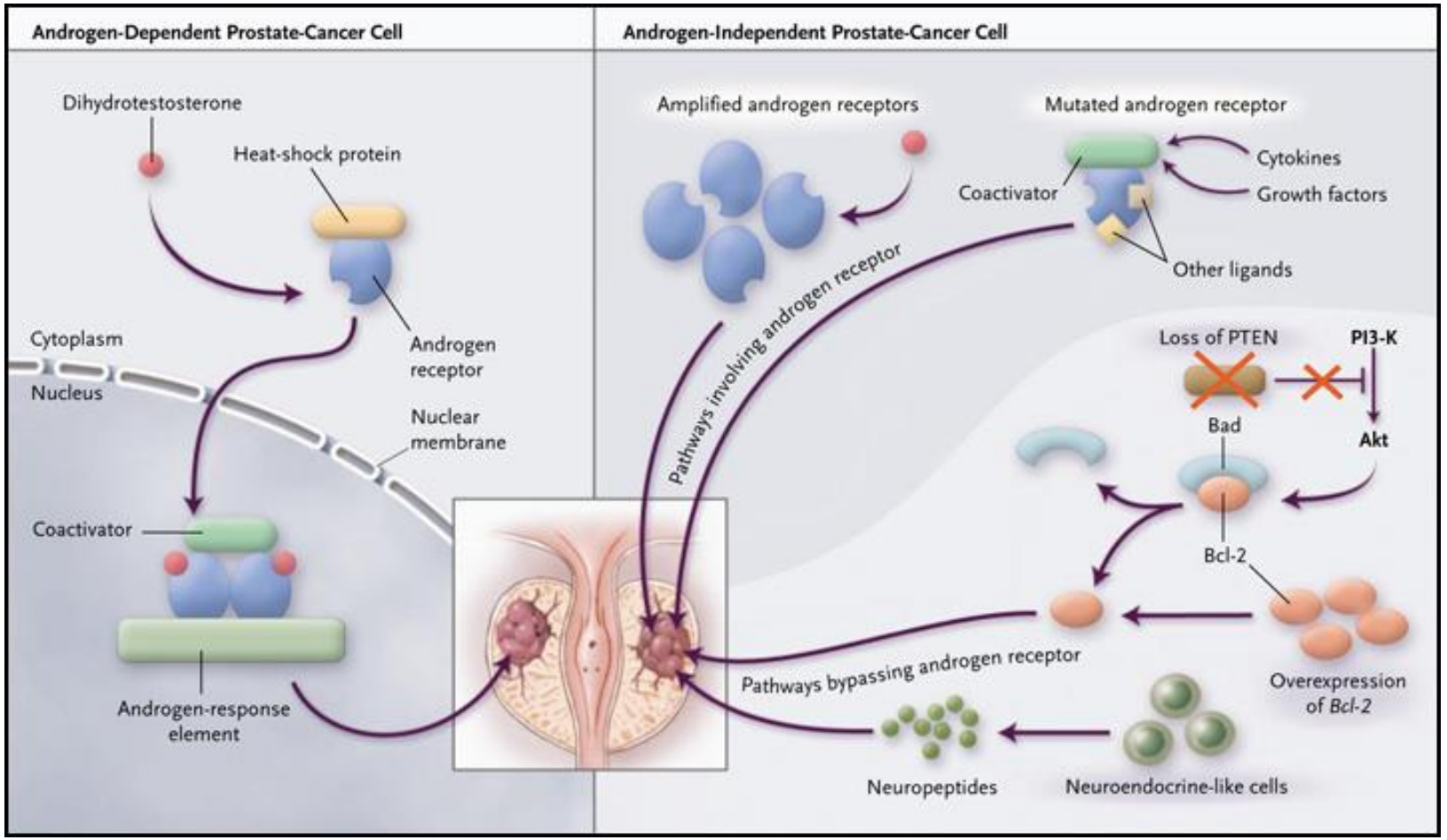
Castration and Testosterone Ablation RX fails after 2 years in Metastatic PC as PC cells switch to non-androgen dep signaling (overexpression Bcl-2 protein)



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Nutrition and Prostate Cancer Prevention

- 75 % of prostate cancer avoidable via better nutritional behaviors – W Willett (1996)

  Dietary Factors:

  1. Alcohol – as few as 3 drinks/wk assoc with 61% increase in prostate CA (Harvard Alumni)
     - Followed 7,612 men from 1988-1993 (mean age-66.6 yrs)

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Prostate Cancer

2. Heterocyclic amines – pan-fried meats shown to increase prostate cancer risk by two-fold (U.S. black Americans have twice the prostate cancer rates as caucasians)

Heterocyclic amines are potent mutagens

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Prostate Cancer

3. Saturated Fat – high animal fat diet assoc with prostate CA (HPFS and others)

Saturated fat intake increases testosterone secretion

Asian men go from 2% lifetime risk to 30%, with increase in animal fat intake (migration studies)

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Prostate Cancer

4. Soy Isoflavones – assoc with reduction of prostate CA:
    - Antiproliferative and Apoptosis
    - Increase SHBG
    - Decrease estrone synthesis
    - Antioxidant
    - Anti-angiogenisis
    - Androgen and estrogen blockade

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Prostate Cancer

- Soy Isoflavone Supplementation in Cancer Patients:
  - Cancer letter – reduced tumor size
  - Nutr and Cancer – slows rise of PSA (100 mg isoflavones, twice per day)

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Prostate Cancer

5. Omega-3 Fats – up to 33% reduction in risk with regular fish consumption (Swedish study of 6,000 men in 30 year follow up – The Lancet –2001)

Animal studies support PG-3 protection against prostate CA, and slow growth of prostate cancer cells

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Source: *Clinical Cancer Research*, 2009 *"Dietary Omega-3 Fatty Acids, Cyclooxygenase-2 Genetic Variation, and Aggressive Prostate Cancer Risk"*

Authors: V. Fradet, I. Cheng, G. Casey, J.S. Witte

- Researchers performed a case-control analysis of 466 men diagnosed with aggressive prostate cancer and 478 healthy men. Diet was assessed by a food frequency questionnaire and researchers genotyped nine COX-2 single nucleotide polymorphisms.

- Researchers divided omega-3 fatty acid intake into four groups based on quartiles of intake. Men who consumed the highest amount of long chain omega-3 fatty acids had a 63 percent reduced risk of aggressive prostate cancer compared to men with the lowest amount of long chain omega-3 fatty acids.

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COX Variant – rs4647310

- The researchers then assessed the effect of omega-3 fatty acid among men with the variant **rs4647310** in COX-2, a known inflammatory gene.

- **Men with low long chain omega-3 fatty acid intake and this variant had a more than five-fold increased risk of advanced prostate cancer.**

- **But men with high intake of omega-3 fatty acids had a substantially reduced risk, even if they carried the COX-2 variant.**

Conclusion:

- "The COX-2 inflammatory gene increased risk of disease, but risk was essentially reversed by increasing omega-3 fatty acid intake by a half a gram (500 mg) per day," said Witte. “

- If you want to think of the overall inverse association in terms of fish, where omega-3 fatty acids are commonly derived, the strongest effect was seen from eating dark fish such as salmon one or more times per week."

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Prostate Cancer

6. Indole-3-Carbinol and Cruciferous Vegetables:

Indole-3- Carb shown to inhibit growth of human prostate cancer cells & encourage apoptosis (Oncogene-2001)

Higher intakes assoc with decreased breast, colon and prostate cancer

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Prostate Cancer

7. Prostate Antioxidants:

a) Lycopene – 6.5 mg per day (40% reduction in risk)

c) Selenium – 200 mcg (approx 50% reduction in risk)

d) Soy isoflavones – 25-50 mg per day (up to 80% reduction in risk)

SELECT STUDY – argues against protective effect of vitamin E (400 IU per day), but did not test Vitamin E Succinate.

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Prostate Cancer

8. Vitamin D – blood levels of 85- 110 nmol/L assoc with marked reduction in prostate cancer incidence (800-1000 IU intake/day) – more recently 1200 IU shown to reduce total cancers in postmenopausal women (2007)

Prostate cells convert 25 OH-Vit D into 1,25 dihydroxy-Vit D, which promotes cell differentiation and slows proliferation

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Prostate Cancer

- Prostate cancer cells usually express Vitamin D receptors (even if androgen receptors absent- similar to breast CA model)

- Vitamin D admin to prostate CA cells slows replication rate and increases differentiation

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Prostate Cancer

- Live above 42nd degree latitude should ingest 1000-2000 IU Vitamin D daily to achieve blood level of 85nmol/L.

- Vitamin D suppl safe up to 2,000-4,000 IU per day

- Study showed that 2000 IU vitamin D administered to prostate cancer patients slowed rise in PSA

- We routinely give prostate cancer patients 10,000 – 50,000 IU per day, with blood monitoring of vit D levels

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Prostate Cancer

9. Zinc – prostate contains more zinc than other tissues (also lycopene)

Low zinc intake assoc with BPH

Zinc suppl inhibits DHT formation (25-30 mg per day)

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Prostate Cancer

10. Cardiovascular Fitness- men with a resting heart rate above 80 bts/min shown to have 60% increased rate of prostate CA:

Sympathetic tone appears to increase risk, as elevated blood pressure also assoc with increased risk (increased androgen synthesis by prostate with sympathetic tone)

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Combination Prostate Supplement : Per 2 capsules:

- Saw Palmtto – 640 mg (std 45% FA & S)
- Pygeum Africanum – 200 mg (std 12% terp)
- Beta-sitosterol – 130 mg
- Soy Isoflavones – 25 mg (250 at 10% std gr)
- Stinging Nettle – 60 mg
- Lycopene – 25 mg

- High Potency Multiple Vitamin

- Essential Fatty Acids (fish, flax, borage seed)

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Gleason score: In The Prognosis Of Established Prostate Cancer (BIOPSY PROGNOSTICATOR)

- Named after Donald F. Gleason, M.D., a **pathologist** at the Minneapolis Veterans Affairs Hospital who developed it with other colleagues at that facility in the 1960s.
- A **Gleason score** is given to prostate cancer based upon its microscopic appearance.
- The higher the Gleason score the worse prognosis (more aggressive).
- To assign a Gleason score, a biopsy is performed. This is done either by removing the gland (prostatectomy) or by sampling the gland with a needle introduced through the rectum.
- The Gleason score ranges from two to ten. A Gleason score of two is associated with the best prognosis and a score of ten with the worst.

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Gleason Score by Grade

Gleason scores are associated with the following features:

- Grade 1 - The cancerous prostate closely resembles normal prostate tissue. The glands are small, well-formed, and closely packed
- Grade 2 - The tissue still has well-formed glands, but they are larger and have more tissue between them.
- Grade 3 - The tissue still has recognizable glands, but the cells

  are darker. At high magnification, some of these cells have left the glands and are beginning to invade the surrounding tissue.
- Grade 4 - The tissue has few recognizable glands. Many cells are invading the surrounding tissue
- Grade 5 - The tissue does not have recognizable glands. There are often just sheets of cells throughout the surrounding tissue.

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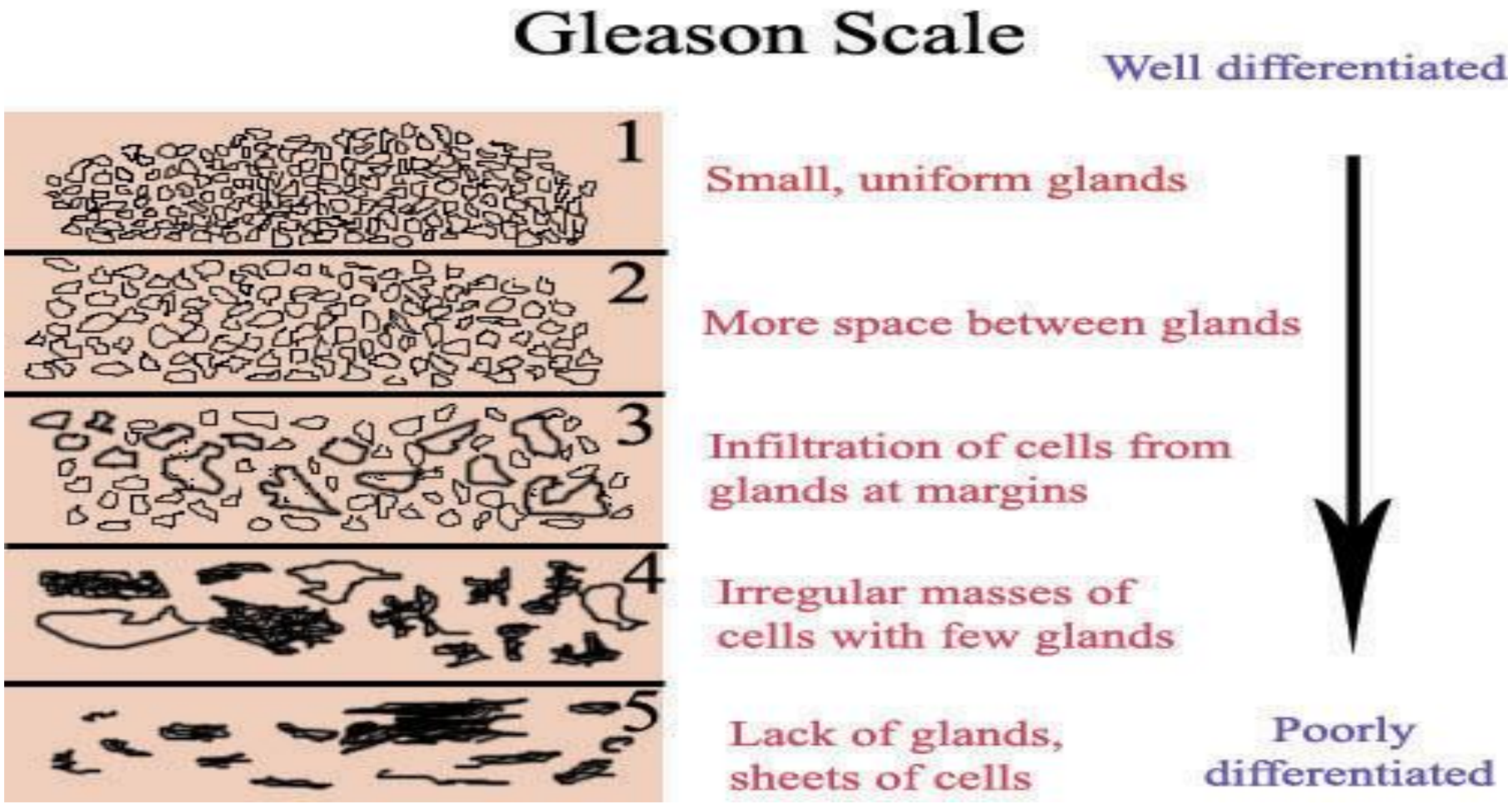
Gleason DF. *The Veteran's Administration Cooperative Urologic Research Group: histologic grading and clinical staging of prostatic carcinoma.* In Tannenbaum M (ed.) Urologic Pathology: The Prostate. Lea and Febiger, Philadelphia, 1977; 171-198.



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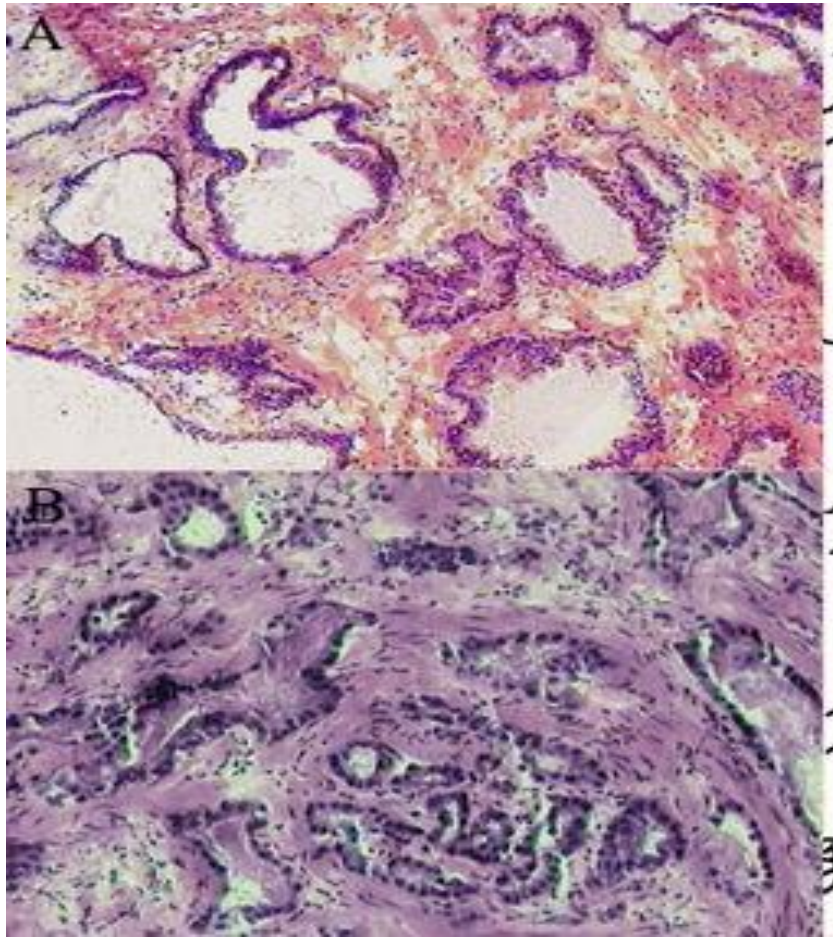
Normal and Malignant Prostate CA Appearance



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Establishing The Final Gleason Score

- A pathologist examines the biopsy specimen and attempts to give a score to the two patterns:
- First - the **Primary Grade,** represents the majority of tumor (has to be greater than 50% of the total pattern seen).
- Second - a **Secondary Grade** - relates to the minority of the tumor (has to be less than 50%, but at least 5%, of the pattern of the total cancer observed).
- These scores are then added to obtain the final Gleason score. For example, a prostate biopsy specimen may exhibit two different patterns, one which is assigned a number two and the other a number three. The final Gleason score in this case would be five.
- Once established the Gleason score helps determine the most appropriate treatment intervention

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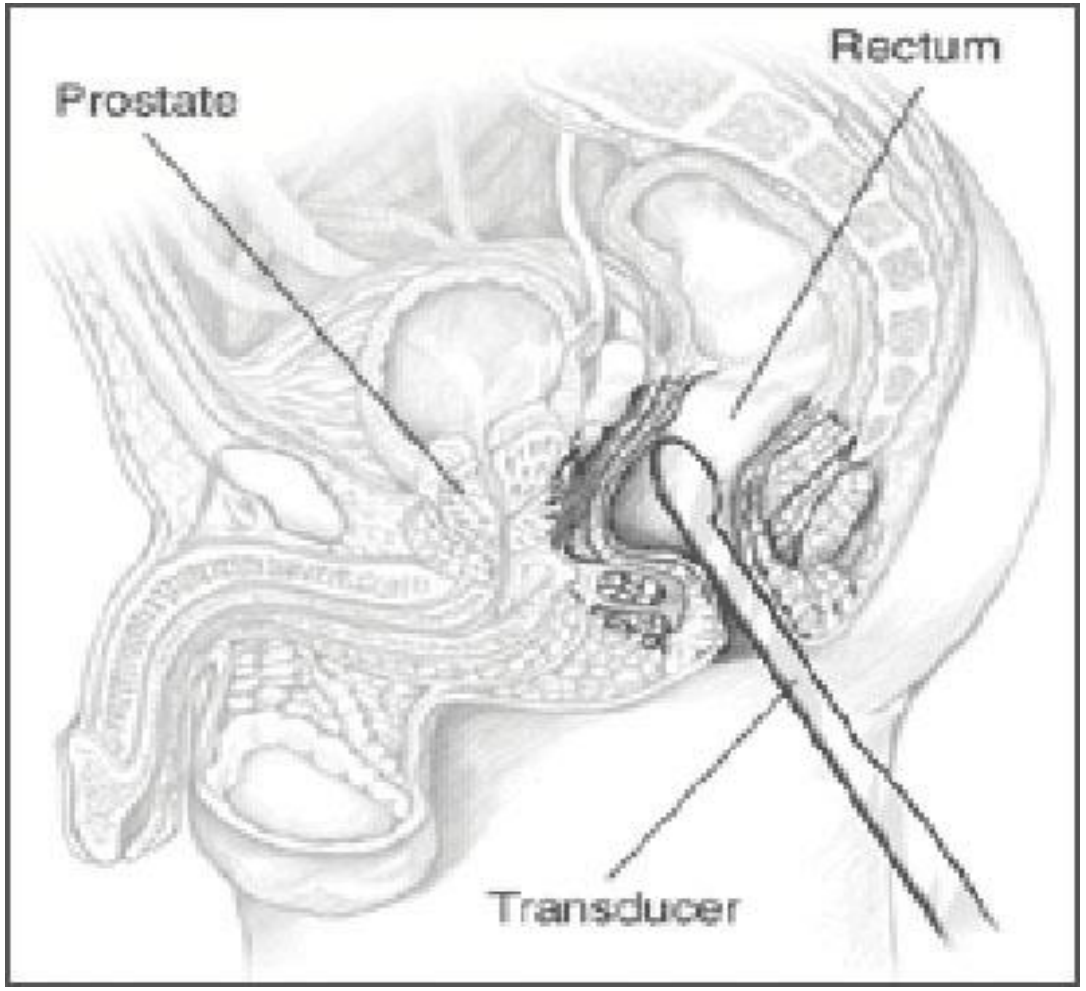
Transrectal Ultrasound of the Prostate (TRUSP) or TRUS

- The transrectal ultrasound involves imaging of the prostate by means of a probe inserted into the rectum that allows visualization of the prostate using sound waves. This method is used by most urologists or radiologists to guide the biopsy needle in order to sample prostate tissue with the intent to diagnose Prostate Cancer (PC). Samples from each section of the prostate are taken (11-multi-site biopsy)

- Most urologists use the TRUSP or TRUS solely for this purpose. However, the TRUSP can provide additional valuable information that includes but is not limited to:
  1. gland volume or GV
  2. areas of abnormal ultrasound pattern termed "hypoechoic" that are of lesser darker and associated with a higher probability of PC involvement
  3. evidence of pathology involving the capsule e.g. capsular penetration
  4. evidence of PC involvement of the seminal vesicles
  5. PSA density or PSAD (PSA divided by gland volume) – in PC cases

  (Prostate Cancer Research Institute - pcri@prostate-cancer.org)

Transrectal ultrasound A probe inserted in the rectum emits sound waves in order to image the prostate



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Adjunctive Nutritional Management Of Prostate Cancer

Human Studies Show That Dietary Modifications and Certain Supplements Can Help Treat Prostate Cancer

Unfortunately, very few oncologists and urologists provide this information to patients

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Prostate Cancer Intervention Trials

A. Soy Isoflavones – In a an intervention study, involving men with existing prostate cancer, supplementation with 100 mg per day of soy isoflavones showed a favorable outcome in stabilizing PSA levels.

- In this study soy isoflavone supplementation decreased rate of rise in serum PSA levels in patients with androgen dependent and androgen-independent prostate cancer.

- Researchers concluded that their data suggests that soy isoflavones may benefit some patients with prostate cancer **by slowing the progression of the disease** and therefore, potentially delaying the development of symptoms, improving quality of life, and perhaps even prolonging survival.

- **Reference**: Hussain M, Banerjee M, Sarkar FH et al. Soy isoflavones in the treatment of prostate cancer. 2003. Nutr and Cancer, 42;2: 111-117

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B. Vitamin D - The administration of cholecalciferol (the kind of Vitamin D you would buy at drug or health food store), at physiological doses, has been shown to decrease or slow the rise in PSA levels in men with prostate cancer in the past number of years, without risk of vitamin D toxicity.

- A recent study to investigate the use of vitamin D in the treatment of prostate cancer was published in the journal, Nutrition and Cancer, in 2005, by TCS Woo and fellow researchers (volume 51, number 1). In this study 15 prostate cancer patients were given 2,000 IU (50 ug) of vitamin D daily and monitored prospectively every 2-3 months.

- In 9 patients, the PSA level **decreased** or remained unchanged (no further rise) and these results were sustained during the 21-month course of vitamin D administration. Analysis also showed that there was a statistically significant decrease in the rate of PSA rise after administration of vitamin D compared with that before vitamin D administration.

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Vitamin D Study Continued

- The median PSA doubling time increased from 14.3 months prior to vitamin D administration to 25 months after commencing vitamin D.

- In fact, 14 of the 15 patients showed a prolongation of the PSA doubling time after vitamin D supplementation was introduced to this group. There were no side effects reported by any patient.

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Vitamin D Study Continued

- The marked prolongation of PSA doubling time is an extremely important outcome to the administration of vitamin D in these patients, according to the recent work of Partin and fellow researchers (J Urol, 2003).

- Partin and fellow researchers showed that the risk of distal metastasis of prostate cancer (with respect to relapse after prostate cancer surgery) at 5 years was 65% to 75% when PSA doubling time was less than 10 months compared with 10-20% when PSA doubling time was greater than 10 months.

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Vitamin D Study Continued

- As such, researchers working in this field point out that agents such as vitamin D that lengthen PSA doubling time or decrease the rate of PSA increase, might be clinically useful in the treatment of prostate cancer cases, with respect to affecting (slowing) the clinical course of the disease, and improving survival rates and quality of life, even if they do not reset the PSA levels into the normal range.

References:

1. Woo TCS, Choo R, Jamieson M et al. Pilot Study: Potential role of vitamin D (cholecalciferol) in patients with PSA relapse after definitive therapy. Nutrition and Cancer. 2005, 5;1: 32-36
2. Partin AW, Pound CR, and Rootselar CV. Natural history of progression after PSA elevation following radical prostatectomy: Update. J Uorl. 2003, 169 (4 suppl): 935

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C. **Lycopene And Prostate Cancer: Human Studies**

Study 1. In one study, the effect of tomato sauce on apoptosis in benign prostate hyperplasia (BPH) tissue and carcinomas was examined. 26 patients who were scheduled for prostatectomy were given tomato sauce pasta entrees (30 mg/day of lycopene) to eat daily for 3 weeks before surgery.

- Patients scheduled for surgery who did not receive the tomato sauce pasta entrees served as control subjects.

Results: Those who consumed the tomato sauce pasta entrees exhibited decreased serum PSA levels and increased apoptotic cell death in BPH tissue and carcinomas

Reference: Kim HS, Bowen P, Chen L, et al.: Effects of tomato sauce consumption on apoptotic cell death in prostate benign hyperplasia and carcinoma. Nutr Cancer 47 (1): 40-7, 2003.

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Study 2. In a 2004 open-label study, patients with hormone-refractory prostate cancer (HRPC) received lycopene supplements daily (10 mg/day of lycopene) for 3 months.

- Of the study's participants, 50% had PSA levels that remained stable, 15% showed biochemical progression, 30% showed a partial response, and one patient (5% of the total sample) exhibited a complete response after treatment.

Reference: Ansari MS, Gupta NP: Lycopene: a novel drug therapy in hormone refractory metastatic prostate cancer. Urol Oncol 22 (5): 415-20, 2004 Sep-Oct

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Study 3. Prostate Cancer Patients received lycopene supplements (30mg/day) or no intervention twice daily for 3 weeks prior to radical prostatectomy.

- Patients who received the lycopene supplements had smaller tumors and lower serum PSA levels than patients who did not receive the supplements.

- These results suggest that lycopene may be beneficial in prostate cancer treatment

Reference: Kucuk O, Sarkar FH, Djuric Z, et al.: Effects of lycopene supplementation in patients with localized prostate cancer. Exp Biol Med (Maywood) 227 (10): 881-5, 2002.

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Study 4. A 2006 study investigated whether lycopene supplements (10 mg/day) would affect PSA velocity in patients with localized prostate cancer.

- There was a statistically **significant decrease** in PSA velocity following lycopene treatment as well as a large, but not statistically significant, increase in PSA doubling time

Reference: Barber NJ, Zhang X, Zhu G, et al.: Lycopene inhibits DNA synthesis in primary prostate epithelial cells in vitro and its administration is associated with a reduced prostate-specific antigen velocity in a phase II clinical study. Prostate Cancer Prostatic Dis 9 (4): 407-13, 2006.

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Study 5. Patients with high-grade prostate intraepithelial neoplasia (HGPIN) received 4 mg of lycopene twice a day or no lycopene supplementation for 2 years.

Results: A greater decrease in serum PSA levels was observed in those treated with lycopene supplements compared with those who did not take the supplementation.

- During follow-up, adenocarcinomas occurred more often in patients who had not received the supplements than in patients who had received lycopene.

- These findings suggest that lycopene may be effective in preventing HGPIN from progressing to prostate cancer

Reference: Bunker CH, McDonald AC, Evans RW, et al.: A randomized trial of lycopene supplementation in Tobago men with high prostate cancer risk. Nutr Cancer 57 (2): 130-7, 2007

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Study 6 - In a Phase II clinical trial (Vaishampayan U et al, 2007) researchers investigated the efficacy of lycopene alone or in combination with soy isoflavones on serum PSA levels in men with prostate cancer.

To be eligible for the study, men with prostate cancer had to have rising serum PSA following local therapy or while on hormone therapy. The study population included 71 patients who had 3 successive rising PSA levels or a minimum PSA of 10 ng/ml at 2 successive evaluations prior to starting therapy.

- Subjects were randomly assigned to receive a tomato extract capsule containing **15 mg of lycopene alone** (n = 38) **or together** with a capsule containing **40 mg of a soy isoflavone** mixture (n = 33) twice daily orally for a maximum of **6 mo.** One patient on the lycopene arm did not receive therapy due to his inability to ingest the study pill.

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- There was no decline in serum PSA in either group. However, 35 of 37 (95%) patients in the lycopene group and 22 of 33 (67%) patients in the lycopene plus soy isoflavone group achieved stable disease, meaning that they achieved **stabilization in serum PSA level.**

- The data suggest that lycopene and soy isoflavones have important adjunctive effects in prostate cancer patients with PSA relapse disease and may delay progression of both hormone-refractory and hormone-sensitive prostate cancer.

Reference:

Vaishampayan U, Hussain M, Seren S, Sarkar F, Fontana J et al. Lycopene and Soy Isoflavones in the Treatment of Prostate Cancer. Nutri and Cancer**.** 2007; 59 (1): 1-7

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D. **Pomegranate Juice**

- Two clinical studies shown that men with established prostate cancer realized a marked slowing of their disease when they drank 8 ounces of pure pomegranate juice each day.

- Reporting at the 104th Annual Meeting Scientific Meeting of The American Urology Association, researchers presented findings showing that men, who had undergone prostate surgery or radiation treatment for localized **prostate cancer,** benefited from drinking 8 ounces per day of pomegranate juice if their PSA levels were still continuing to rise.

- In men giving the pomegranate juice the doubling time of their PSA was extended to 60 months, compared to only 15.4 months prior to pomegranate juice administration.

- Previously, a study in the Journal of Clinical Cancer Research in 2006 showed that men, with established prostate cancer, extended the PSA doubling time from 15 months to 54 months when they began drinking 8 ounces of pomegranate juice each day

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How Does Pomegranate Juice Work?

No one knows for sure but the juice is very rich in a class of unique polyphenol antioxidants known as ellagitannin compounds.

It's possible that these, or other compounds, slow the rate at which prostate cancer cells replicate and/or trigger mechanisms that encourage programmed cell death of existing prostate cancer cells.

Phase II and III trials are planned to better understand the extent to which pomegranate juice can protect the prostate gland and be used in adjunctive management of established prostate cancer cases.

Note: Pomegranate Juice contains carbohydrate calories, and thus, is precluded from the ketogenic diet plan.

However, it can be used to help prevent prostate cancer and as follow-up intervention in prostate cancer survivors (post-treatment)

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E. Melatonin

- Low Melatonin levels assoc. with increased risk of breast cancer and prostate cancer

- Melatonin shown to improve cancer-fighting abilities of immune system and slows rate or cell division, even in certain cancer cells

- Dr. Lissoni (Italy) uses high dose melatonin to help control progression of breast and prostate cancer (10-20 mg daily)

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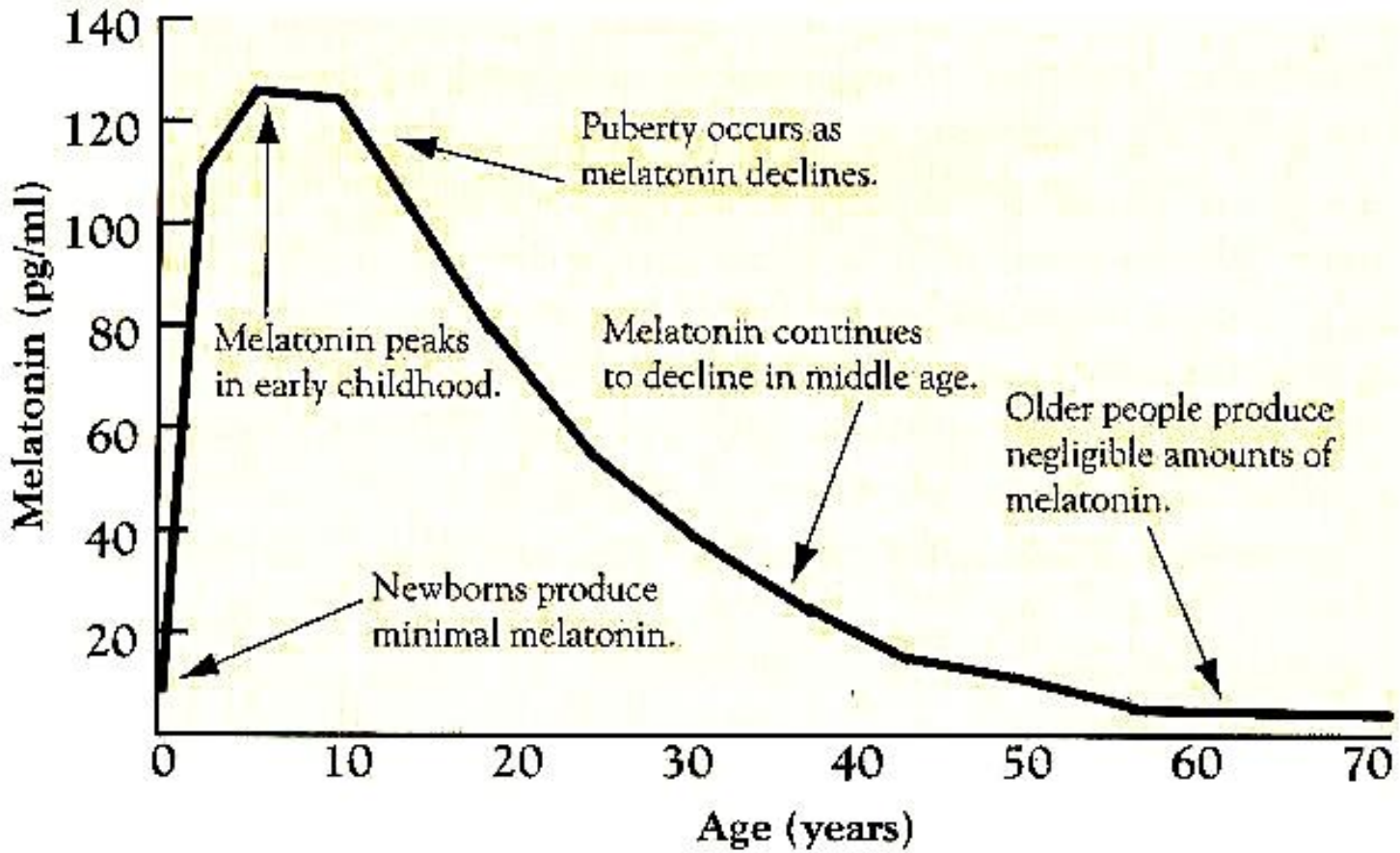
Age-Related Decline In Melatonin



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Melatonin Receptors On CD4 Cells: Immune Modulation Effects

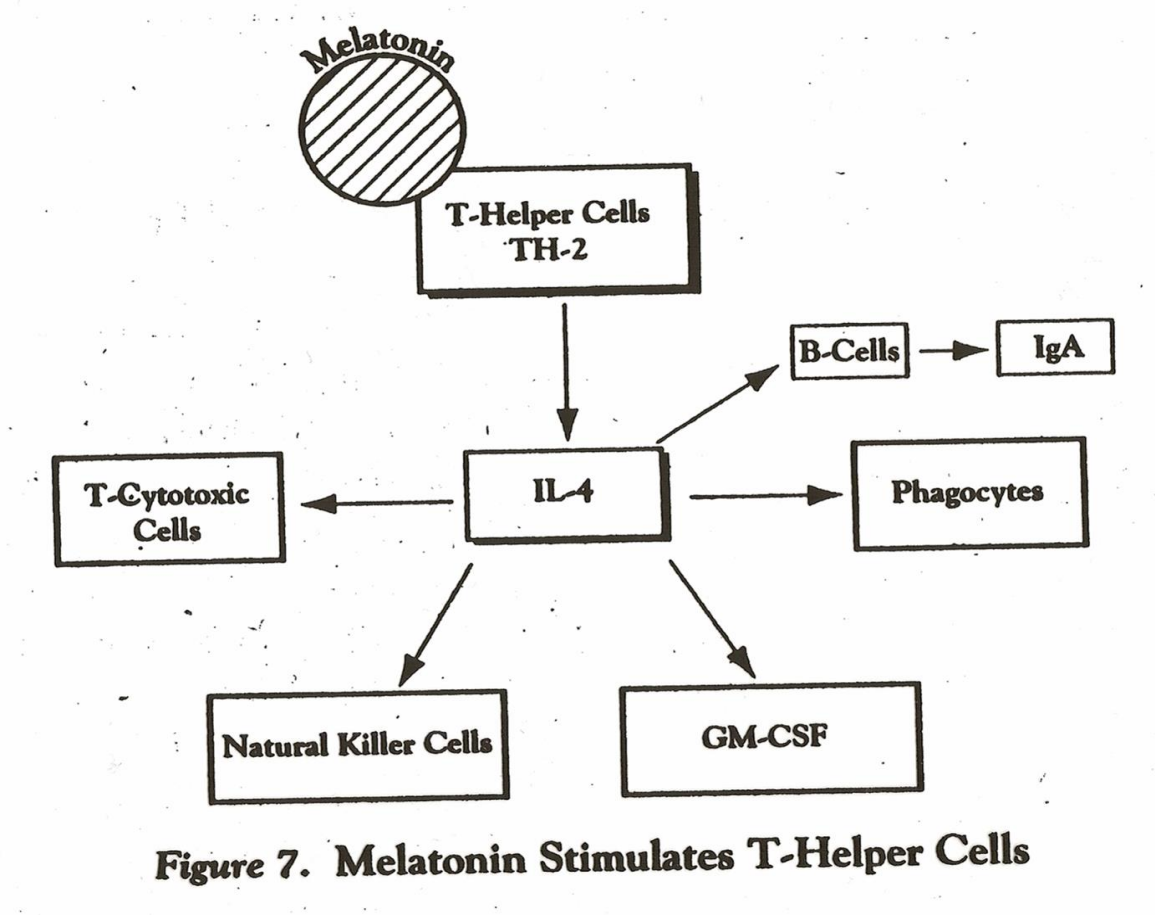

Figure 7. **Melatonin Stimulates T-Helper Cells**

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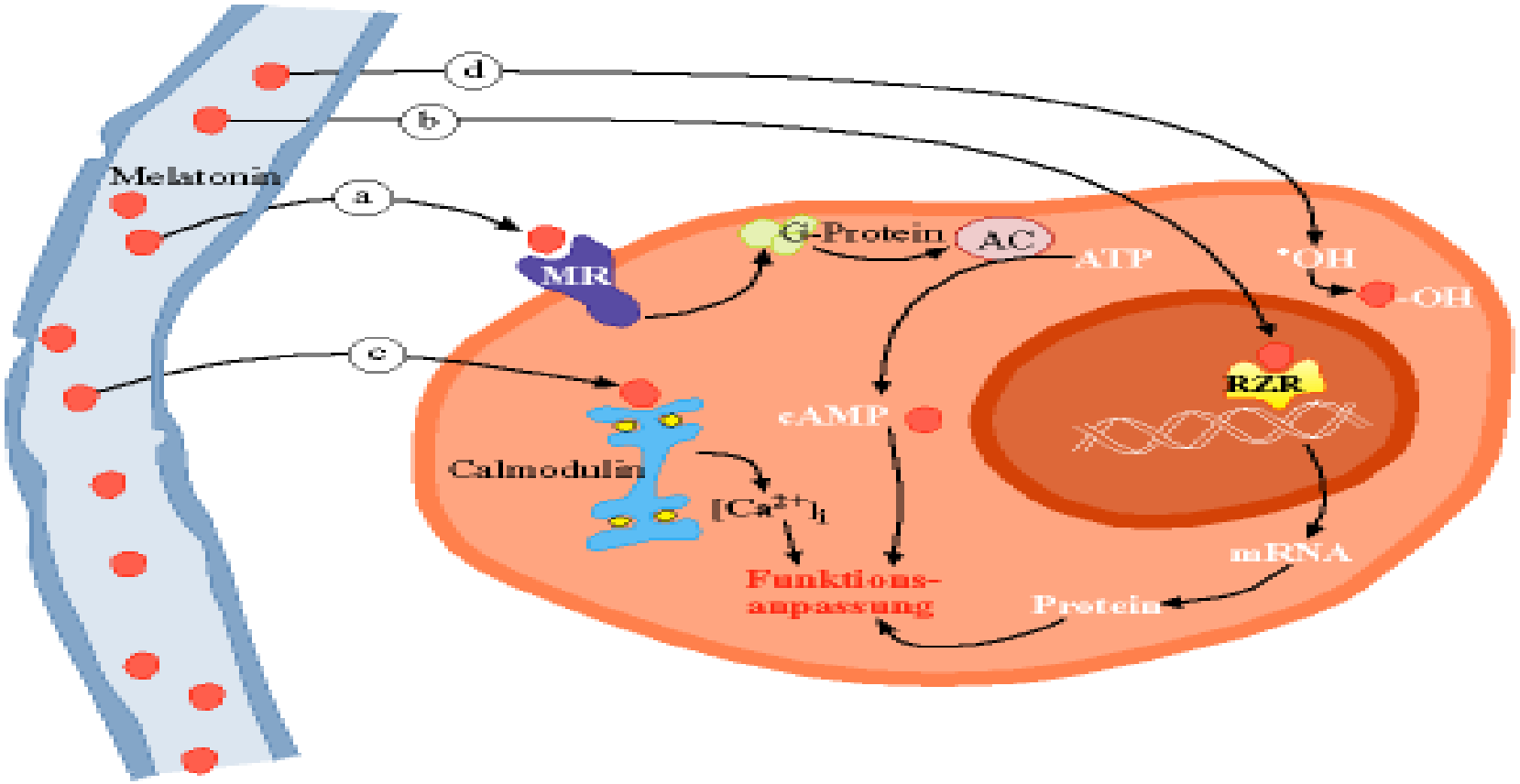
Melatonin Receptors: Breast, Prostate Cells and Cancer Cells

1. Slows Cell Replication Rate - via calmodulin and gene inhibition
2. Antioxidant
3. Up-regulates Detoxification



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F. Antioxidants and Low Animal Fat Diet –

In the September 2005 issue of *The Journal of Urology*, Dr Dean Ornish published a study testing the effectiveness of an intensive dietary and lifestyle program as the sole treatment of prostate cancer in men with low to moderate Gleason Scores.

The program consisted of a low animal fat diet (with the exception of some fish, and emphasis on fruits, vegetables, legumes, soy products and other vegetarian foods (and dairy-free). He also supplemented these men with antioxidants (vitamin C, selenium and vitamin E), and included moderate aerobic exercise, and stress management interventions in the treatment group.

The daily antioxidant supplement dosages were:

- Vitamin C – 2000 mg
- Vitamin E – 400 IU
- Selenium – 200 mcg

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- Ornish studied 93 men who had chosen not to undergo conventional invasive treatment for prostate cancer.

- Half of these men were randomly allocated to the Ornish program, while the remainder served as a non-treated comparison group.

- After 12 months, the PSA of the treated group of men decreased an average of 0.25 ng/ml or 4%,and the PSA of the non-treated group of men increased an average of 0.38 ng/ml or 6%.

Reference:

Ornish Dean et al: Intensive lifestyle changes may affect the progression of prostate cancer. The Journal of Urology Vol.174:1065, 2005

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G. Ground Flaxseed Supplementation

- 161 Prostate cancer patients scheduled at least 21 days before prostatectomy were randomly assigned to one of the following arms: (*a*) control (usual diet), (*b*) flaxseed-supplemented diet (30 grams per day), (*c*) low-fat diet (<20% total energy), or (*d*) flaxseed-supplemented, low-fat diet. Blood was drawn at baseline and before surgery.

- Tumors were assessed for rates of proliferation and programmed cell death (apoptosis). Men followed the protocol an average of 30 days.

- Results showed that the men given the ground flaxseed supplement (not flaxseed oil) had a slower replication rate of their prostate cancer cells than did men not taking flaxseed supplementation and men using only a low fat diet.

- Researcher's Conclusions: "Findings suggest that flaxseed is safe and associated with biological alterations that may be protective for prostate cancer."

Reference:

Demark-Wahnefried W. Flaxseed Supplementation (Not Dietary Fat Restriction) Reduces Prostate Cancer Proliferation Rates in Men Presurgery.Cancer Epidemiol Biomarkers Prev 2008;17(12):3577–87)

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H. Saw Palmetto and Lycopene (A case report)

A 62-year-old man with androgen-independent metastatic prostate cancer that had failed to respond to multiple treatment regimens stopped all conventional therapy and began 10 mg/day of lycopene and 300 mg of saw palmetto 3 times per day.

- The prostate-specific antigen (PSA) level decreased from 365 ng/ml to 140 ng/ml after 1 month and to 8.1 ng/ml after 2 months. A repeat bone scan revealed an improvement of bony metastases. He has continued the lycopene and saw palmetto and has remained asymptomatic for an unspecified period of time.

- Note – Saw Palmetto contains Beta-sitosterol, which in experimental and animal studies has shown an ability to induce programmed cell (apoptosis) death of certain prostate cancer cell lines. Most researchers attribute the dramatic disease reversal effect in the above case to this biological process.

Reference:

Matlaga BR, Hall MC, Stindt D, Torti FM. Response of hormone refractory prostate cancer to lycopene. J Urol 2001;166:613.

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Catechins - Prevent Prostate Cancer in High-risk Men (2006)

Cancer Res. 2006 Jan 15;66(2):1234-40.

Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study.

Bettuzzi S[1], Brausi M, Rizzi F, Castagnetti G, Peracchia G, Corti A.

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Abstract

Green tea catechins (GTCs) proved to be effective in inhibiting cancer growth in several experimental models. Recent studies showed that 30% of men with high-grade prostate intraepithelial neoplasia (HG-PIN) would develop prostate cancer (CaP) within 1 year after repeated biopsy. This prompted us to do a proof-of-principle clinical trial to assess the safety and efficacy of GTCs for the chemoprevention of CaP in HG-PIN volunteers. The purity and content of GTCs preparations were assessed by high-performance liquid chromatography [(-)-epigallocathechin, 5.5%; (-)-epicatechin, 12.24%; (-)-epigallocatechin-3-gallate, 51.88%; (-)-epicatechin-3-gallate, 6.12%; total GTCs, 75.7%; caffeine, <1%]. Sixty volunteers with HG-PIN, who were made aware of the study details, agreed to sign an informed consent form and were enrolled in this double-blind, placebo-controlled study. Daily treatment consisted of three GTCs capsules, 200 mg each (total 600 mg/d). After 1 year, only one tumor was diagnosed among the 30 GTCs-treated men (incidence, approximately 3%), whereas nine cancers were found among the 30 placebo-treated men (incidence, 30%). Total prostate-specific antigen did not change significantly between the two arms, but GTCs-treated men showed values constantly lower with respect to placebo-treated ones. International Prostate Symptom Score and quality of life scores of GTCs-treated men with coexistent benign prostate hyperplasia improved, reaching statistical significance in the case of International Prostate Symptom Scores. No significant side effects or adverse effects were documented. To our knowledge, this is the first study showing that GTCs are safe and very effective for treating premalignant lesions before CaP develops. As a secondary observation, administration of GTCs also reduced lower urinary tract symptoms, suggesting that these compounds might also be of help for treating the symptoms of benign prostate hyperplasia.

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Catechins Improve Clinical Profile In Men With Localized Prostate Cancer (2009)- Cancer Prevention Research

Tea Polyphenols Decrease Serum Levels of Prostate-Specific Antigen, Hepatocyte Growth Factor, and Vascular Endothelial Growth Factor in Prostate Cancer Patients and Inhibit Production of Hepatocyte Growth Factor and Vascular Endothelial Growth Factor *In vitro*

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1. **Note:** J. McLarty and R.L.H. Bigelow contributed equally to this work.

Abstract

The purpose of this study was to determine the effects of short-term supplementation with the active compounds in green tea on serum biomarkers in patients with prostate cancer.

Twenty-six men with positive prostate biopsies and scheduled for radical prostatectomy were given daily doses of Polyphenon E, which contained 800 mg of (−)-epigallocatechin-3-gallate (EGCG) and lesser amounts of (−)-epicatechin, (−)-epigallocatechin, and (−)-epicatechin-3-gallate (a total of 1.3 g of tea polyphenols), until time of radical prostatectomy. Serum was collected before initiation of the drug study and on the day of prostatectomy. Serum biomarkers hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF)-I, IGF binding protein-3 (IGFBP-3), and prostate-specific antigen (PSA) were analyzed by ELISA. Toxicity was monitored primarily through liver function enzymes. Changes in serum components were analyzed statistically using the Wilcoxon signed rank test. Cancer-associated fibroblasts were treated with EGCG, and HGF and VEGF protein and mRNA levels were measured.

HGF, VEGF, PSA, IGF-I, IGFBP-3, and the IGF-I/IGFBP-3 ratio decreased significantly during the study. All of the liver function tests also decreased, five of them significantly: total protein, albumin, aspartate aminotransferase, alkaline phosphatase, and amylase. The decrease in HGF and VEGF was confirmed in prostate cancer-associated fibroblasts *in vitro*.

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Green Tea Catechins and Prostate CA

High-Grade Intra-prostatic Neoplasia (carcinoma in situ)

- A 2006 study showed that green tea catechins (GTCs) were highly effective in reversing premalignant prostate lesions (high grade prostate intra-epithelial neoplasia); an established precursor to prostate cancer.
- Treatment group ingested daily GTCs supplements (total 600 mg/d).
- After 1 year, only 1 tumor was diagnosed among the 30 GTCs-treated men, whereas 9 cancers were found among the 30 placebo-treated men (3% vs 30% prostate cancer incidence).
- Men in GTCs treated group also had PSA levels that were constantly lower than the placebo-treated group throughout the study period.
- Supplementation with GTC's also improved symptoms of prostate enlargement and reduced lower urinary tract symptoms.
- No significant side effects or adverse effects were reported by the men supplementing with GTCs

Reference:

- Bettuzzi S, Brausi M, Rizzi F et al. Chemoprevention of Human Prostate Cancer by Oral Administration of Green Tea Catechins in Volunteers with High-Grade Prostate Intraepithelial Neoplasia: A Preliminary Report from a One-Year Proof-of-Principle Study. Cancer Res January 15, 2006 *66;* 1234

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Green Tea Catechins In Localized Prostate Cancer

- Based on success of 2006 study described previously, a second study using GTCs was published in 2009 (Cancer Prevention Research).

- In this study GTCs were provided to men with **established localized prostate cancer**, who were awaiting surgical treatment involving radical prostatectomy.

- 26 men with positive prostate biopsies ingested a supplement containing 800 mg per day GTCs, until time of radical prostatectomy (median dosing period was 34.5 days).

- Serum was collected before initiation of the study and on the day of prostatectomy.

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The study showed that GTCs supplementation in these men produced a decrease in many prostate cancer biomarkers, including:

- Prostate Specific Antigen (PSA)

- Hepatocyte Growth Factor (HGF) – the stromal tissue around cancer cells is known to secrete this growth factor, which promotes cancer cell division and increased tumor vascularization to promote metastasis. High HGF signifies higher risk for metastasis.

- Vascular Endothelial Growth Factor (VEGF) – this growth factor promotes the growth of new blood vessels to feed the tumor and promote metastasis. High VEGF levels signified higher risk for metastasis

- Insulin-like Growth Factor and its Binding Proteins (IGF-I, IGFBP-3, and the IGF-I/IGFBP-3) – Higher IGF-1 and lower IGF-1 Binding Protein levels encourage more rapid cell division of cancer cells. In this study the IGF-I/IGFBP-3 ratio decreased significantly during the study.

- Liver Function Tests – In this study all of the liver function tests also decreased, five of them significantly: total protein, albumin, aspartate aminotransferase, alkaline phosphatase, and amylase.

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Proposed Mechanism of Action:

- (EGCG and ECG) shown to inhibit the HGF/c-Met signaling pathway in both breast and prostate carcinoma cells, in experimental studies.
- Hepatocyte Growth Factor (HGF) is normally secreted by mesenchymal cells and acts primarily upon epithelial cells and endothelial cells, but also acts on haemopoietic progenitor cells.
- It has been shown to have a major role in embryonic organ development, specifically in myogenesis, in adult organ regeneration and in wound healing.
- The C-Met receptor is normally expressed by cells of epithelial origin. HGF normally stimulates the c-Met receptor on target tissues, which prompts them to replicate via up-regulation of the tyrosine kinase pathway. Thus, it plays an important role in embryonic growth and wound healing.
- In prostate cancer, the transmembrane receptor c-Met is often over-expressed (a greater number of c-Met receptors than is considered normal) in primary tumors and metastases.

- High levels of c-Met are directly correlated with a higher Gleason score and associated with poorly differentiated tumors. Additionally, high serum levels of the c-Met ligand, HGF, have been found to be associated with metastatic disease and decreased overall survival.

- Often the overproduction of HGF occurs in cancer-associated fibroblasts located in the stromal tissue surrounding the tumor. Many studies have now shown that the tumor stroma plays a very important role in cancer progression. A number of cells associated with the stroma, including macrophages, endothelial cells, and fibroblasts, provide factors that facilitate proliferation, survival, and invasion of tumor cells.

- As such, studies show that dysregulation of the HGF/c-Met pathway leads to increased proliferation, motility, and invasion of cancer cells.

- Other *in vitro* experiments show that GTCs also block the production of VEGF and HGF in at least two different prostate cancer–associated fibroblast cell lines

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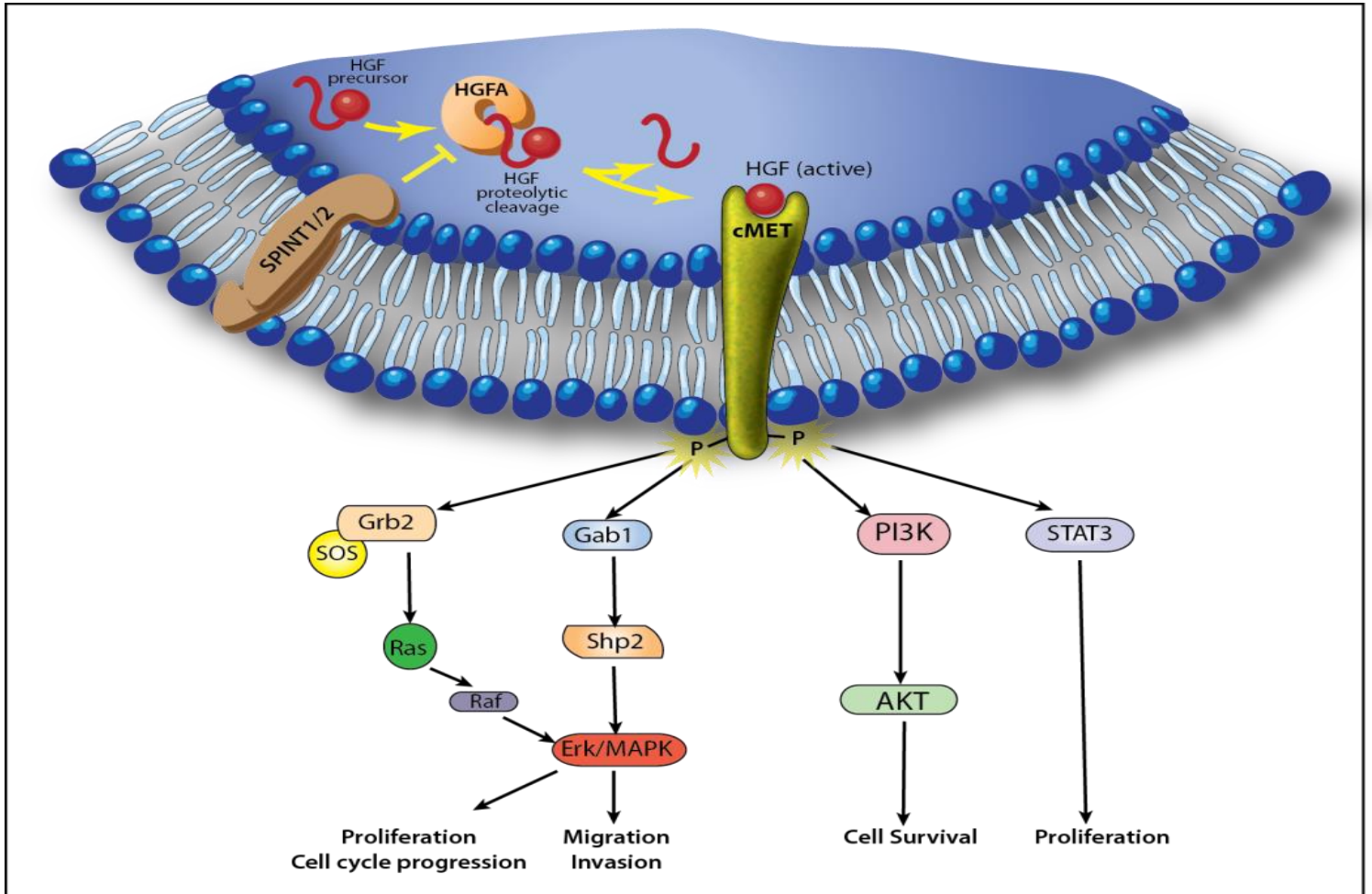
HGF/Met C Signaling Pathway



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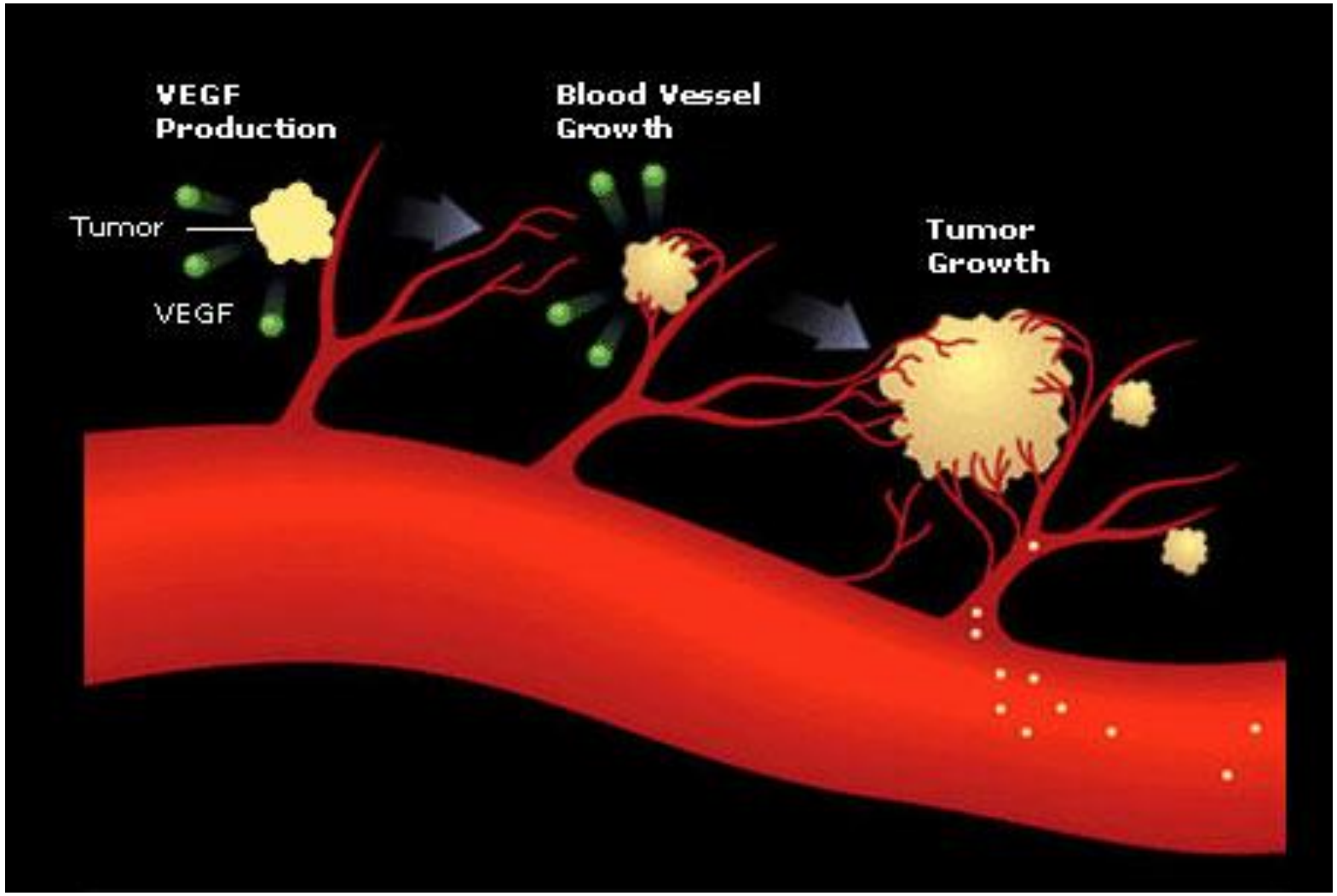
Soy Isoflavones and GTC's Induce Anti-Angiogenesis In Cancer Cells



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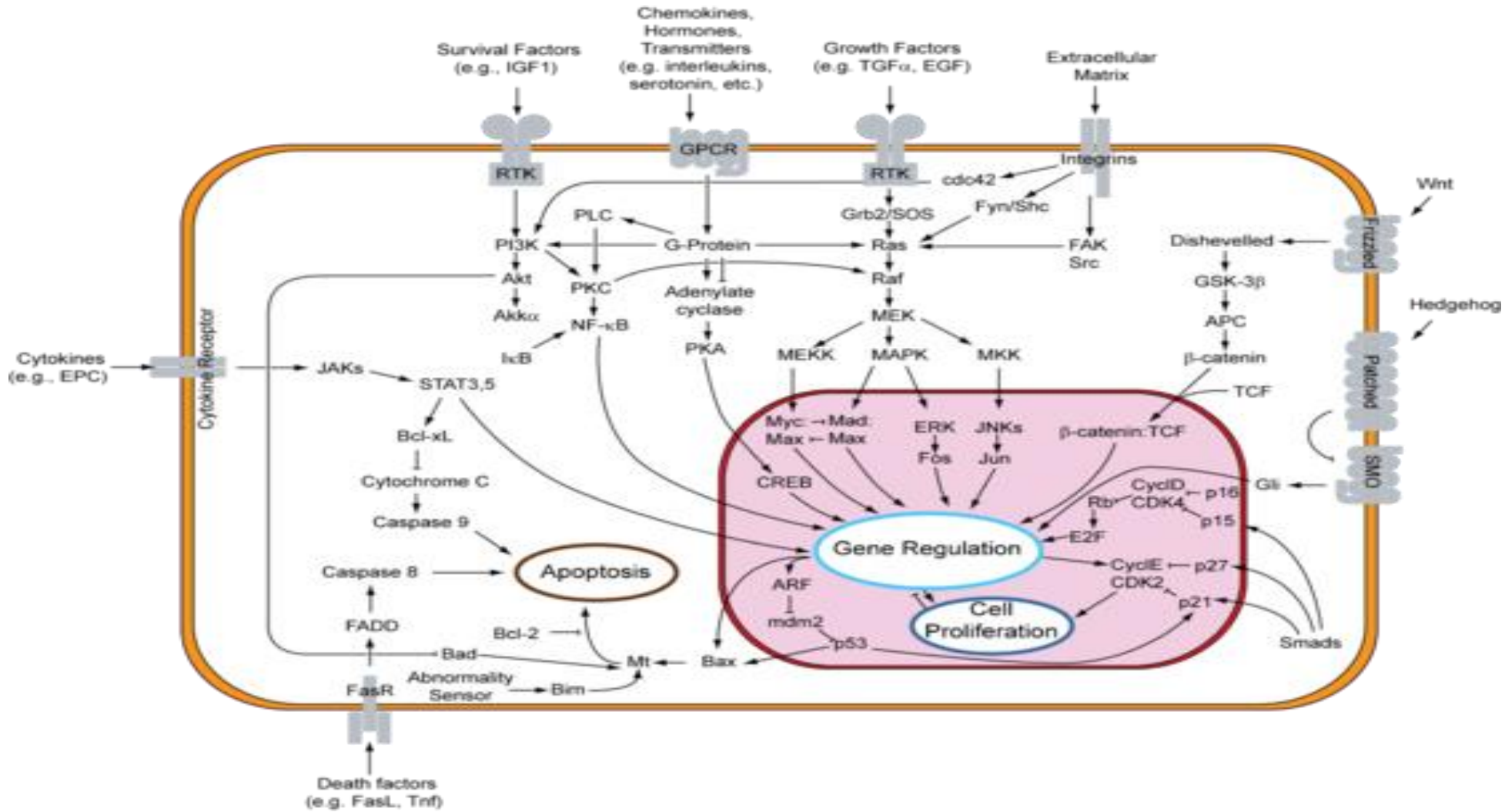
Key Signaling Pathways



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Summary

- Overall, data suggests that supplementation with green tea catechins could be useful adjuvant therapy in men with prostate cancer by lowering the levels of cytokines (HGF, VEGF) that contribute to prostate cancer progression

- Prostate cancer is the second leading cause of cancer mortality in men in the United States, with 27,000 dying each year. Rates of recurrence for early-stage disease are relatively high, and mortality rates for late-stage disease have not improved significantly over the past 10 years

- In regard to prostate cancer prevention as much as 75% of prostate cancer is attributable to dietary and lifestyle factors, according to data published in the Journal of the National Cancer Institute.

Reference:

- McLarty J, Bigelow R, Smith M et al. Tea Polyphenols Decrease Serum Levels of Prostate-Specific Antigen, Hepatocyte Growth Factor, and Vascular Endothelial Growth Factor in Prostate Cancer Patients and Inhibit Production of Hepatocyte Growth Factor and Vascular Endothelial Growth Factor *In vitro.* Cancer Prev Res July 2009 *2;* 673

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Vegan Diet Reduces Prostate Cancer Risk by 35%

Jan 2016 study in American Journal of Clinical Nutrition **(**Part of Adventists Health Study-2)

Showed - Men who are Vegans had a 35% Lower Risk of Prostate Cancer compared to non-vegan men

Study Followed over 26,000 men. During study, 1079 men developed prostate cancer

Researchers showed – Vegan Men had a 35% lower risk of Pr CA compared to non-vegans

Especially true for white males, with similar trend for black male vegans, although assoc. not quite as strong.

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Not surprising, as many plant foods contain nutrients shown to inhibit prostate cancer.

Examples:

- Cruciferous vegetables – broccoli, Brussels sprouts, cabbage, cauliflower, bok choy, turnips
- Tomatoes – lycopene
- Soy beans and soy products – isoflavones and protease inhibitors
- Peas and Beans – lignins, protease inhibitors
- Green Tea – catechins (polyphenols)
- Pomegranate Juice –ellagic acid
- Ground Flaxseed – EL and ED

Many studies show consumption of theses foods associate with decreased prostate cancer

And Supplements using ingredients from some of these plant-based foods have been used as Adjunctive Treatment to Help Improve Outcomes in Pr CA patients (isoflavones, lycopene, flaxseed, catechins)

Take Home Message:

Most patients not going to become strict vegans, but encouraging them to including more plant foods with anti-cancer properties appears prudent to help prevent Pr CA

Pr CA - accounts 27% of all male cancers, and is 2nd leading cause cancer death in men

For women – Many of the same plant foods that reduce Pr CA, also shown to reduce risk of Br CA.

Reference : http://ajcn.nutrition.org/content/103/1/153.abstract

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Melatonin and Prostate Cancer

- This study looked at the association between urine levels of main breakdown product of melatonin, 6-sulfatoxymelatonin, and risk of prostate cancer.

- Researchers conducted a case-cohort study of 928 Icelandic men from the AGES-Reykjavik cohort between 2002 and 2009. They collected first morning void urine samples at recruitment, and asked the participants to answer a questionnaire about sleep patterns.

- The researchers found that one in seven men reported problems falling asleep, one in five men reported problems staying asleep, and almost one in three reported taking sleeping medications.

- The median value of 6-sulfatoxymelatonin in the study participants was 17.14 nanograms per milliliter of urine. Men who reported taking medications for sleep, problems falling asleep, and problems staying asleep had significantly lower 6-sulfatoxymelatonin levels compared with men without sleep problems.

- During study, 111 men were diagnosed with prostate cancer, including 24 with advanced disease. The researchers found that men whose 6-sulfatoxymelatonin levels were **higher than the median value (17.14 ng/ml) had a 75 percent decreased risk for advanced prostate cancer**. **A 31 percent decreased risk for prostate cancer overall was observed as well.**

Reference

- American Association for Cancer Research (AACR). "Melatonin may lower prostate cancer risk." ScienceDaily. ScienceDaily, 20 January 2014. <www.sciencedaily.com/releases/2014/01/140120085058.htm>.

  http://www.sciencedaily.com/releases/2014/01/140120085058.htm

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Melatonin

At physiological concentrations, melatonin suppresses cell growth and multiplication and inhibits cancer cell proliferation in vitro through specific cell-cycle effects.

- At pharmacological concentrations, melatonin suppresses cancer cell growth and multiplication. At physiological and pharmacological concentrations, melatonin acts as a differentiating agent in some cancer cells and lowers their invasive and metastatic status by altering adhesion molecules and maintaining gap junction intercellular communication.

- In other cancer cell types, melatonin, alone or with other agents, induces programmed cell death. (http://physics.fau.edu/observatory/lightpol-melatonin.html#Melat_Summ_NCI)

David Blask, M.D., Ph.D.
Laboratory of Experimental Neuroendocrinology/Oncology
Bassett Research Institute
Cooperstown, NY.

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Compelling evidence for the use of other supplements in the management of prostate cancer, also include:

1. Modified Citrus Pectin

2. Vitamin E Succinate

3. Chinese Scullcap – inhibits 12-lipoxygenase

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Nutrition and Lifestyle Modification To Support Prostate Health

1. Consume a diet that is low in saturated fat, transfats, deep fried foods and cholesterol
2. Remain at or near your ideal body weight.
3. Consume alcohol in moderation or not at all.
4. Consume tomato and tomato products at least 4 times per week.
5. Consume soy products, such as tofu, veggie burgers, miso soup, soy nuts and soymilk, at least 3 times per week.
6. Ingest cruciferous vegetables a minimum of 3-5 times per week.
7. Remain fit, especially from a cardiovascular fitness standpoint, striving to achieve a resting heart rate below 60 beats per minute.
8. Avoid pan-fried meats and other sources of heterocyclic amines (charred BBQ meats and blackened fish and meats).
9. Have 2 tablespoons of ground flaxseed per day
10. Drink 8 ounces of pomegranate juice per day
11. Maintain Vitamin D blood levels above 85 nmol/L
12. Eat fish twice per week
13. Drink 3-5 cups of green tea, and 2-4 cups of coffee (Or instead of green tea, take green tea supplement yielding 300-600 of polyphenols per day, with at least 50% coming from catechin)

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Supplements

1. High Potency Multiple Vitamin and Mineral Supplement that contains the following levels of antioxidants and vitamin D, shown to help inhibit prostate cancer development in various studies:
   - Vitamin C – 1,000 mg
   - Vitamin E (succinate) – 400 IU
   - Vtiamin D - 1000 IU
   - Selenium - 200 mcg
   - Lycopene (5%) – 6 mg

2. Take an Essential Fatty Acid Supplement each day that contains 400 mg each of borage seed oil, flaxseed oil, fish oil (30%EPA/20% DHA).

3. Additional Vitamin D (1000 - 3000 IU) during the winter months if you live above or below the 40th degree latitude, ensuring a blood level of at least 85nmol/L.

4. Green Tea Catechins – take a supplement containing 300-600 mg of green tea catechins derived from decaffeinated green tea.

5. After age 40 take a Prostate Support Supplement that contains specific ingredients that block the build-up of the dangerous form of testosterone (DHT) and blocks the over stimulation of testosterone and estrogen on the prostate gland. The 40 Plus Supplement Should Contain:

   Saw Palmetto - 640 mg (standardized to 45% fatty acids and sterols)
   Pygeum Africanum – 100 mg (standardized to 25% triterpenes)
   Beta-Sitosterol – 144 mg
   Soy Extract – 100 mg (20% isoflavones)
   Stinging Nettle - 60 mg (5:1)
   Lycopene (5%) – 25 mg
   Pumpkin Seed Extract (4:1) – 50 mg

6. Melatonin – take 1-3 mg of melatonin 60-90 minutes before bedtime after age 40

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Adjunctive Nutrition and Supplementation Recommendations For Patients With Prostate Cancer or a PSA Level Above 2.5 or a PSA Velocity that has Increased Abruptly Within a One year Period

Dietary and Lifestyle Prescription:

- No red meat, pork, lamb, duck
- No deep fried foods, no foods that are cooked to completion via pan-frying in oil
- No cheese, no milk or yogurt above 1% milk fat, no egg yolks, no butter, no cream, no mayonnaise
- No frozen yogurt or ice cream
- No sugar, honey or brown sugar in coffee or espresso
- No alcohol of any kind (including red wine)
- Eat at least one cruciferous vegetable per day (broccoli, cabbage, Brussels sprouts, kale, bok choy, cauliflower)
- Eat soy products if possible (stir fry tofu with mixed vegetables, edamame, roasted soy nuts, soy milk)
- No high fat pastries (cheat with a biscotti, or low fat muffin)
- Eat beans and peas daily if possible - including vegetarian lentil soup
- 8 ounces of pomegranate juice per day
- Drink 3-5 cups of green tea daily
- Need 30 mins of aerobic exercise at least 4 days per week for insulin and glucose control – these influence the rate of cell division and growth.

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Supplements

1. High-Potency Multiple Vitamin and Mineral – antioxidant enriched, B-50 complex. 1000 IU vitamin D etc.)

2. Essential Oils – (1200 mg capsules) - 3 capsules per day – Or 1200 mg fish oil supplement (twice daily) (at least 30% EPA/20%DHA)

3. Vitamin D – (at least another 3,000 IU per day) – have vitamin D blood level checked. It needs to be at or above 85nmol/L (35ng/ml)

4. Prostate Formula – 2 capsules, twice per day

5. Melatonin – 3-5 mg 90 mins before bedtime

6. Green Tea Catechins supplement - 600 mg of catechins/polyphenols daily

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7. Lycopene – 20 mg per day

8. Ground flaxseed – 25 gms (1 heaping tablespoons) once per day – mix into low fat yogurt or protein shake or juice.

9. Soy Isoflavones – 200 mg per day (find a supplement that contains this amount)

10. Optional – Indole-3 carbinol/sulforaphane supplement

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Female Reproductive Health Issues:

The role of nutrition, supplementation and lifestyle factors in:

1. Menopausal Management
2. Reducing Breast Cancer Risk
3. Fibrocystic Breast Disease
4. PMS (premenstrual Syndrome)
5. Uterine Fibroids
6. Polycystic Ovarian Disease

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Natural Management Of Menopause

- Menopausal Hormonal Changes:
  - 90% decline in estrogen
  - 66% decline in progesterone
  - 50% decline in testosterone

  - Compensatory increase in FSH, LH and noradrenaline (hot flashes, night sweats, insomnia, anxiety)

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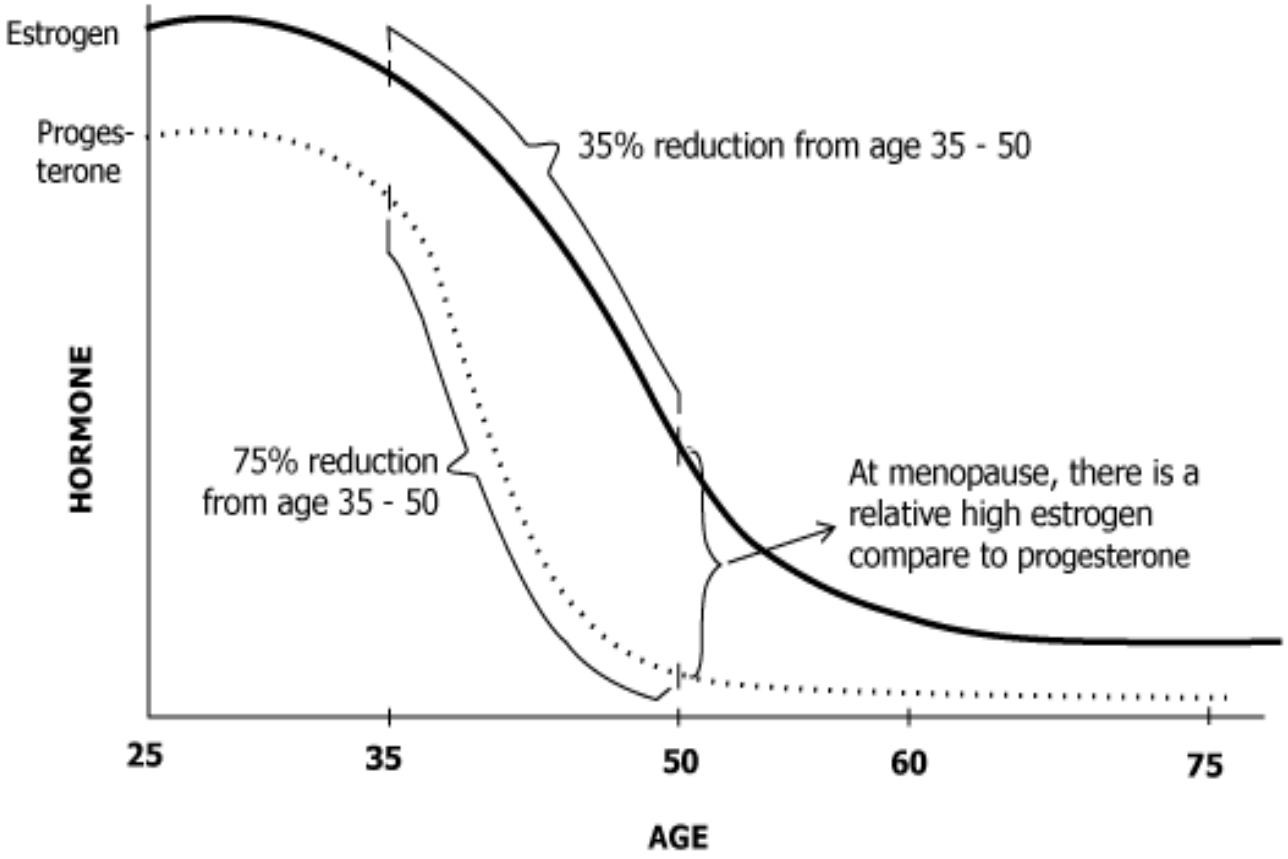
Age-Related Decline In Estrogen and Progesterone In Women



- Other Physiological Outcomes:
  - Bone loss
  - Decreased LDL-receptors and clearance
  - Skin atrophy and aging
  - Vaginal dryness
  - Decreased breast density – improves diagnostic accuracy of mammograms

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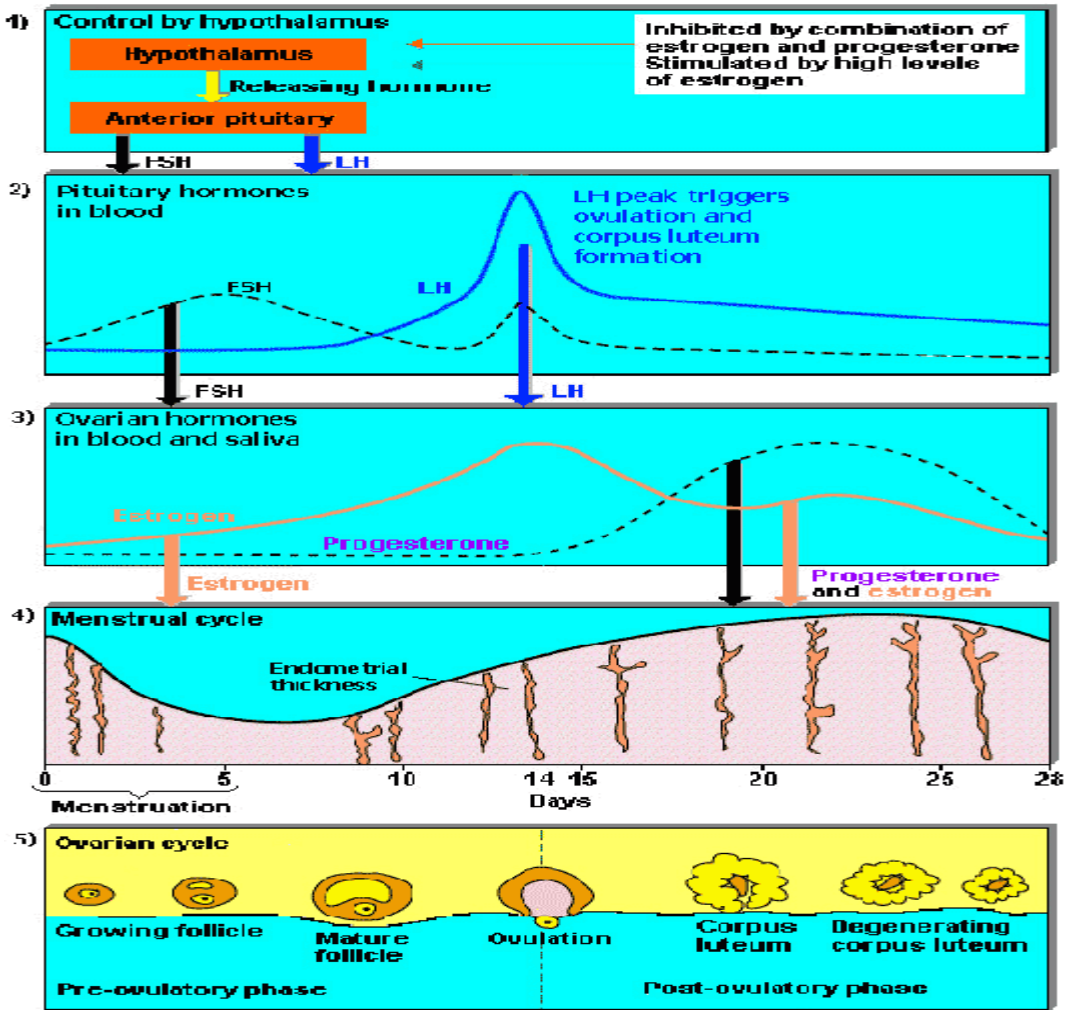
Menstrual Cycle Hormones and Events



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- Medical Solution: HRT (WHI study):
  - Breast CA increase 26%
  - Heart attack increase 29%
  - Stroke increase 41%
  - Nurses Health Study – 2.3% increase risk Breast CA per yr on HRT (10 yrs equals 23% increased risk)
  - Breast cancer incidence among U.S. women dropped by 7% from 2002 to 2003, possibly because of a decrease in hormone replacement therapy usage, according to a study presented Thursday at the 29th Annual San Antonio Breast Cancer Symposium, the *New York Times* reports (Kolata, *New York Times)*

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- Natural Alternative To HRT (why):
  - 1/3 life in postmenopausal yrs (quality)
  - Reduction of disease risk and symptoms

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Compendium of Pharmaceuticals — **Black Cohosh** used during first 50 yrs of the 1900's. (Native to North America)
Wide spread use in Germany and other countries

1. **Black Cohosh** – contains triterpene glycosides with estrogen potency of estriol (weakest estrogen)

Double-blind studies:

- Decreases release of FSH, LH and noradrenaline
- Reduces menopausal symptoms
- No overstim of breast or reproductive tissues
- Maintains vaginal tissue integrity
- Supports skin integrity (anti-aging)


Black Cohosh flower

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Dosage: 80 mg, twice daily (std to 2.5% triterpene glycosides)

Side Effects (occas): headache, skin rash, GI upset

Precautions: Previous breast or ovarian CA
(may enhance tamoxifen)

Other Drug Interactions: None

- 2. Soy Extract – contains isoflavones (genistein, diadzein)
  Studies show:
  - Weak estrogen effect
  - Decrease hot flashes
  - Stim beta receptors – slow cellular replication
  - Shown to reduce mitosis/apoptosis ratio in breast cancer patients – suggesting anti-cancer benefits (apoptosis)
  - Reduce bone loss
  - Decrease cholesterol
  - Support skin integrity (and antioxidant)

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Dosage: 50-75 mg per day of isoflavones

(500 mg soy extract at 10% grade of isoflavones yields 50 mg of isoflavones)

Side Effects: itching, eczema, nausea, dizziness, abdominal pain, skin rash and sweating

Precautions: Previous breast or ovarian CA

Other Drug-Nutrient Interactions: None

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Soy Isoflavone Content Of Foods

- Tofu (1/2 cup) – **25 mg**
- Soy Milk unfortified (8oz) – 10 mg
- Soy Milk fortified (8oz) – 43 mg
- Soybeans Roasted (1/4 cup) **– 78 mg**
- Soybeans, green cooked (e.g. edamame) (1/2 cup) – **50 mg**
- Soybeans, black cooked (½ cup) - 40 mg
- Soybeans, yellow cooked (½ cup) - 78 mg
- Miso (1 tablespoon) - 7 mg
- Soy protein isolate powder (1/3 cup) - **53 mg**
- Textured soy protein, dry (¼ cup) - 33 mg
- Tempeh (½ cup) - 53 mg

www.soyfoods.org (Soy foods of America)

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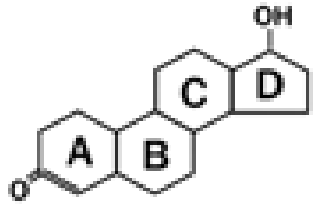
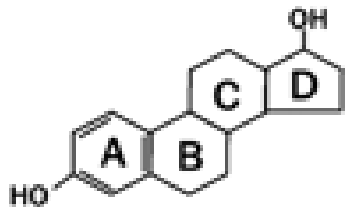
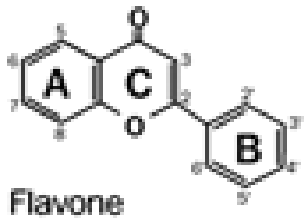
Molecular Structure of Estadiol compared to Common Phytoestrogens



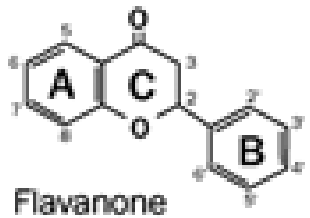
Testosterone



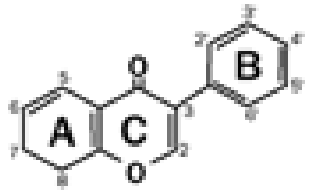
17β – Oestradiol



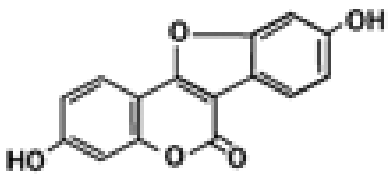
Flavone



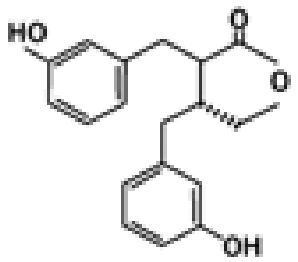
Flavanone



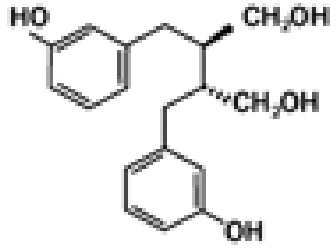
Isoflavone



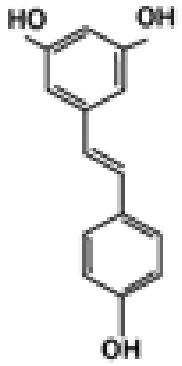
Coumestrol



Enterolactone



Enterodiol



trans-Resveratrol

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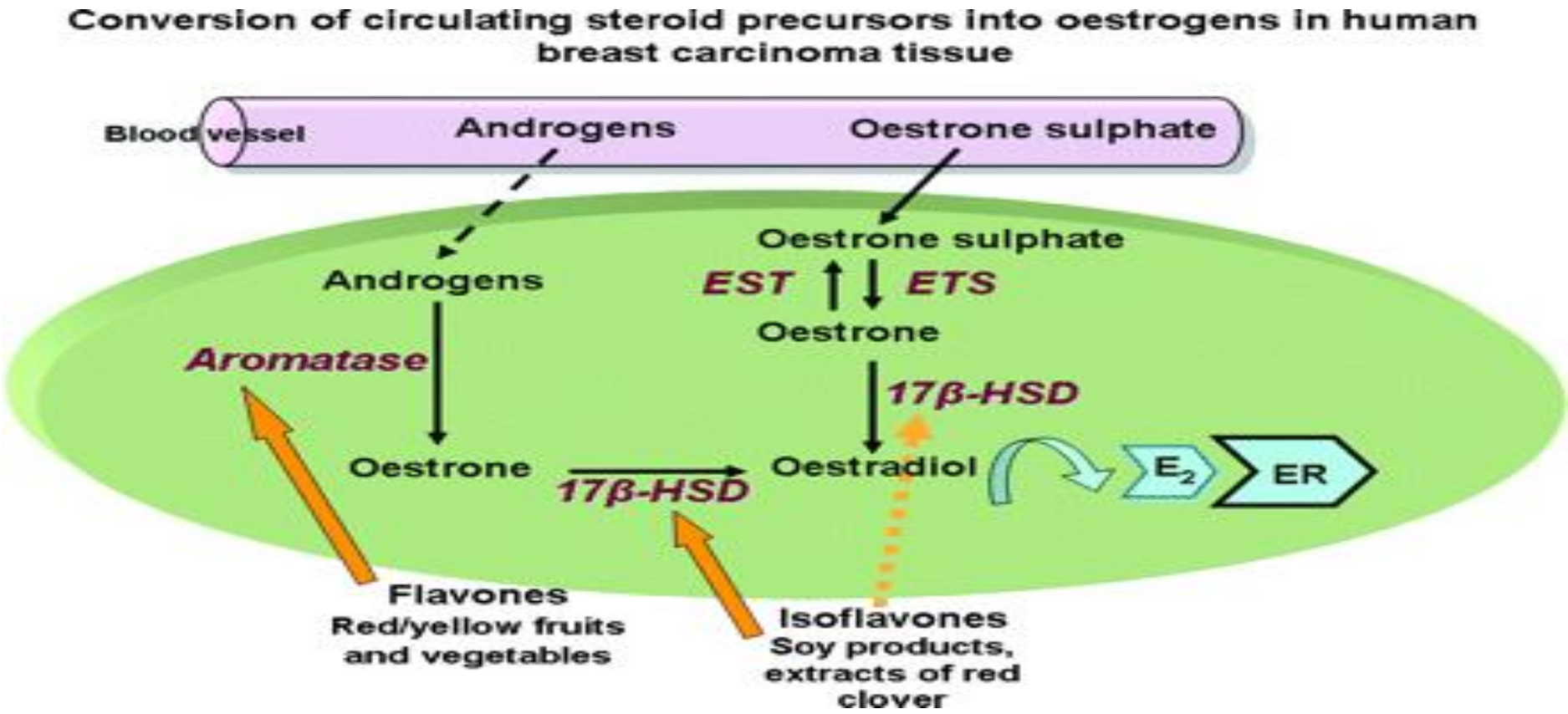
Aromatase inhibitors include: isoflavones, flavones (quercetin) indole-3 carbinol and ENL and END

17 beta HSD inhibitors include genistein and diadzein –soy isoflavones



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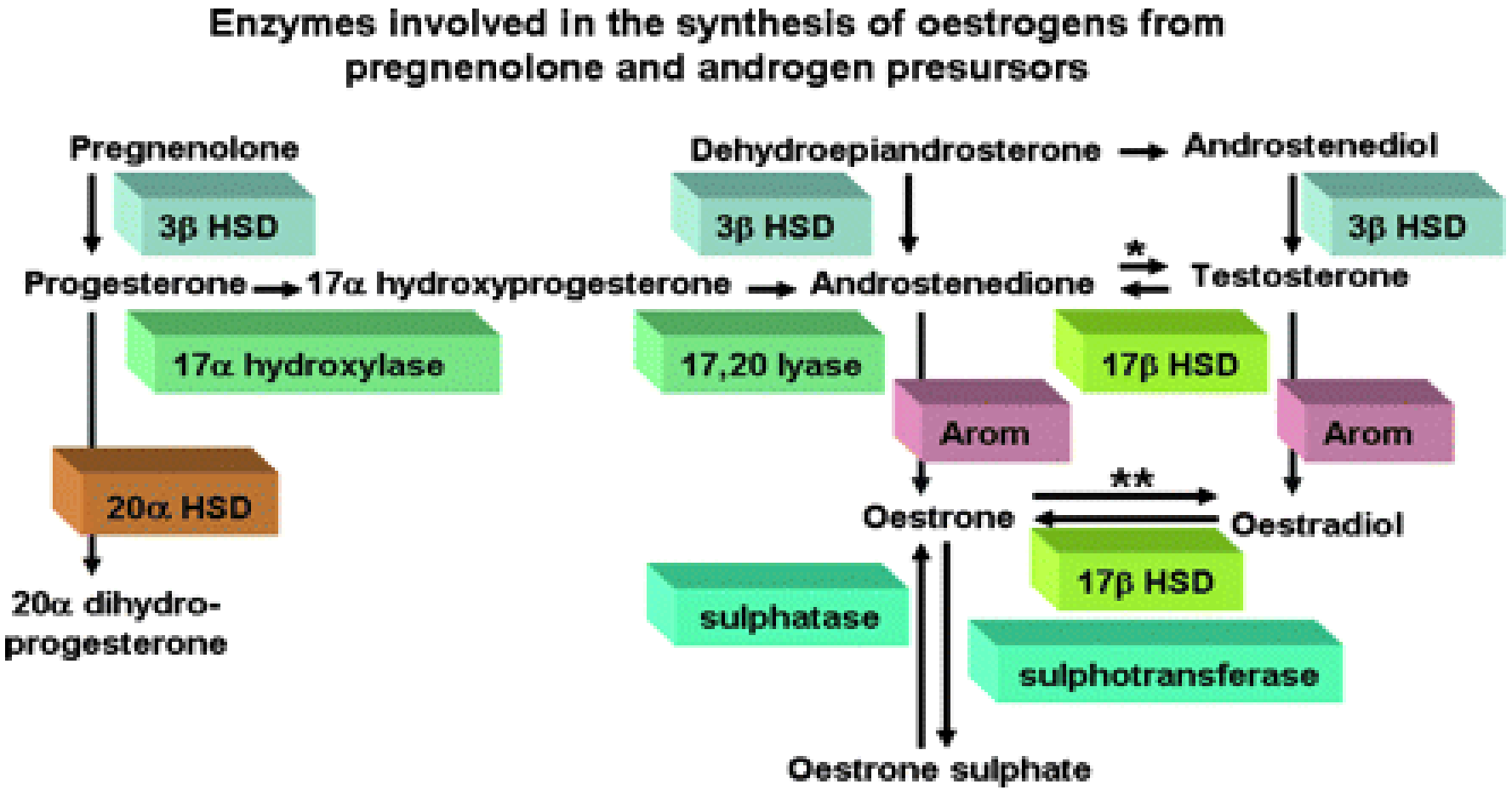
The isoflavones genistein and diadzein inhibit:
17ß-Hydroxysteroid dehydrogenase (**17ßHSD**) isoforms, which catalyze the final step in the formation of estradiol (E2) from estrone (E1)



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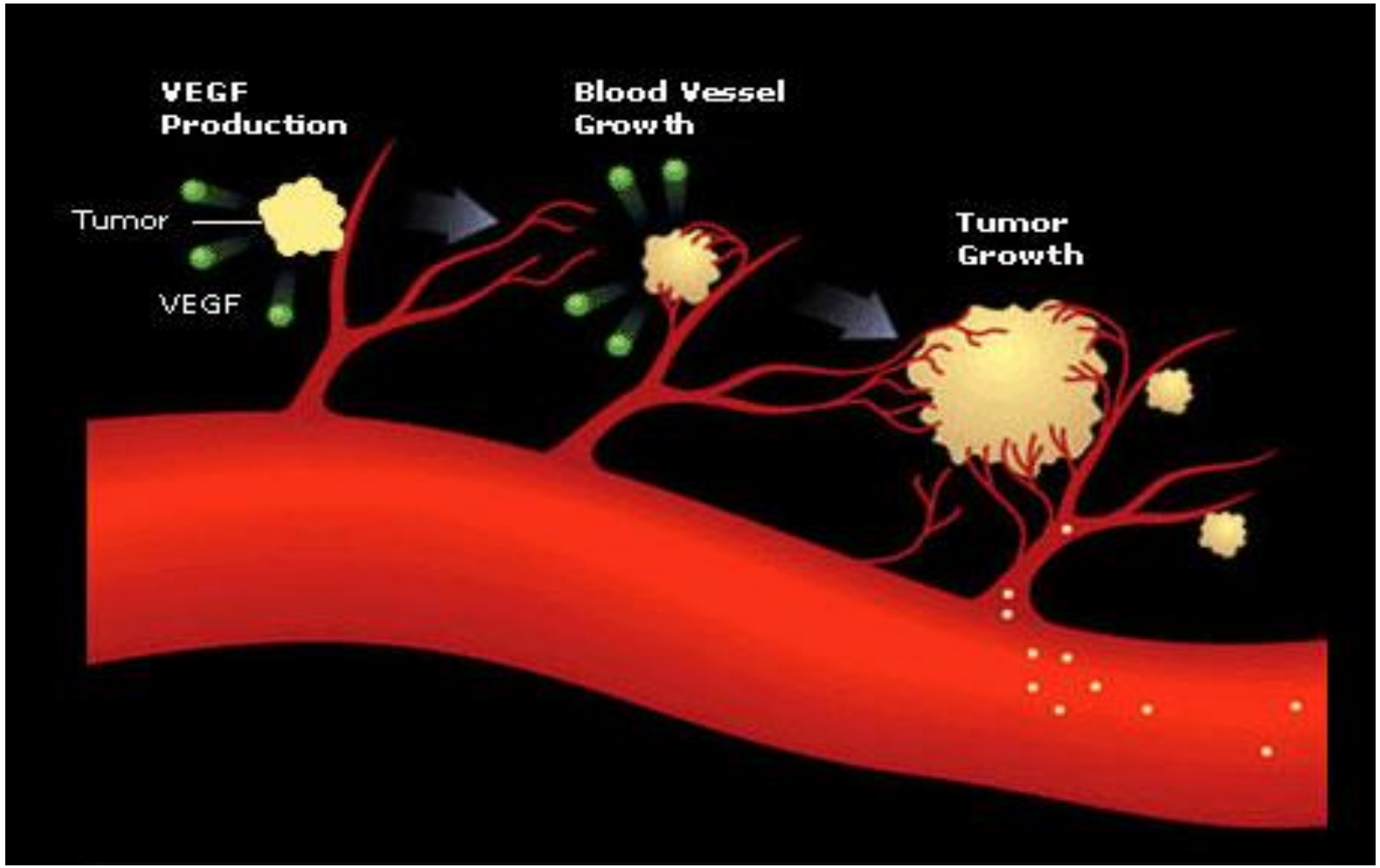
Soy Isoflavones Induce Anti-Angiogenesis In Cancer Cells by Inhibiting VEGF Release



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- 3. Gamma-Oryzanol – a natural component of rice bran oil:
  - Blocks release of FSH and LH
  - Reduces menopausal symptoms – (prescription drug in Japan)
  - Reduces cholesterol – (prescription drug in Japan)

- **Dosage:** 150 mg, twice per day.
- **Side Effects**: No significant reports
- **Precautions:** Previous breast and ovarian CA
- **Interactions**: No Drug or Nutrient Interactions

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- Example of Menopause Support Supplement:

1. Black Cohosh- 80 mg, standardized to 2.5% triterpene glycosides
2. Soy Extract – 125 mg, standardized to 20% isoflavones
3. Gamma-Oryzanol – 150 mg

- Dosage: 2 capsules (1-4 capsules)
- Success Rate – approx 80%

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Potentially Dangerous Herbs:

- Dong Quai (angelica species) – bleeding disorders, skin rash
- Red Clover Isoflavones – bleeding disorders, skin rash
- Licorice – hypertension & Bleeding

Coumarins are dangerous natural agent in regards to bleeding disorders

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Must Also Support Bone Density

- Calcium – 1500 mg per day
- Vitamin D – 1200-1500 IU
- Magnesium – 500-1000 mg
- Icariin Flavonoid – 60 mg
- Silica – 1-3 mg
- Boron – 1-3 mg
- Weight Bearing Exercise

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Natural Hormone Replacement

Natural Progesterone: (from wild yam):

200 mg (mg capsules)

25 mg (topical cream)

Bioidentical Hormones: Not proven to be safe (human experiment encouraged by Suzanne Somers and some MD's and ND's

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Breast Cancer (1:8 women)

- Approx – 50% of breast cancer is from faulty dietary and lifestyle practices
- Approx – 30% of breast cancer is protected against from having a full term pregnancy and breast feeding before age 30
- Approx – 20% of breast cancer has a strong genetic link (but not all women with genetic risk develop breast cancer – so a gene-environmental relationship exists in many of these cases)

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J Natl Cancer Inst 1996

Estimates of cancer deaths avoidable by dietary change

Types of cancer	Percent avoidable		
	Doll-Peto (1981)	Willett (1994)	Range (1994)
Lung	20	20	10-30
Colon/rectum	90	70	50-80
Breast	50	50	20-80
Prostate	(with other)	75	20-80
Pancreas	50	50	10-50
Stomach	35	35	30-70
Endometrium	50	50	50-80
Gall bladder	50	50	50-80
Larynx, bladder, cervix, mouth, pharynx, esophagus	20	20	10-30
Other types	10	10	—
Overall estimate	35	32	20-42

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Genetic Risk For Breast Cancer

Approximately 15-20% of breast cancer cases occur in women who **inherit** genetic mutations in key proto-oncogenes, especially:

1. BRCA1 and BRCA2
2. HER-2 (EGFR type 2 cell membrane receptors)

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Oncogenes and Cancer

- Oncogenes are mutated genes that contribute to cancer development by disrupting a cell's ability to control its own growth and DNA repair mechanisms.

- Normally mitosis (cell division) is a carefully regulated event, requiring the activation of one protein to activate another, in what is known as a signal transduction cascade. This cascade eventually culminates in changes in gene expression that prepares the cell for mitotic events.

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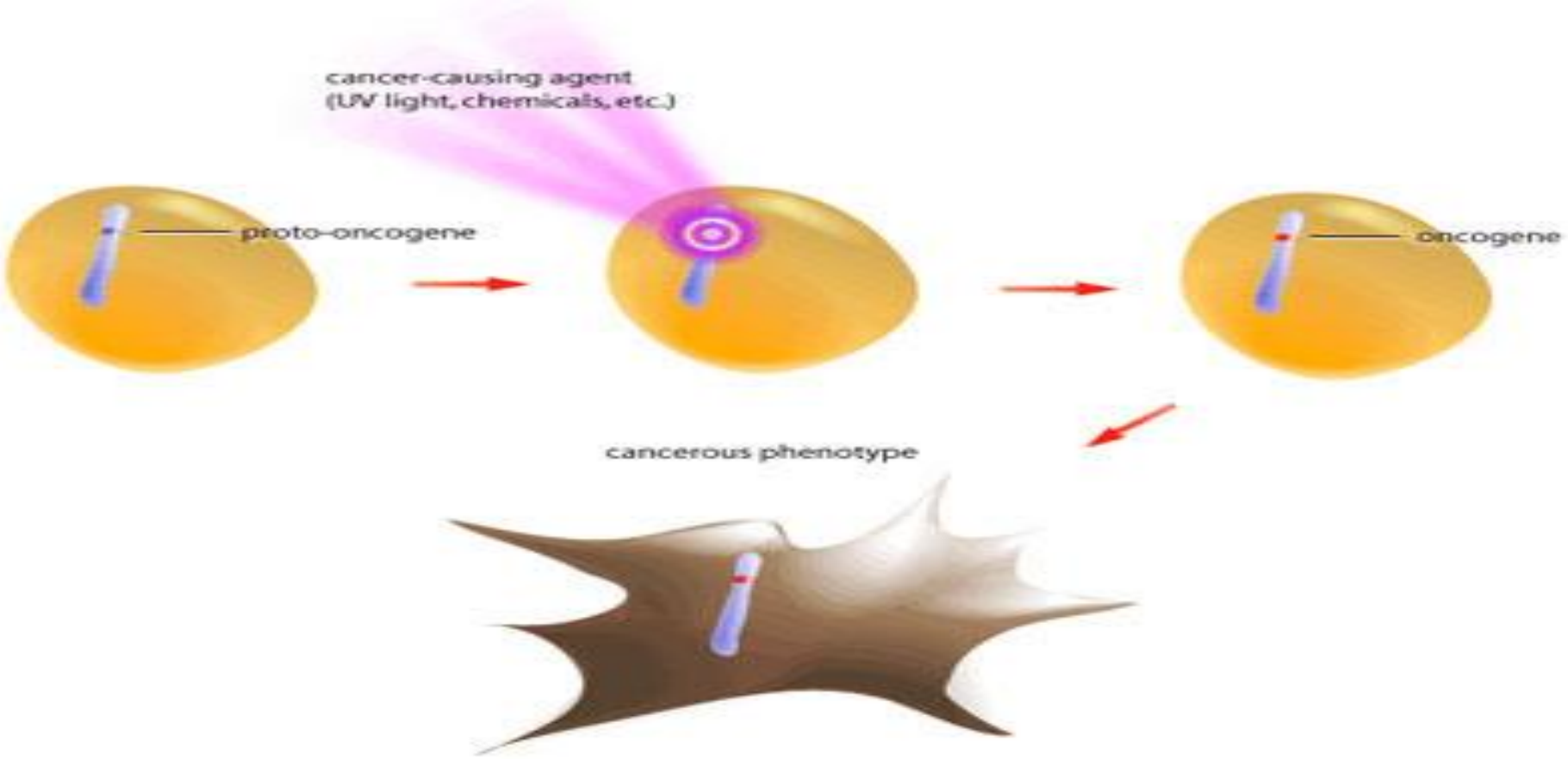
Proto-oncogenes can become oncogenes. Proto-oncogenes encode for normal cellular proteins involved in growth signaling pathways. When these genes become mutated as a result of exposure to chemicals, radiation, or other carcinogens, these genes are

called oncogenes.



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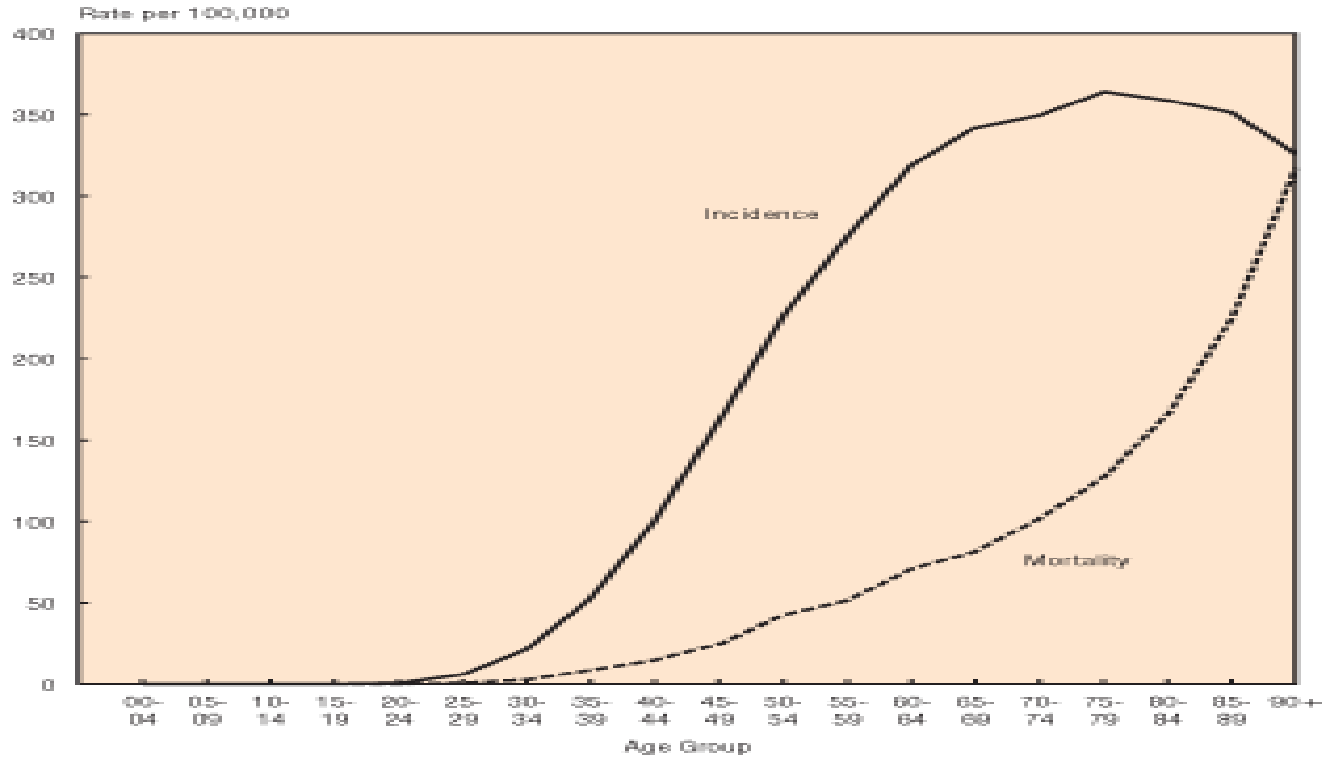
Breast Cancer Incidence With Age In Canada

Figure 13.1
Age-Specific Incidence and Mortality Rates for Breast Cancer, Females, Canada, 1999-2003



Source: Surveillance Division, CCDPC, Public Health Agency of Canada

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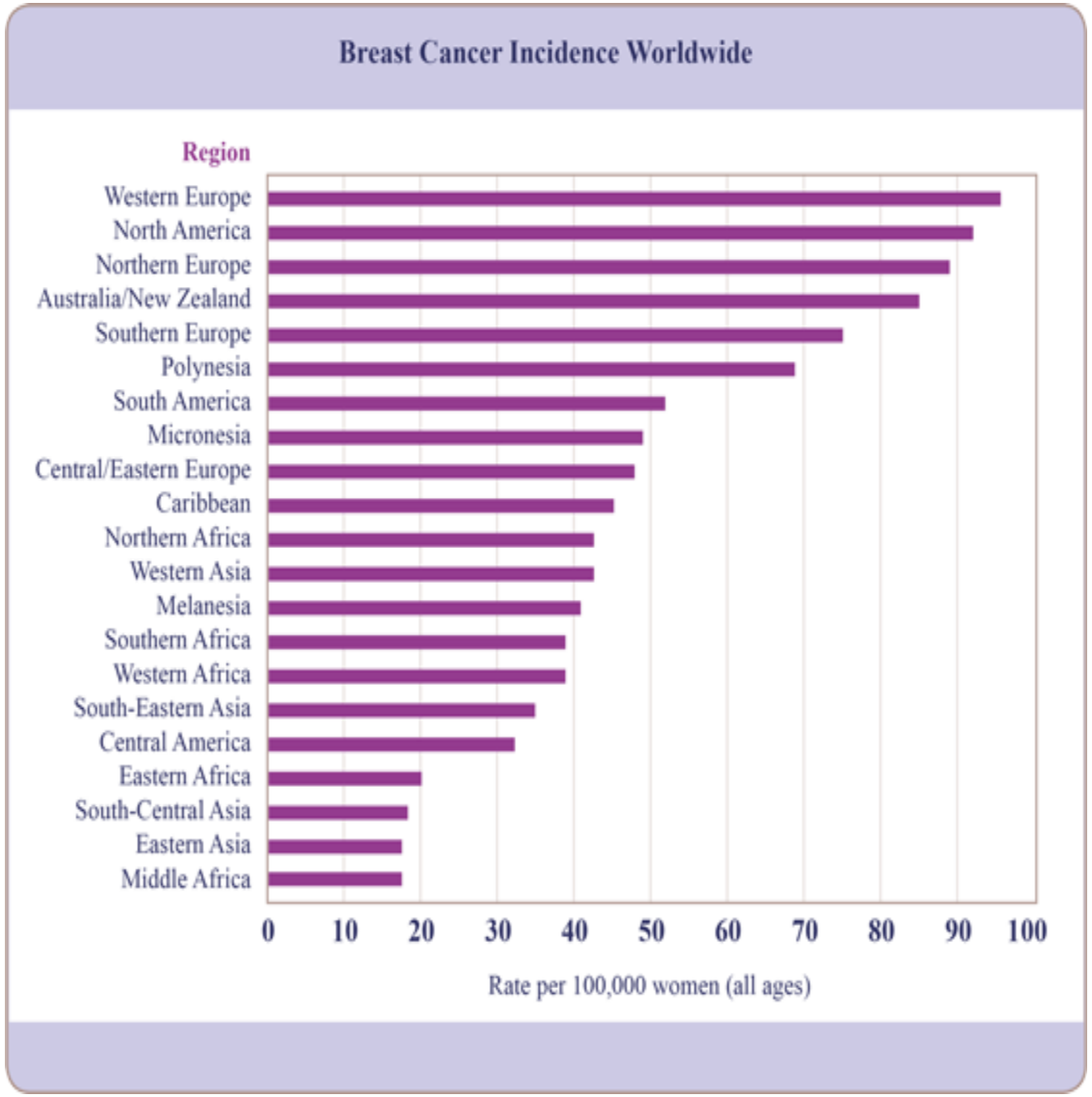

Increasing Affluence Moves People Away From Plant-based Diets and Increases Reproductive and Colon Cancers Particularly

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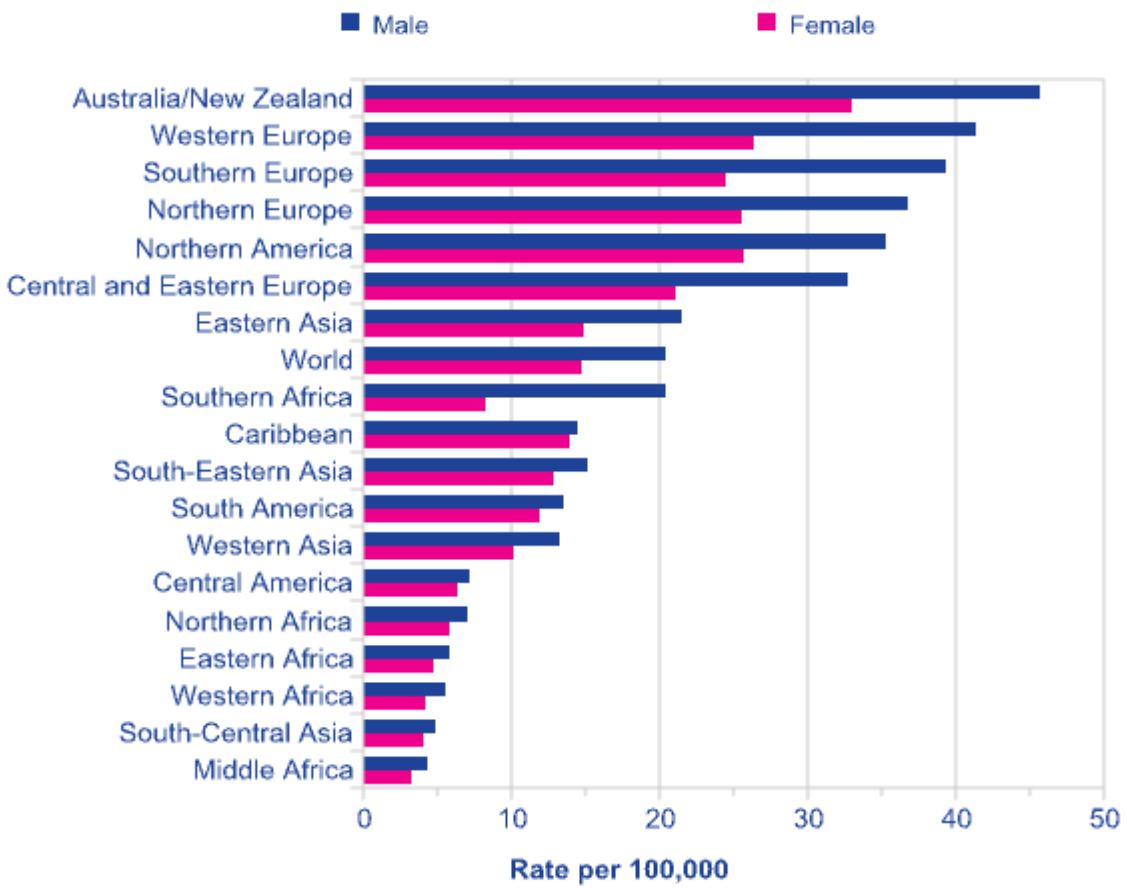
Colon Cancer Incidence



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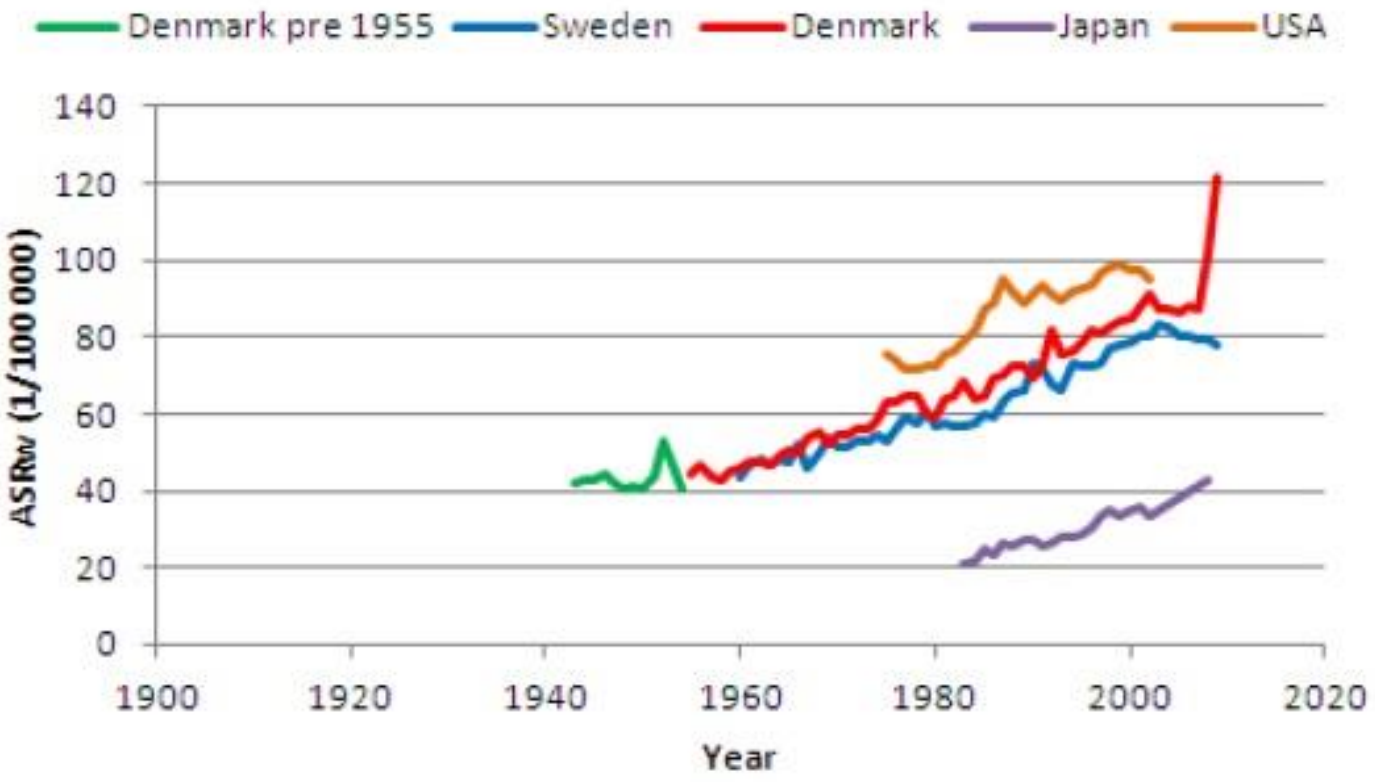
Age-standardized breast cancer incidence in women from Denmark, Sweden, United States, and Japan.



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Breast Cancer Genetics (BRCA1&2)

BRCA1 (**breast cancer 1)** is a human gene that belongs to a class of genes known as **tumor suppressors**, which maintains genomic integrity to prevent uncontrolled proliferation.

The multifactorial BRCA1 protein product is involved in:

- DNA damage repair
- Ubiquitination (protein degradation)
- Transcriptional regulation
- And other functions.

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BRCA1 and BRCA2 – works synergistically with other surveillance genes (ATM), tumour suppressor genes (p53) and DNA repair genes to:

1. Repair damaged proto-oncogenes (PTEN)
2. Induce apoptosis if DNA repair is not possible
3. Induce DNA repair enzymes to fix DNA adducts, DNA single or double strand breaks or other DNA damage (free radical damage) or DNA adducts.

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- A mutated *BRCA1* gene usually makes a protein that does not function properly because it is abnormally short.

- **Researchers believe that the defective BRCA1 protein is unable to help fix mutations that occur in other genes (PTEN).**

- This allows DNA damage and mutations to accumulate, which may allow cells to grow and divide uncontrollably to form a tumor.

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- Once a mutation occurs (incorrect base pair substitution) in a proto-oncogene – enzymes can not repair it (Permanent mutations passed on to all daughter cells)

- As mutations accumulate in proto-oncogenes, there is a greater chance that cancer will develop

Therefore – it is vital for the cell to:

1. Identify DNA damage

2. Repair DNA damage properly without inserting the wrong base (e.g. excision enzymes)

3. Induce apoptosis if excessive damage occurs

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If a woman with a family history of breast cancer inherits a defective form of either BRCA1 or BRCA2, she has an estimated up to 80% chance of developing breast cancer in western world countries.

Researchers also think that the two genes are linked to ovarian, prostate, and colon cancer, and BRCA2 likely plays some role in breast cancer in men.

("Where is the ERBB2 gene located?" in Genetics Home Reference, U.S. National Library of Medicine, 2004, http://ghr.nlm.nih.gov/geneerbb2 (accessed February 8, 2005)

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Genes vs Environment

- Several studies carried out in the past decade have reported higher rates of *BRCA1* and *BRCA2* gene mutations in Ashkenazi (Eastern and Central Europe ancestry) Jewish women than in the general population in different countries.

- This fact has also been associated with a higher lifetime risk of developing ovarian and breast cancer among Ashkenazi women, the latter ranging from 38% by age 50 to 59% by age 70.

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Brazil Study

- Different from the reported scientific literature about a higher breast cancer incidence among Ashkenazi women in North America and Europe than in the general population, breast cancer seems to present a *moderate pattern of occurrence among* ***Brazilian*** *Ashkenazi Jewish women* **suggesting that dietary and lifestyle factors can suppress breast cancer in high women with genetic vulnerability.**

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- These results suggest that germ mutations seem insufficient to induce higher breast cancer risks by themselves, but environmental interaction would also be necessary to modulate gene expression related to familial breast cancer.

- Koifman S. *Breast Cancer Res* 2001, **3:**270-275)

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BRCA1 Mutations And Breast Cancer
December 9th, 2007 in Medicine & Health / Genetics

- In 1997, Dr. Parsons led one of the two teams that independently discovered the PTEN **(phosphatase and tensin homolog),** one of the most important tumor suppressor genes altered in breast cancer, as well as in brain and prostate cancers.

- PTEN is now recognized to be mutated in about 30 percent of all cancers, making it the **second most mutated gene in cancer after p53.**

- Knocking out PTEN sends a strong pro-growth signal on tumor cells. This is unlike the BRCA1 mutation, which only predisposes the cells to accumulate genetic damage and sends an indirect signal for cell growth.

- “Once a cell loses PTEN, it has a growth advantage over its neighbors and starts on the road to cancer,” said Dr. Parsons.

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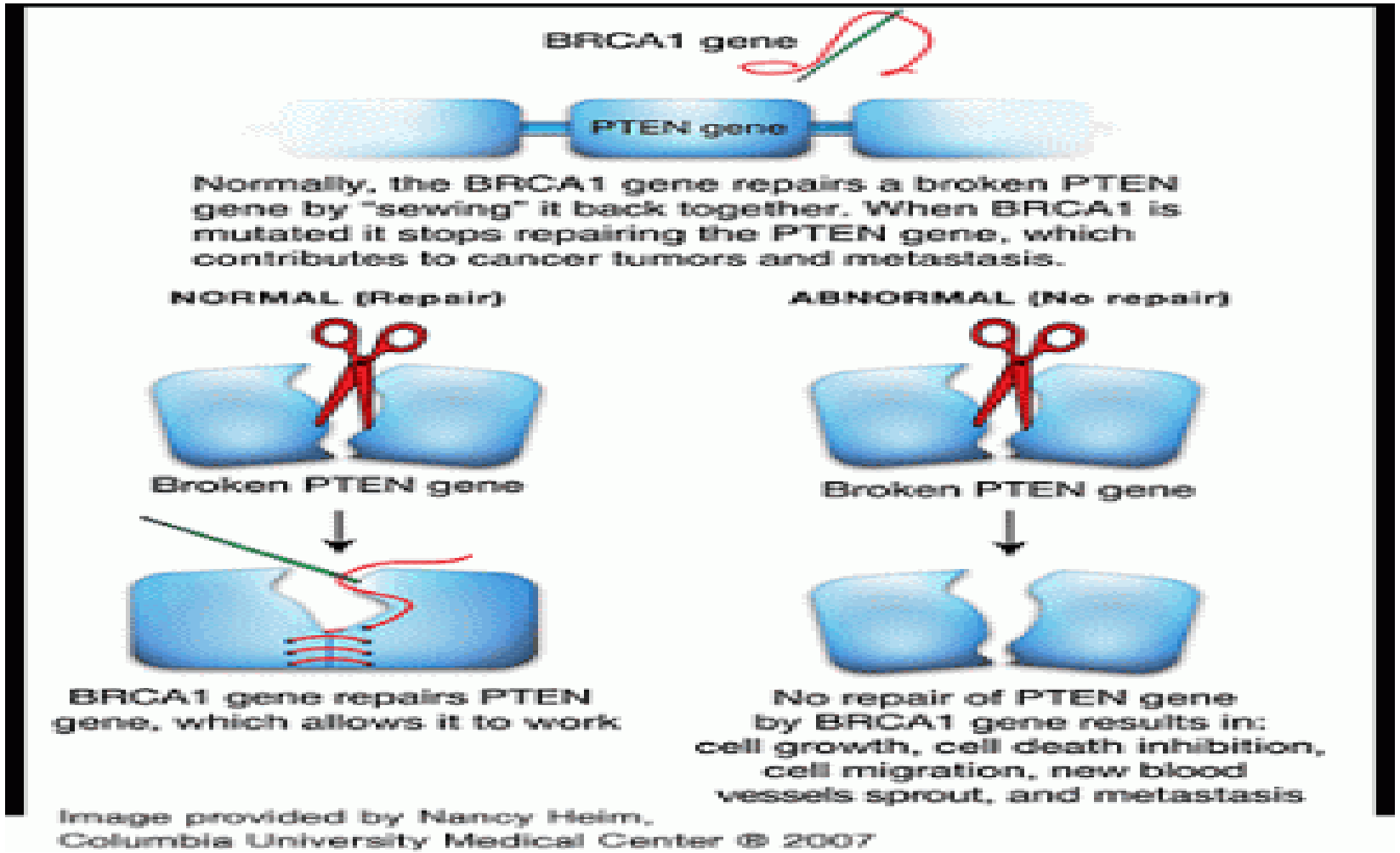
Genetic Risk:
BRCA1(2) Gene Mutation And Breast Cancer (Prostate CA)



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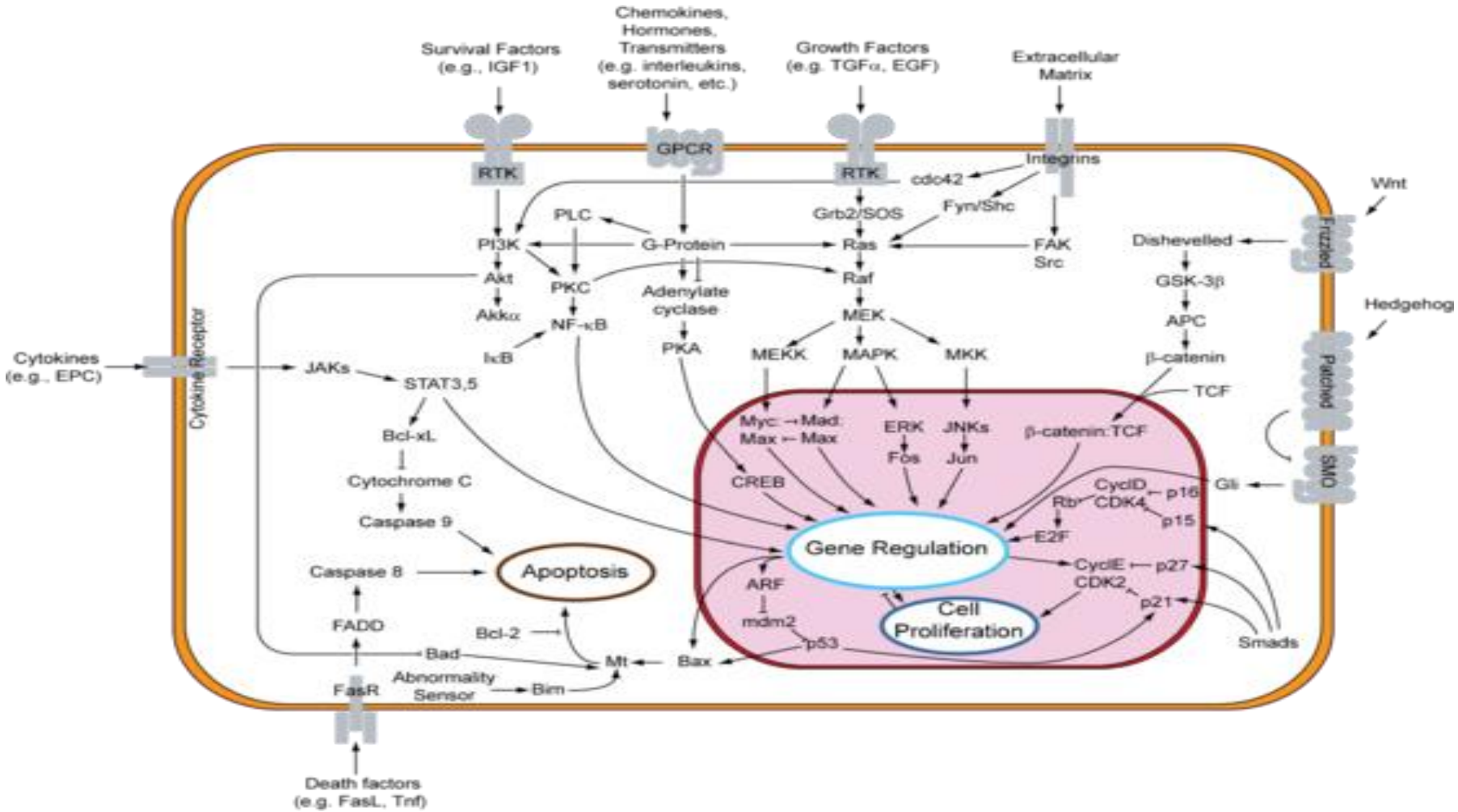
Her-2 and Tumor Suppressor Genes



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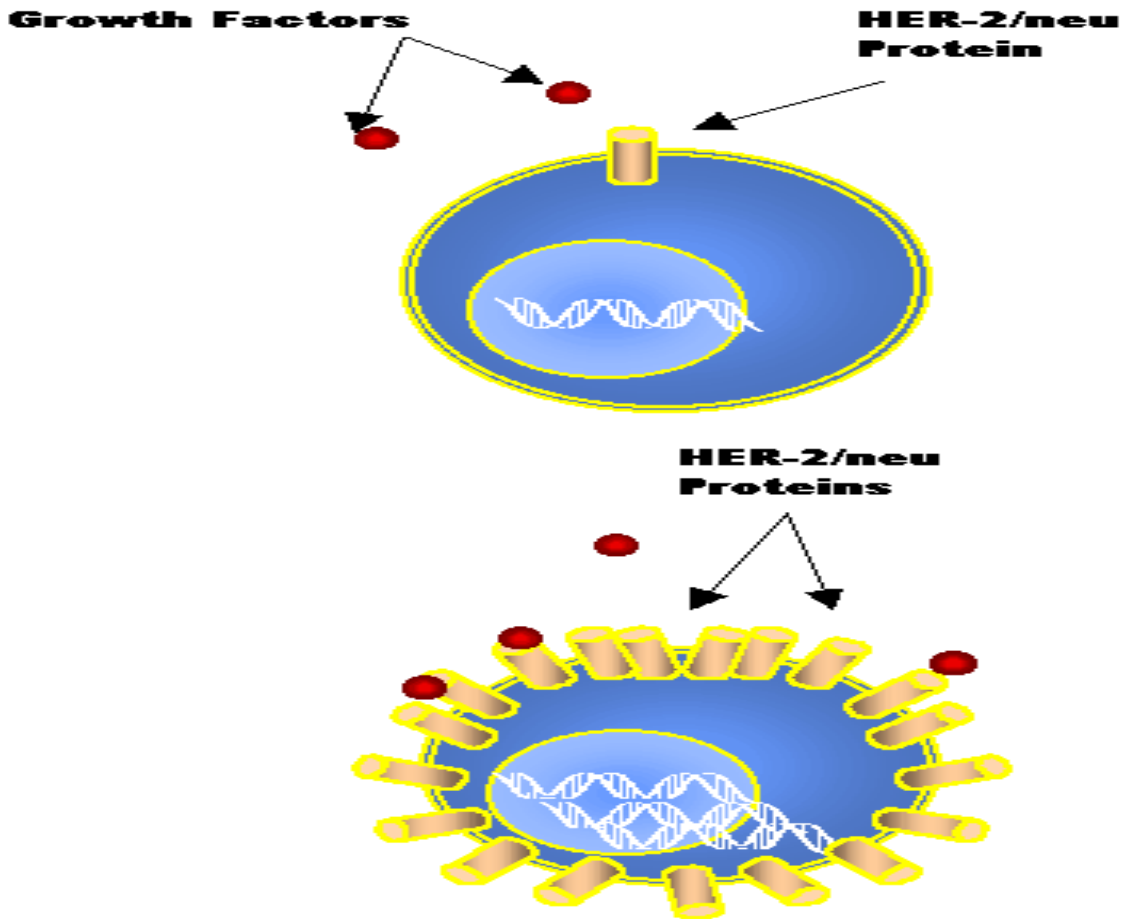
Over Expression of Her-2



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BRCA1 & 2 Assoc With EGFR Over expression

(van der Groep P, et al)

We conclude that invasive breast carcinomas in patients with a BRCA1 or BRCA2 germ-line mutation show a high frequency of EGFR over expression

Thus, we urge further investigation into the mechanisms of EGFR over expression and into new preventive strategies through EGFR targeting. (van der Groep P, et al) e.g curcumin, monoclonal antibodies against HER-2 Receptors

Up to 40% of Breast Cancer Cases Involve Over expression of Erb-2 (HER-2) Receptors (hyperproliferation)

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Some Natural Agents Shown To Silence HER-2 (Epidermal Growth Factor II):

- Curcumin
- Vitamin E Succinate
- Vitamin D

Medical Treatment = Herceptin (monoclonal antibody that destroys HER-2 Receptor)

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Epidermal Growth Factors Receptors As An Oncogene

- In its proto-oncogenic form it requires binding of the growth factor molecule to enable its kinase activity. The catalytic domain then proceeds to transfer phosphate groups to its target proteins to activate them, which ultimately leads to translation of proteins involved in mitosis.

- The oncogenic form of *egfr produces a receptor that does not* require binding of growth factor, but instead is constitutively active. In this way the oncogene product is capable of always activating the pro-growth pathway in the absence of progrowth signals

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- Oncogenes are mutated forms of proto-oncogenes; these genes are often involved in growth signaling and antiapoptotic pathways.

- When proto-oncogenes mutate to become oncogenes they retain their functionality, but are no longer capable of responding to normal regulatory signals.

- At present, over 100 oncogenes have been identified in various cancers.

Reference

ONCOGENES: THE (AUTOSOMAL) DOMINANT EVIL

Brandon Stott and Michelle Wyse. The Science Creative Quarterly (August 2003)

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Green Tea Catechins and Breast CA

- The American Association of Cancer Research published a study in October 2012 showing that supplementation of catechins from green tea showed important anti-cancer benefits in women with diagnosed breast cancer, who were awaiting surgery.

- Many studies over the years have shown a link between green tea and cancer prevention.

- In this study researchers treated a group of women with various doses of green tea catechins (400, 600 or 800 mg, twice per day) or a placebo for six months. All the women had been diagnosed with hormone –receptor negative breast cancer and were awaiting surgical resection.

- The results showed that the green tea catechins had a significant impact on cell signaling mechanisms that encouraged cancer cell suicide (apoptosis). The catechins also toned down pathways linked to metastasis (spreading of the tumor through the body) and reduced secretion of growth factors that enable tumors to feed themselves with new blood vessels (VEGF).

Reference:

- http://www.eurekalert.org/pub_releases/2012-10/aafc-moa101112.php

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Vitamin D Doubles Breast Cancer Survival

- Over the past 20-25 years various studies have shown that women who have higher blood levels of vitamin D have an associated lower incidence of breast cancer (1,2,3).

- In recent years (2007) a large 4-year clinical trial, involving 1179 healthy postmenopausal women (over the age of 55), reported that the women given vitamin D supplementation (1100 IU per day) and calcium supplementation (1400-1500 mg per day) showed a 77% reduction in incidence of all combined invasive cancer, including breast cancer, compared to women given the placebo (4).

- A study published in March 2014 in the journal Anticancer Research has now shown that breast cancer survivors would be well advised to keep their vitamin D blood level within the ideal range. The study by B. Sharif et al showed that breast cancer patients with high levels of vitamin D in their blood were twice as likely to survive the disease compared to women with low levels of vitamin D (5).

- These researchers analyzed data from five large breast cancer studies, involving a total of 4,443 breast cancer patients, with an average follow-up period of nine years. ***The data showed that women who had an average vitamin D blood level of 30ng/ml experienced survival rates double that of women who had an average blood vitamin D blood level of 17ng/ml.***

- The researchers pointed out that the average vitamin D blood level in patients with breast cancer in the United States is 17ng/ml (5).

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- In Canada blood levels of vitamin D is usually reported in nmol/L, not ng/ml. Thus, for Canadians it is worth noting that 30ng/ml is equal to about 75nmol/L, whereas 17ng/ml is equal to about 42nmol/L.

- In their concluding statements B. Sharif et al suggest that breast cancer patients may be well advised to increase their blood level of vitamin D to 80ng/ml (approximately 200nmol/L), based on all available evidence (5).

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How Does Vitamin D Prevent Breast Cancer?

- Vitamin D has been shown to reduce cancer development and progression in a number of ways:

- Vitamin D slows down the rate of cell division, which reduces the likelihood that cancerous mutations will emerge.

- Vitamin D promotes maturation (differentiation) of newly formed cells, which reduces transformation to a cancerous state.

- Vitamin D favourably modulates the function of immune cells, many of which are responsible for identifying and destroying emerging cancer cells (1,2,3,4,5).

- Vitamin D is responsible for increasing the cell's production of a surface receptor (antennae) known as **E-cadherin,** which enables the cell to bind to and communicate with adjacent cells or supporting tissues. Very aggressive cancer cells tend to have low levels of E-cadherin, which enables them to replicate unchecked by adjacent cells, giving themselves the green light to invade adjacent tissues and spread into the blood and lymphatic system in their quest to metastasis throughout the body (6,7,8).

- Studies show that many cancer cells maintain vitamin D receptors on their cell surface. When vitamin D (25-hydroxycholecalciferol D) attaches to this receptor it stimulates the synthesis of E-cadherin, which in turn puts the brakes on the ability of cancer cells to invade adjacent tissues and metastasize. (5,6)

- B. Sharif and fellow researchers suggest that it is the expression of E-cadherin by cancer cells that likely explains why breast cancer patients with higher blood levels of vitamin D are less likely to have further progression of their disease after standard medical treatment (6).

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- In a follow-up interview regarding the study (March 2014), coauthor Dr. Cedric F. Garland, professor in the Department of Family and Preventive Medicine at the University of California, San Diego School of Medicine, pointed out that "a 2011 meta-analysis by Garland and colleagues estimated that a serum vitamin D blood level of 50 ng/ml (about 125 nmol/L) is associated with a 50 percent lower risk of breast cancer.

- "While there are some variations in absorption, those who consume 4,000 IU per day of vitamin D from food or a supplement normally would reach a serum level of 50 ng/ml. Garland urged patients to ask their health care provider to measure their levels before substantially increasing vitamin D intake" (9).

- Vitamin D toxicity is not known to occur until reaching a vitamin D blood level at or above 100 ng/ml (250nmol/L), so there is a large margin of safety when taking vitamin D supplements (3).

References:

- Garland F, Garland C, Gorham E, Young J Jr. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. Prev Med 19: 614-622, 1990
- Grant WB. Ecologic studies of solar UV-B radiation and cancer mortality rates. Recent Results Cancer Res 164: 371-7, 2003.
- Vieth R. Vitamin D and cancer mini-symposium: the risk of additional vitamin D. Ann Epidemiol 19: 441-445, 2009.
- Lappe JM,Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr 85: 1586-1591, 2007.
- Sharif B. Mohr, Edward D. Gorham, June Kim, Heather Hofflich And Cedric F. Garland. Meta-analysis of vitamin D sufficiency for improving survival of patients with breast cancer. Anticancer Research 34(3): 1163-1166, 2014
- Pena C, Garcia JM, Silva V, Rodriguez R, Alonso et al. E-cadherin and vitamin D receptor regulation and SNAIL and ZEB1 in colon cancer: clinicopathological correlations. Hum Mol Genet 14(22):3361-70, 2005
- G Berx, et al. E-cadherin inactivation in lobular carcinoma in situ of the breast. EMBO J. 14(24): 6107–6115, 1995.
- G Berx, et al. E-cadherin is inactivated in a majority of invasive human lobular breast cancers by truncation mutations throughout its extracellular domain. Oncogene 13(9): 1919–1925, 1996.
- Science Daily: Vitamin D increases breast cancer patient survival study show. March 6, 2014. http://www.sciencedaily.com/releases/2014/03/140306163236.htm

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Soy and Breast CA Recurrence

- A study presented in 2011, at the *102nd American Association for Cancer Research 102nd Annual Meeting* (April 2-6), showed that the consumption of soy products by **breast cancer** survivors reduced their risk of cancer recurrence and progression, compared to **cancer** survivors who ingested little or no soy foods.

- The report featured data that combined four National Cancer Institute-funded studies: the *Shanghai Breast Cancer Survival Study*; the *Life After Cancer Epidemiology Study*; the *Women's Healthy Eating and Living Study*; and the *Nurses' Health Study*. Together this included 18,312 women between the ages of 20 and 83 years, who had previously been diagnosed with invasive primary **breast cancer**.

- Nine years after the initial **diagnosis of breast cancer** diagnosis the combined **data showed the following:**

- Those who consumed the highest amounts of soy isoflavones (more than 23 mg per day) were compared with the outcomes of those whose intake was lowest (0.48 mg per day or lower). Women in the highest intake category of more than 23 mg per day had a 9 percent reduced risk of mortality and a 15 percent reduced risk for recurrence, compared to those who had the lowest intake level.

Reference:

- American Association for Cancer Research (2011, April 5). Soy isoflavones not a risk for breast cancer survivors, study finds. *ScienceDaily*.

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How Soy Isoflavones Reduce Risk of Cancer

1. Lower endogenous estrogen levels (aromatase and 17B-HSD inhibition) – see next slide

2. Stimulate the production of sex hormone-binding globulin by the liver (which in turn leads to more bound and less free estradiol, reducing the amount of estrogens available for binding with estrogen receptors)

3. Inhibit the enzymes that promote cell proliferation (protein tyrosine kinase, DNA topoisomerase and ornithine decarboxylase)

4. Inhibit angiogenesis (which prevents the building of life-supporting blood vessels in and around malignant tumors), provide antioxidant defense and induce cell differentiation.

5. Further, the weak estrogenic potential (more than 1,000 times weaker than estradiol) of soy isoflavones do not elicit a strong estrogenic response and thus have an anti-estrogenic effect that tends to inhibit the growth and proliferation of estrogen-dependent cancer cells, as demonstrated by the research of A. Molteni et al.

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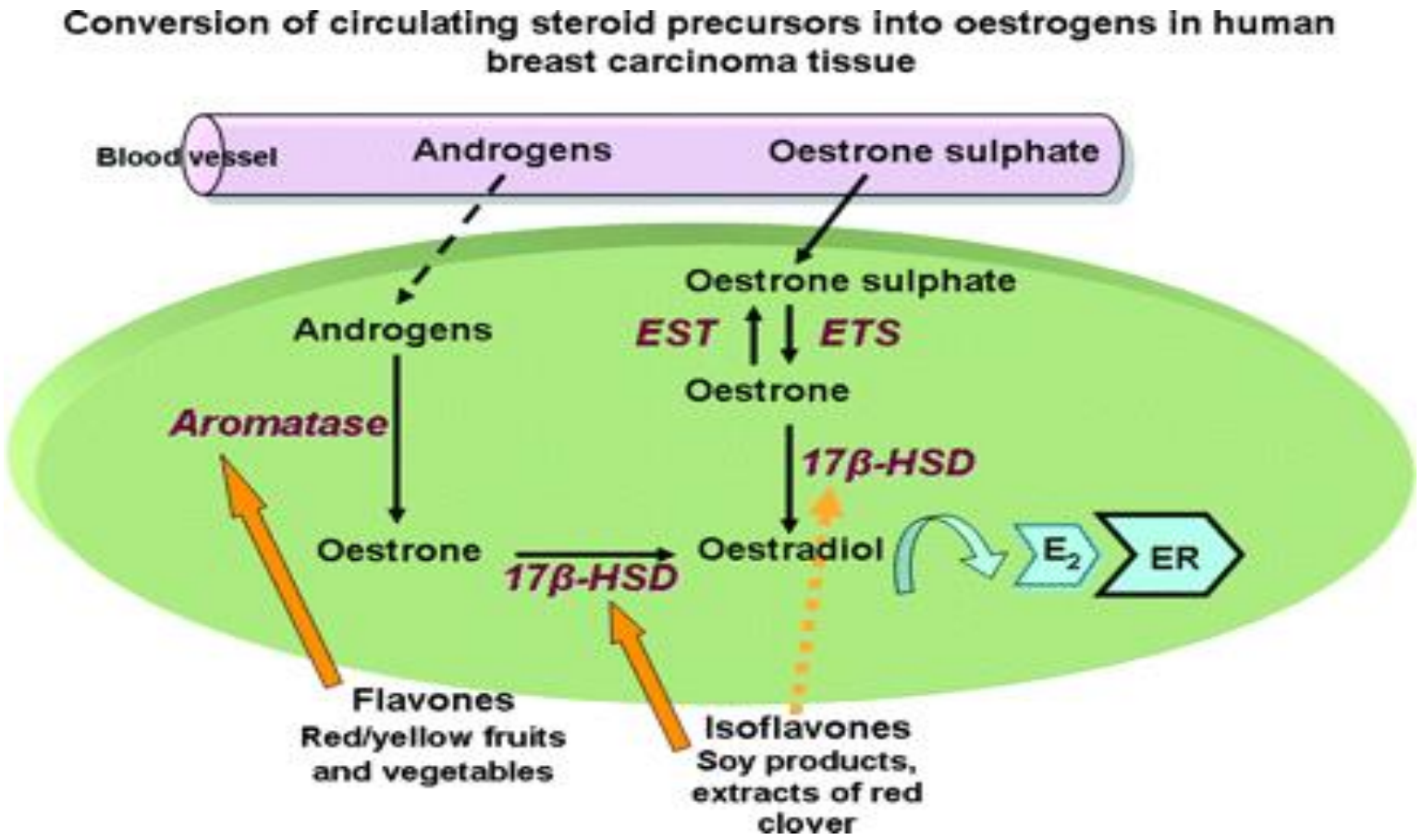
Aromatase inhibitors include: isoflavones, flavones (quercetin) indole-3 carbinol and ENL and END

17 beta HSD inhibitors include genistein and diadzein –soy isoflavones



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Soy Isoflavones – cont-d

- The recent study by **M Sartippour** et al, provides further evidence that a high intake of soy isoflavones may not only prevent reproductive cancers, but may be beneficial in controlling the progression and recurrence of breast cancer.

- In a similar intervention study, involving men with existing prostate cancer, supplementation with 100 mg per day of soy isoflavones showed a favorable outcome in stabilizing PSA levels (M Hussain et al, Nutrition and Cancer, 2003). In this study, soy isoflavone supplementation was shown to decrease the rate of rise in serum PSA (prostate specific antigen) levels in patients with androgen dependent and androgen-independent prostate cancer.

References:

- Sartippour MR, Rao JY, Apple S et al. A pilot clinical study of short-term isoflavone supplements in breast cancer patients. 2004. Nutr and Cancer, 49;1: 59-65
- Molteni A, Brizio-Molteni L, and Persky V. In vitro hormonal effects of soybean isoflavones. 1995. J Nutr, 125: suppl:751S-756S
- Hussain M, Banerjee M, Sarkar FH et al. Soy isoflavones in the treatment of prostate cancer. 2003. Nutr and Cancer, 42;2: 111-117

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Multivitamin and Antioxidant Supplements Shown to Reduce Breast Cancer Recurrence

Study published in Breast Cancer Research and Therapy (Nov 2011)

Study followed women who had been treated for breast cancer looking at their survival and relapse rates during the 2-yr follow-up period after breast cancer treatment

Results:

- Study showed that women who were in the top 25% of following a healthy lifestyle, who regularly took a multiple vitamin supplement, had a 60-70% reduction in risk of dying from any cause during the study

- A healthy lifestyle was defined as a healthy diet (consuming at least 5.5 servings of fruits and vegetables per day) and being at least moderately physically active (being non-sedentary for 16 hours/week).

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Results showed that the addition of the multiple vitamin supplement **enhanced survival outcomes by 60-70% in these women**

However, in women who didn't follow a healthy lifestyle (diet remained poor and were non active) the addition of a multiple vitamin supplement **alone** did not improve survival to any degree.

Take Home Message:

That's why they're called supplements – they are intended to supplement or enhance the metabolic effects of a healthy diet and exercise.

Supplements by themselves, in many cases, can't reverse the effects of unhealthy dietary and lifestyle practices.

Previous study showed similar outcome:

- A Shanghai China study followed 4,877 breast cancer survivors and examined antioxidant supplement use (vitamin C, vitamin E, and/or multivitamins) during the first six months post-diagnosis.
- Results showed that supplement use was associated with decreased risk of cancer recurrence by 22% and overall mortality by 18%.

Reference:

- Kwan ML, Greenlee H, Lee VS, Castillo EP, Gunderson EP, Habel LA, et al. Multivitamin Use and Breast Cancer Outcomes in Women with Early-Stage Breast Cancer: The Life After Cancer Epidemiology (LACE) Study. Breast Cancer Res Treat. 2011 Nov; 130(1): 195–205.

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Saturated Fat and Total Fat Linked to Breast Cancer

Study published in Journal of the National Cancer Institute in April, 2014

The EPIC study has been following 337,327 women living in 10 different European countries
EPIC is the acronym standing for “European Prospective Investigation into Cancer and Nutrition (EPIC)”

Study showed that women who consume the highest amount of total fat and particularly saturated fat in their diet:

- Have up to a **50% increased** for breast cancer compared to women eating the least amount of total fat and saturated fat.

- Study analyzed data from 10,062 Breast Cancer patients from the EPIC study with 11.5 years of follow-up.

It’s one of the largest human cancer studies ever undertaken, so we believe the results are meaningful

Many previous human studies, as well animal studies show that total fat and especially saturated fat increases breast cancer risk

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The EPIC study researchers point out that breast cancer is divided into various subclasses of disease:

- Estrogen Receptor Positive or Estrogen Receptor Negative
- Progesterone Receptor Positive or Progesterone Receptor Negative
- Her-2 Positive or Her-2 Negative.

The EPIC study showed that a high total fat diet and especially saturated fat increases risk of Estrogen and Progesterone Receptor Positive Breast Cancer

And Saturated Fat, in particular, increases risk of the very aggressive – Her-2 positive breast cancer

In fact, it seems that saturated fat may causes the over-expression of the Her-2 receptor that greatly increases the risk of this form of breast cancer

As only 10-20% of breast cancer is known to be due to genetic inheritance. the findings of the EPIC study are very meaningful – 50% increased risk of breast cancer linked to high fat and especially high saturated fat diet

As a means to prevent breast cancer I have encouraged women over the years to reduce their total fat and saturated fat intake by eliminating or greatly reducing:

Beef, Pork, High fat dairy products, deep fried foods, creamy salad dressings, breaded meats, high fat pastries etc.

Reference: S. Sieri, P. Chiodini, C. Agnoli, V. Pala, F. Berrino, A. Trichopoulou, V. Benetou, E. Vasilopoulou, M.-J. Sanchez, M.-D. Chirlaque, P. Amiano, J. R. Quiros, E. Ardanaz, G. Buckland, G. Masala, S. Panico, S. Grioni, C. Sacerdote, R. Tumino, M.-C. Boutron-Ruault, F. Clavel-Chapelon, G. Fagherazzi, P. H. M. Peeters, C. H. van Gils, H. B. Bueno-de-Mesquita, H. J. van Kranen, T. J. Key, R. C. Travis, K. T. Khaw, N. J. Wareham, R. Kaaks, A. Lukanova, H. Boeing, M. Schutze, E. Sonestedt, E. Wirfalt, M. Sund, A. Andersson, V. Chajes, S. Rinaldi, I. Romieu, E. Weiderpass, G. Skeie, E. Dagrun, A. Tjonneland, J. Halkjaer, K. Overvard, M. A. Merritt, D. Cox, E. Riboli, V. Krogh. **Dietary Fat Intake and Development of Specific Breast Cancer Subtypes**. *JNCI Journal of the National Cancer Institute*, 2014. Vol 106, issue 5. http://jnci.oxfordjournals.org/content/106/5/dju068

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Top 12 Ways to Prevent Breast CA - Overview

1. **Minimize your intake of high fat animal foods, with the exception of fish.** This includes red meat, pork, milk and yogurt above 1% MF, cheese above 3% milk fat, other high fat dairy products (ice cream, butter, whipped cream etc), and organ meats.

2. **Stay Lean** – women who are overweight after menopause have documented three-times greater risk of developing **breast cancer**

3. **Perform A Minimum Of 30 Minutes Of Endurance Exercise, Five Times Per Week** – Women who are physically active detoxify excess estrogens more effectively, and are less prone to **cancer**. As such, endurance exercise helps slow breast cell replication rates, which reduces cancer risk

4. **Take A High Potency Multiple Vitamin Containing Optimal Levels of Vitamin E Succinate, Vitamin D**, **Vitamin B12 and Folic acid:**

- **Vitamin E** Succinate – 400 IU; **Vitamin D** – 1000 IU; Vitamin B12 – 50 mcg; Folic Acid – 400 mcg

5. **Drink Less Alcohol And Get A B-50 Complex From Your High Potency Multiple Vitamin and Mineral Supplement** – Alcohol intake can double risk of **breast cancer**, although **supplementation** with certain B-vitamins has been shown to mitigate this risk to some degree

6. **Take A Supplement Containing Fish Oil, Flaxseed Oil and Borage Seed Oil and Eat Fish Twice Per Week** – this combination of **essential fatty acids** promotes synthesis of prostaglandin hormones that slow breast cell division and reduce inflammation, reducing risk of cancer.

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7. Consume Cruciferous Vegetables and Indole-3-Carbinols Daily – these vegetables contain indole-3 carbinol and sulforaphanes, which detoxify carcinogens, slow breast cancer cell division, reduce build up of dangerous estrogens and have other anti-cancer properties regarding breast **cancer prevention** (additional reading on cruciferous vegetables and breast cancer: http://www.meschinohealth.com/blog/breast-cancer/2012/08/07/peitc-cruciferous-vegetables-shown-inhibit-breast-cancer-mechanisms-blood-marker-discovered)

8. Take Two Heaping Tablespoons of Ground Flaxseed Each Day– flaxseeds release 800-times more enterolactone and enterodiol to the bloodstream than any other food or supplement. These phytonutrients reduce breast cancer risk in similar ways as cruciferous vegetables and are shown to reverse fibrocystic breast disease

9. Eat At Least One Serving Of A Soy Food Each Day – soy foods and supplements contain phytonutrients shown to reduce breast cancer risk, improve management of breast cancer cases and reduce breast cancer recurrence (additional reference: http://www.meschinohealth.com/blog/justin/2012/03/27/soy_benefits_breast_cancer)

10.Consider Taking A Daily Supplement With Curcumin and Other Natural Anti-Inflammatories (White Willow Extract, Ginger, Boswellia) – All of these nutrients block production of prostaglandin series-2, which is linked to **cancer development**, and curcumin also inhibits the Her-2 breast receptor, which is over active in up to 40% of breast cancer case.

11. Drink 3-6 cups green tea or take 3 capsules Adeeva Body Burn daily – catechins decrease VEGF and Hepatic growth factors involved in breast cancer invasion/migration, and green tea catechins have improved the molecular profile of patients with breast cancer awaiting surgery.

12. Melatonin: 0.5 – 3.0 mg after age 40 (increase the dosage with age)

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12 Steps To Prevent Breast Cancer – More Details

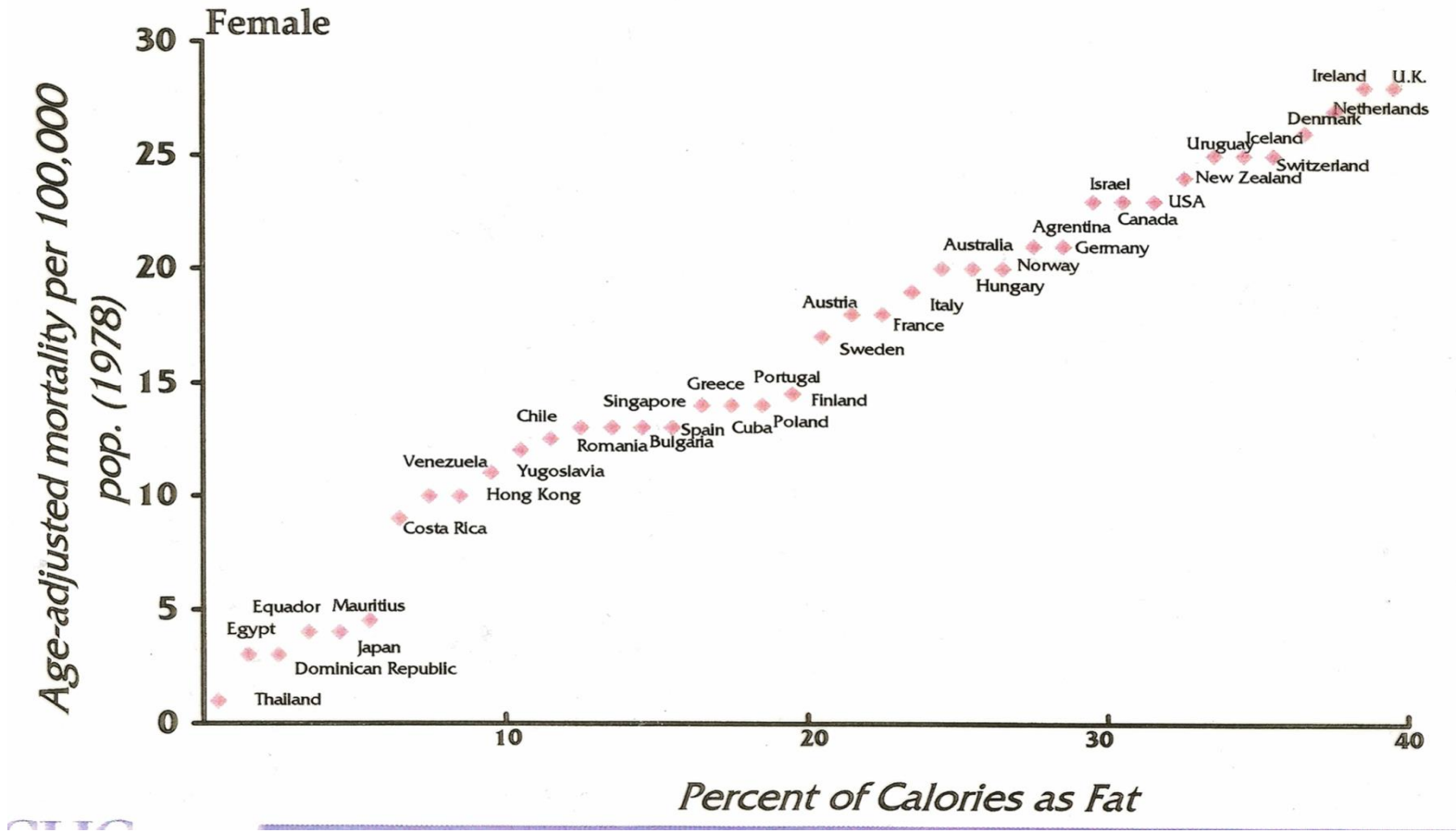
1. **Don’t eat high fat animal foods (except fish) and pastries**

- Increase cell division rate of breast and endometrial cells (saturated fat, cholesterol and arachidonic acid)

- More genetic mistakes occur

- Vegetarians have lower cancer rates in our society (e.g. 7th Day Adventists)

Breast Cancer and Dietary Fat



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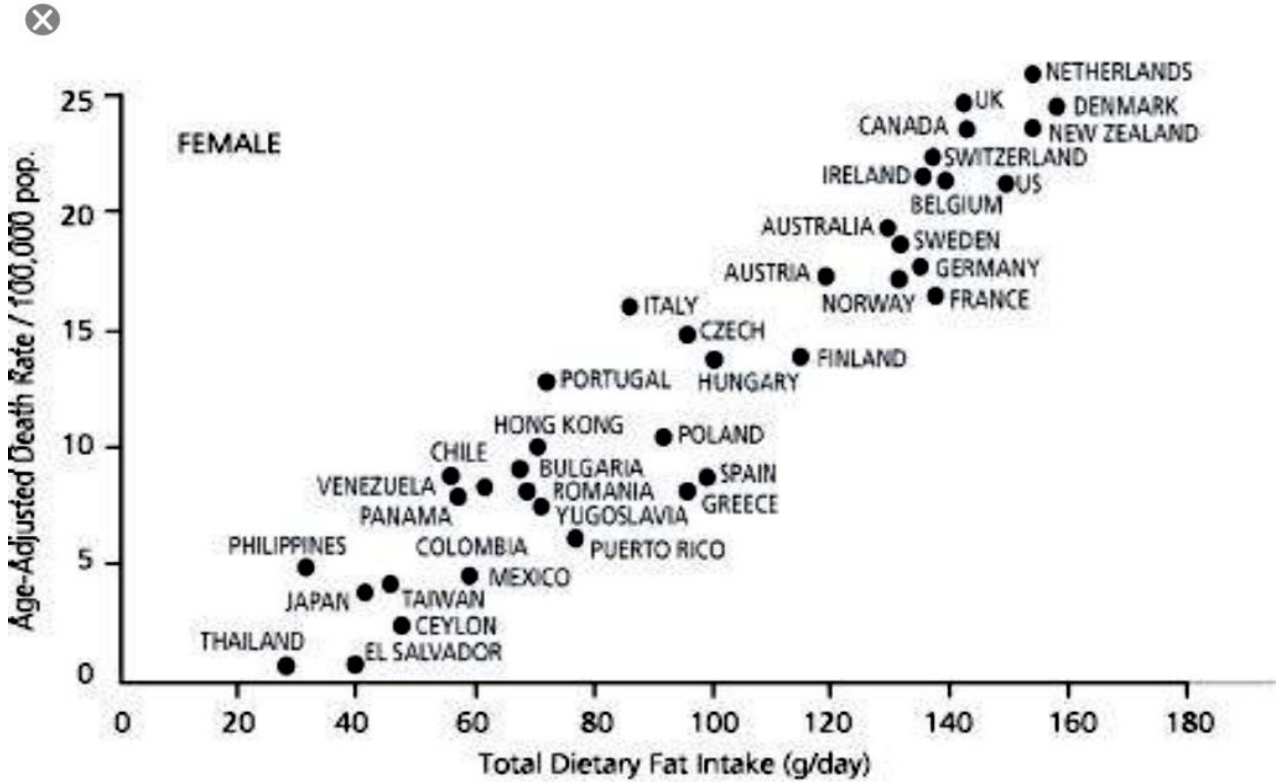
High Fat Diet Increases Breast Cancer

Risk: Most recent study: 30-40% higher risk in women consuming the most saturated fat



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2. Stay Lean (3x greater risk of breast cancer after age 50 if overweight)

- Waist Circumference at or below 33 inches
- Too much estrone synthesis in fat cells leads to over stimulation of breast and endometrial cells
- Similar to adverse effects of hormone replacement therapy

Table 2. Mean and range of serum levels of estrone, total estradiol, and unbound and bioavailable estradiol (New York University Women's Health Study, 1985-1990)*

	Case subjects (n = 130)	Control subjects (n = 251)
Estrone, pg/mL		
Mean†	14.0	11.4
Range	2.96-53.47	0.43-51.83
Total estradiol, pg/mL		
Mean‡	33.6	27.7
Range	9.5-105.5	3.0-183.0
Free estradiol, %		
Mean‡	1.42	1.34
Range	0.75-2.19	0.60-2.44
Free estradiol, pg/mL		
Mean‡	0.47	0.36
Range	0.22-1.40	0.02-3.06
Albumin-bound estradiol, %		
Mean‡	58.9	54.1
Range	30.8-81.6	36.5-87.4
Albumin-bound estradiol, pg/mL		
Mean‡	19.4	14.7
Range	3.9-78.9	1.1-110.8
SHBG-bound estradiol, %		
Mean‡	39.7	44.6
Range	10.7-62.3	16.7-68.1
SHBG-bound estradiol, pg/mL		
Mean	12.8	11.9
Range	4.2-51.3	1.5-78.2

*Means of absolute amounts are geometric means; for values espressed as percentages, arithmetic means were computed. Percent albumin-bound estradiol was not measured but was calculated by difference from the percentage of the other two fractions. Absolute amounts of estradiol fractions were calculated by multiplying each percent fraction by total estradiol. SI units conversion factor for estrone and estradiol = 3.671.

†Paired t test $P<.01$.

‡Paired t test $P<.001$.

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3. Minimum Of 30 Minutes Of Endurance Exercise, 5 Times Per Week

- Increased estrogen detoxification in liver
- Increased SHBG (less available estrogen to stimulate breast and endometrial cells)
- Helps keep you leaner

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4. Take A High Potency Multiple Vitamin Containing:

- **Vitamin E Succinate –** shows impressive cancer preventive properties

- **Vitamin D** – 1000-2000 IU usually get Vitamin D into ideal range

- Know your blood level of Vitamin D (above 85nmol/L is protective) (but below 250 nmol/L)

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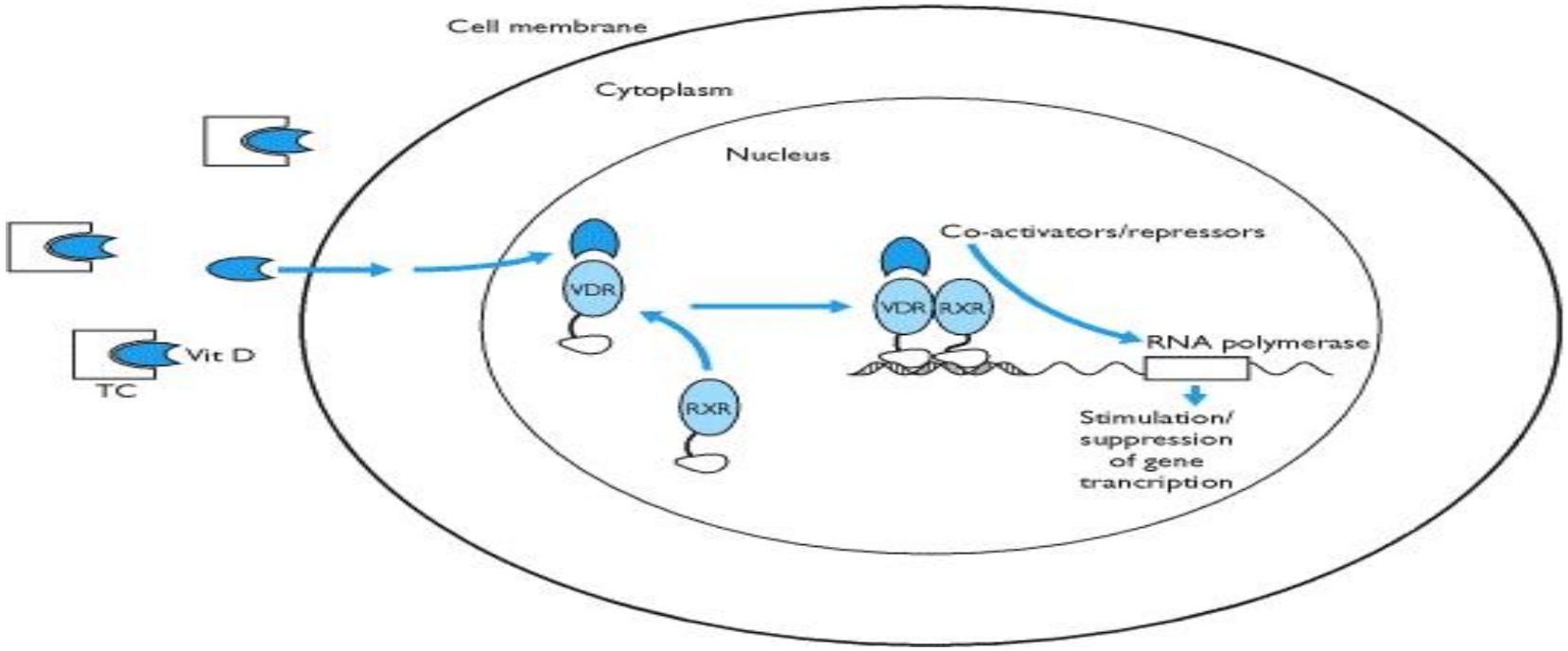
Vitamin D Slows Cell Division and Promotes Cell Maturation

- In circulation vitamin D is bound to the globulin, transcalciferin (TC), with only a small fraction existing in free form. The free form crosses the cell membrane and the nuclear membrane where, in target cells, it interacts with a vitamin D receptor (VDR). This induces dimerization with the retinoic acid receptor (RXR), DNA binding and interaction of receptors with transcription factors resulting in stimulation or inhibition of gene transcription



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Vitamin E Succinate

1. Inhibits Bcl-2
2. Activates the Fas Death Receptor
3. Down Regulates Epidermal Growth Factor Receptors
4. Blocks Angiogenesis In Cancer Cells

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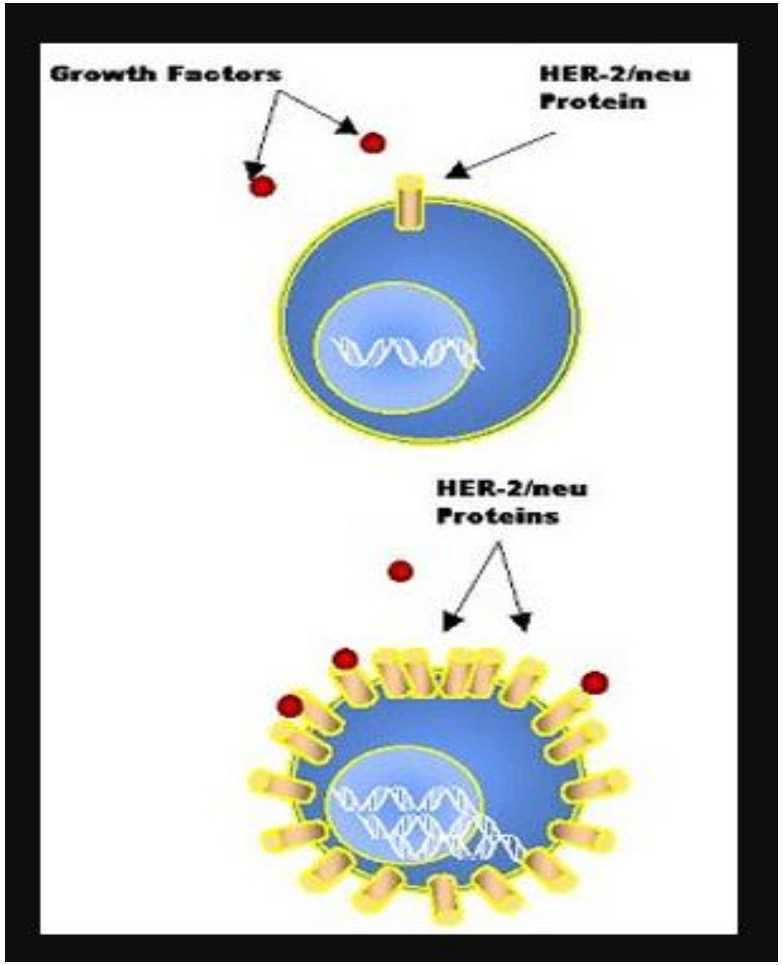
VES Inhibits Epidermal Growth Factor Receptors HER-2(ErbB2) – breast, colon, prostate cancer



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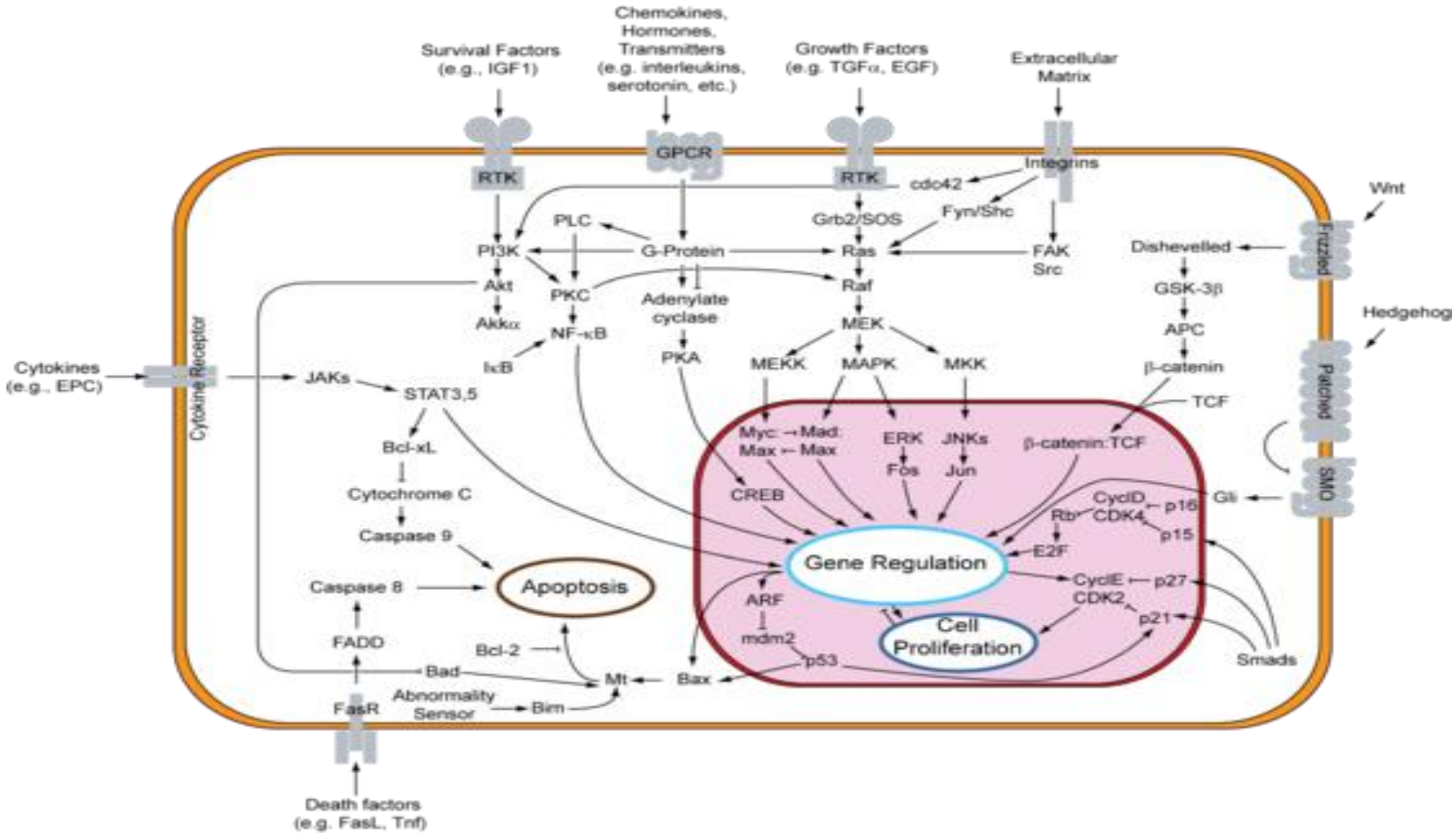
Vitamin E Succinate: Bcl-2; Death Receptors, Her-2



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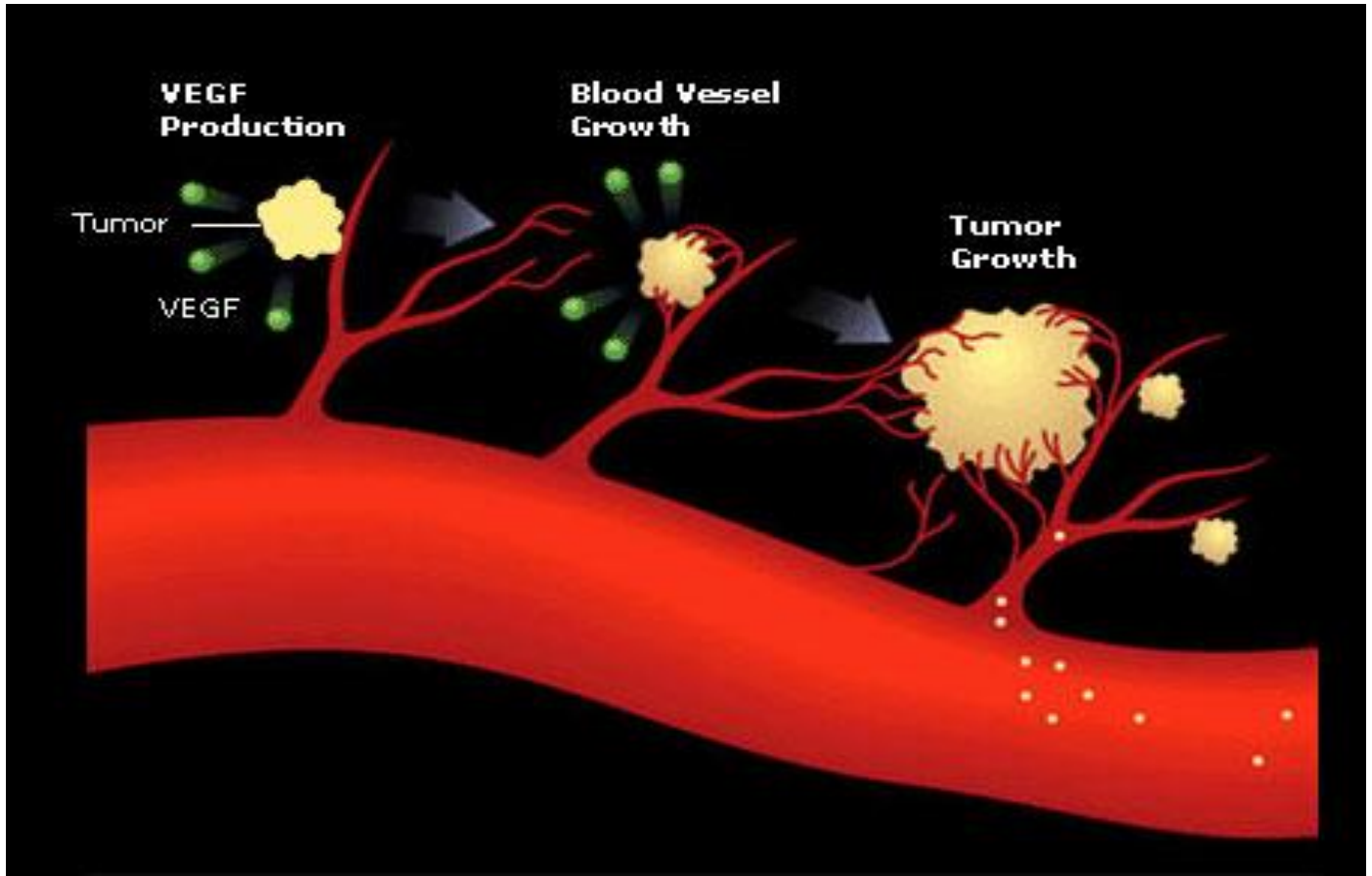
VES: Inhibits release of VEGF inhibiting cancer growth and metastasis



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Each Day – A High Potency Multiple Vitamin containing 400 IU of Vitamin E Succinate

Lockwood and Folkers – showed that high doses of antioxidants, essential fatty acids and coenzyme Q10 could halt progression of breast cancer in women after receiving medical treatment (Mol Aspects Of Med 1994 and 1995)

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5. Drink Less Alcohol And Get A B-50 Complex, As Part Of Your High Potency Multiple Vitamin and Mineral Supplement (Vitamin B12, folic acid)

More than one alcoholic drink per day assoc with doubling the risk of breast cancer (and colon cancer)

Folic acid appears to guard against alcohol risk for breast cancer via methylation of chromosomes

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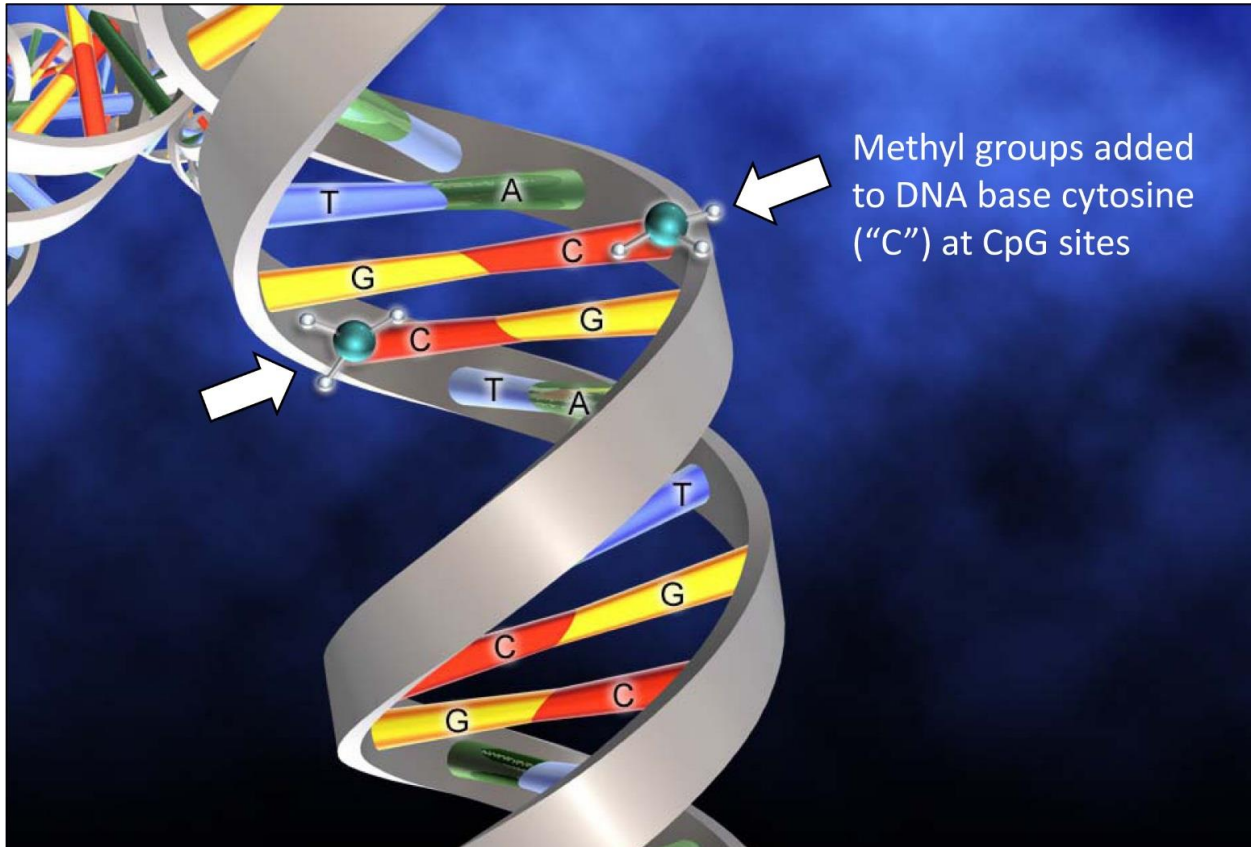
DNA Methylation Requires Active Form of Folic Acid



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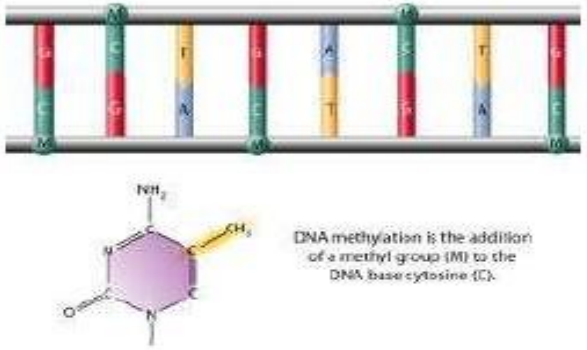
Methylation Helps Prevent Over Stimulation of Cell Division (Folic acid, Vit B12)

Introduction: DNA Methylation



DNA methylation is the addition of a methyl group (M) to the DNA base cytosine (C).

- CH_3 inhibits transcription factors from attaching to DNA
- Gene(s) silenced/inactivated, esp. if promoter region is methylated
- Hypermethylation -> inactivated genes;
- Hypomethylation -> genomic instability
- Catalyzed by presence of DNA Methyltransferase (DNMT) enzymes

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6. Take Supplement Containing Fish, Flaxseed and Borage Seed Oil, and Eat Fish Twice Per Week

- Omega-3 fats (from Fish and Flaxseed Oil) converted into hormones that slow the rate of cell division

- Borage (GLA) shown to reduce inflammatory process assoc with fibrocystic breast disease

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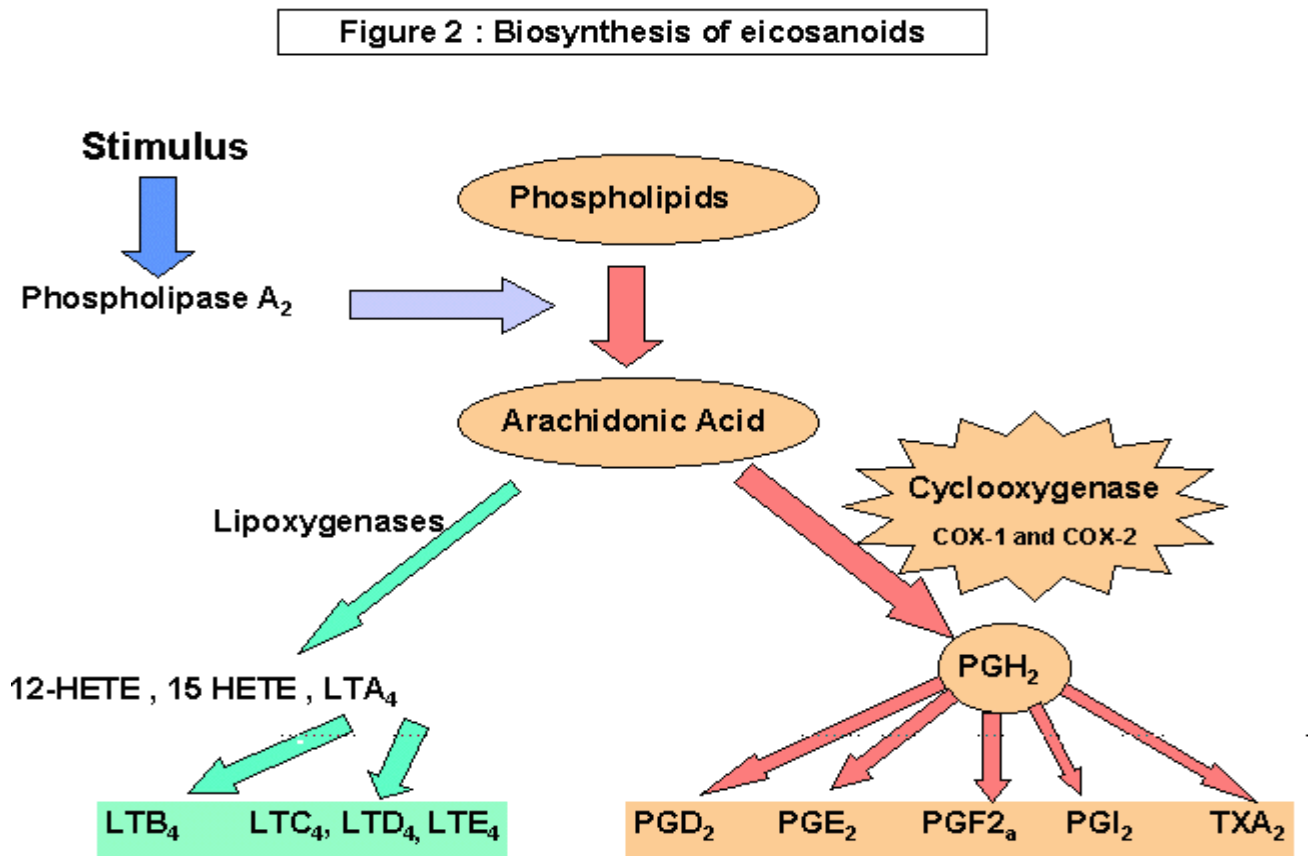
Prostaglandins Increasing Cancer Risk (12-HETE and PG-2)



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7. Consume Cruciferous Vegetables and Indole-3-Carbinols Daily

Broccoli, Brussels Sprouts, Cabbage, Cauliflower, Bok Choy (fewer cancers with these foods)

- Enhance Detoxification of excess estrogens
- Block build-up of Estrone in fat cells
- Decrease the 2-OH to 16-OH Estrone ratio

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8. Consume At Least One Serving Of A Soy Food Each Day

Countries with high soy intakes have 75% lower breast cancer incidence

Soy Isoflavones Protect In Many Ways:

- Block ability of emerging breast cancer cells from making Estrone and beta-Estradiol

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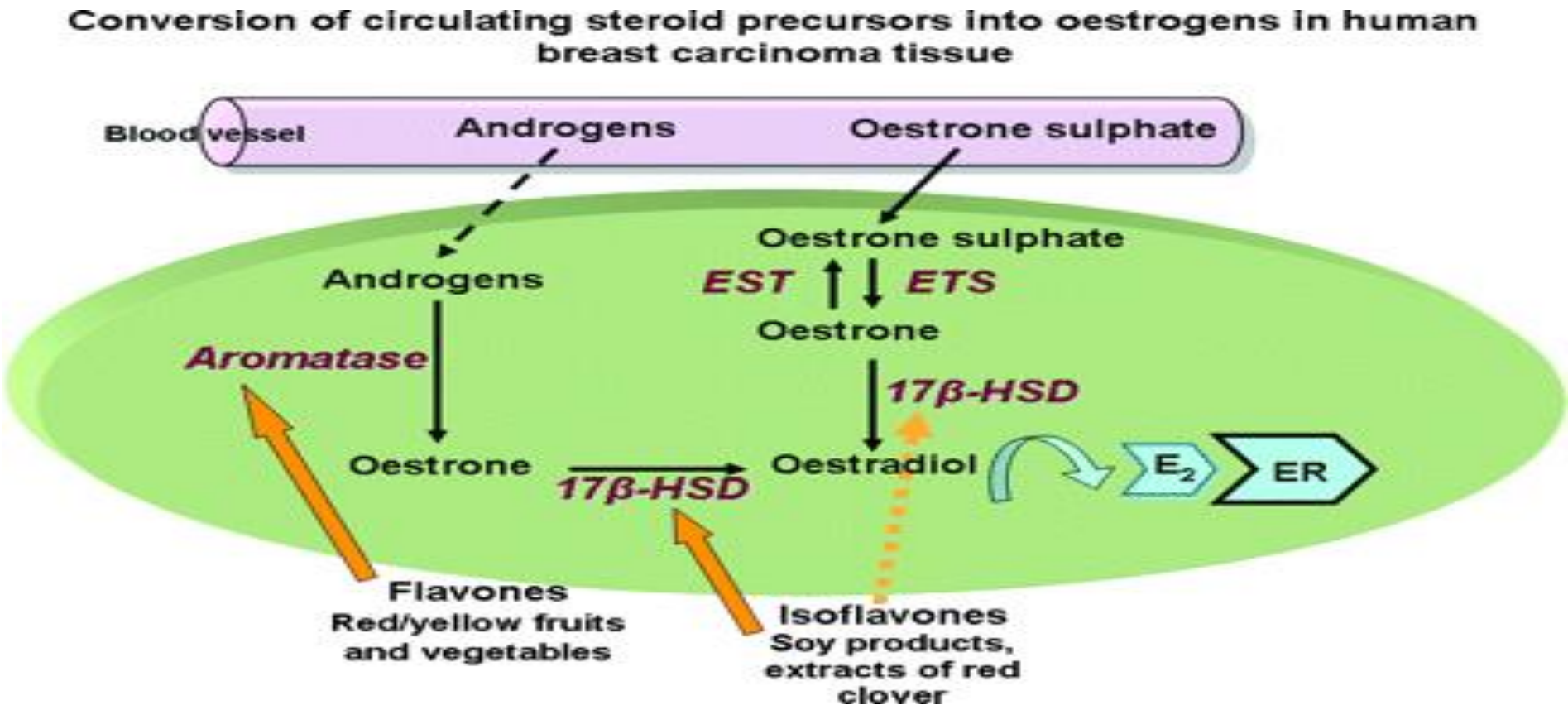
Aromatase inhibitors include: isoflavones, flavones (quercetin) indole-3 carbinol and ENL and END

17 beta HSD inhibitors include genistein and diadzein –soy isoflavones



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Other Ways Soy Isoflavones Reduce Cancer Risk:

- Anti-angiogenesis
- Apoptosis
- Detoxification of excess estrogens in liver
- Block formation of Estrone In Fat Cells
- Increase Apoptosis/Mitosis Ratio

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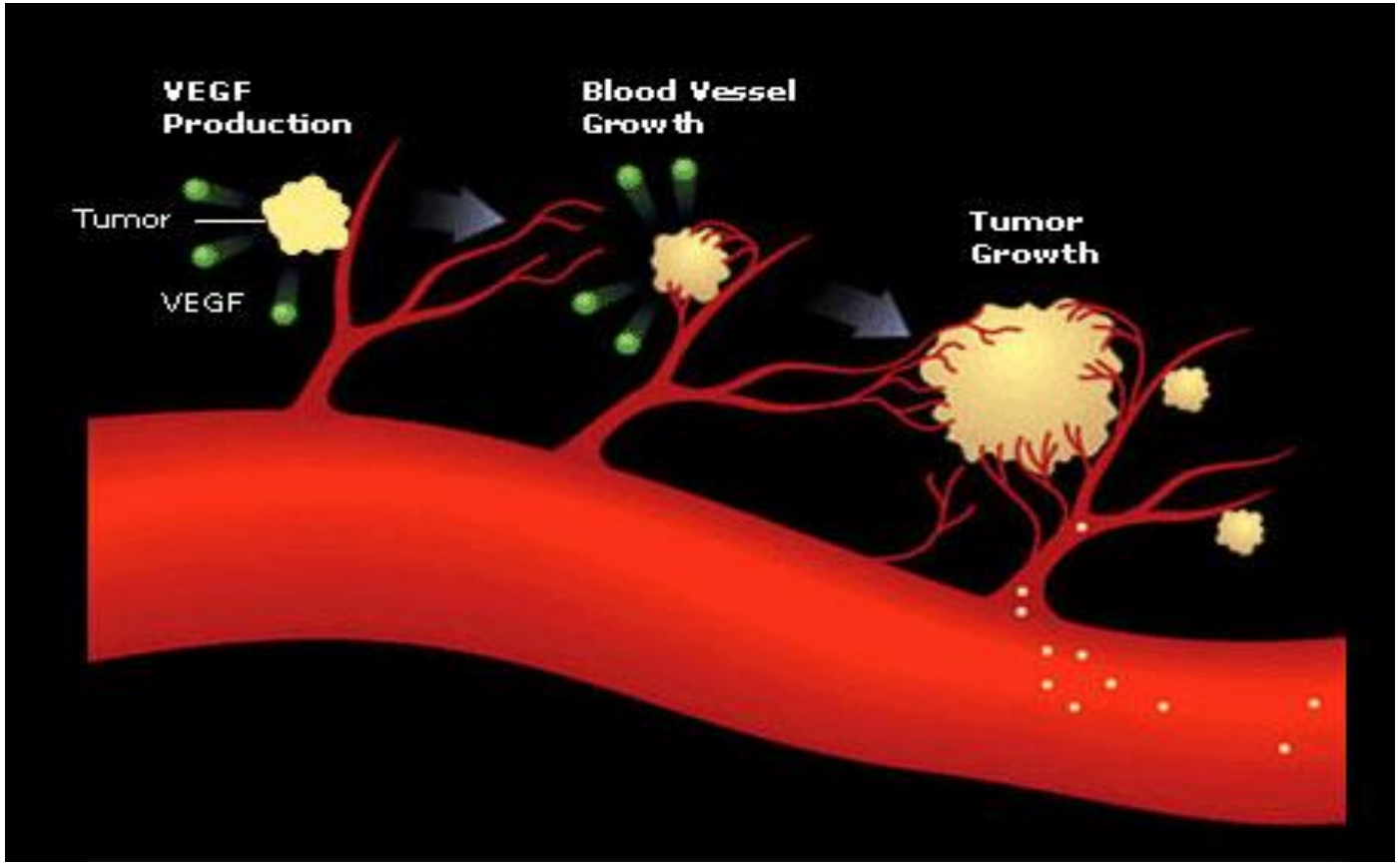
Soy Isoflavones inhibit release of VEGF, inhibiting cancer growth and metastasis



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9. Take Two Heaping Tablespoons of Ground Flaxseed Each Day

- ENL and END block formation of Estrone in fat cells
- ENL and EDL block formation of Estrone in emerging breast cancer cells
- Shown to reverse fibrocystic breast disease

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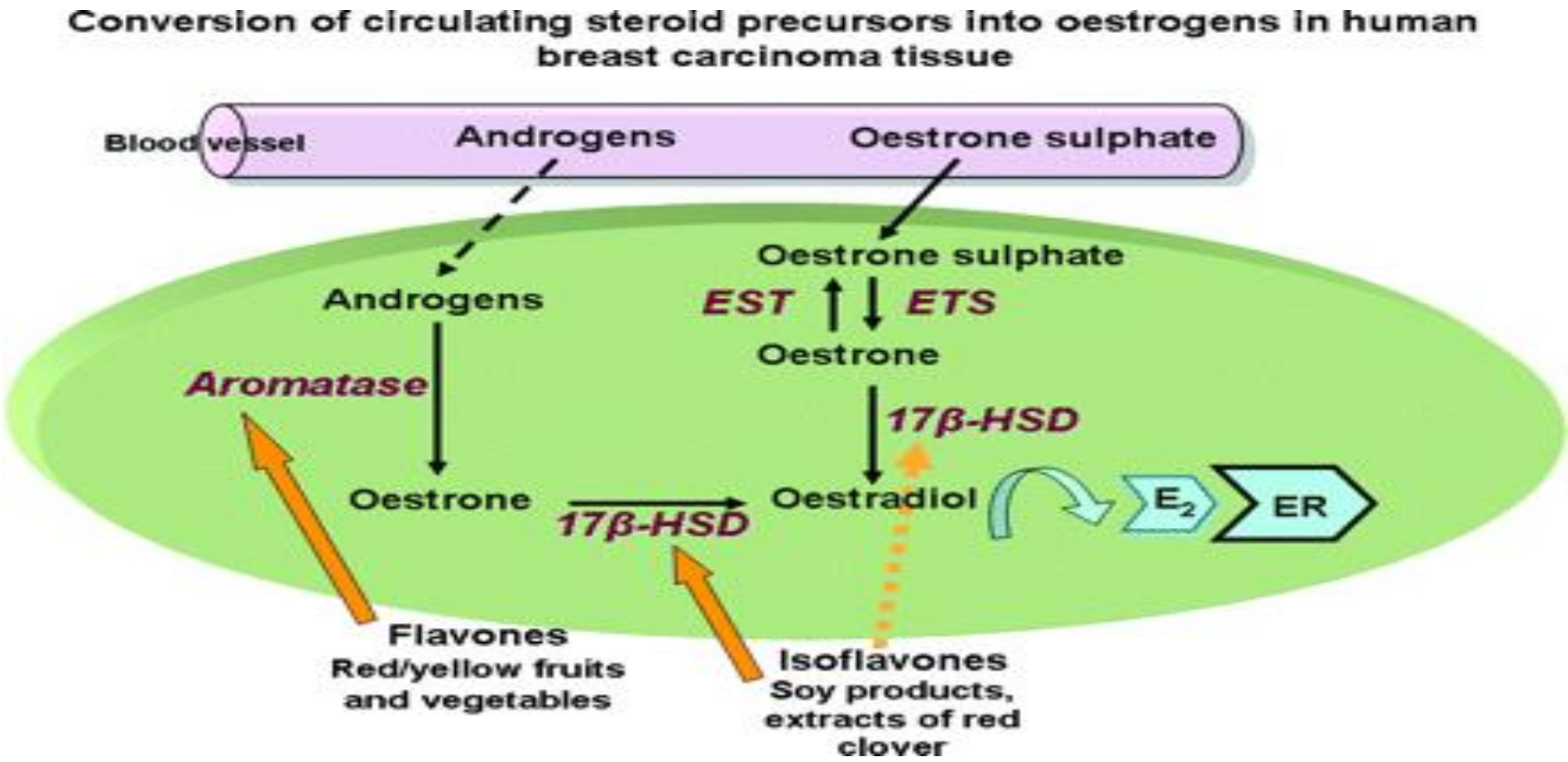
Aromatase inhibitors include: isoflavones, flavones (quercetin) indole-3 carbinol and ENL and END

17 beta HSD inhibitors include genistein and diadzein –soy isoflavones



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10. Consider Supplementation With Curcumin and Other Natural Anti-Inflammatory Agents (EGFR's) Erb-2 genetic risk

- Tone Down Her-2 Receptor involved in approx 40% of all breast cancer cases

- Decrease formation of PG-2 inflammatory hormones that speed up cell division (ASA can cause bleeding)

Nature's Relief – 1-2 capsules per day

1. Curcumin
2. White Willow Bark Extract
3. Ginger
4. Boswellia

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11. Take Melatonin after age 40 (.5 mg – 3 mg, one hour before bedtime) and sleep in a dark room

- Lower Melatonin levels assoc. with increased risk of breast cancer

- Melatonin shown to improve cancer-fighting abilities of immune system

- Dr. Lissoni (Italy) uses high dose melatonin to help control progression of breast and prostate cancer (http://link.springer.com/article/10.1007%2Fs005200100281)

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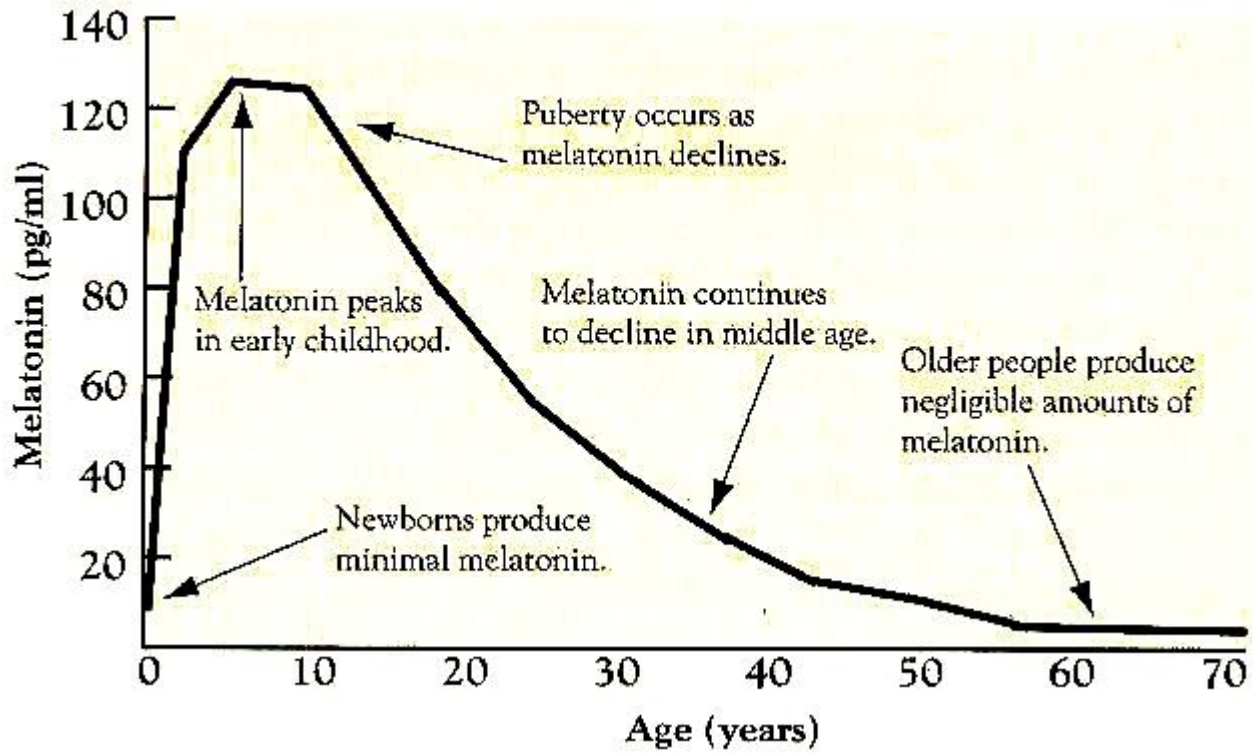
Age-Related Decline In Melatonin



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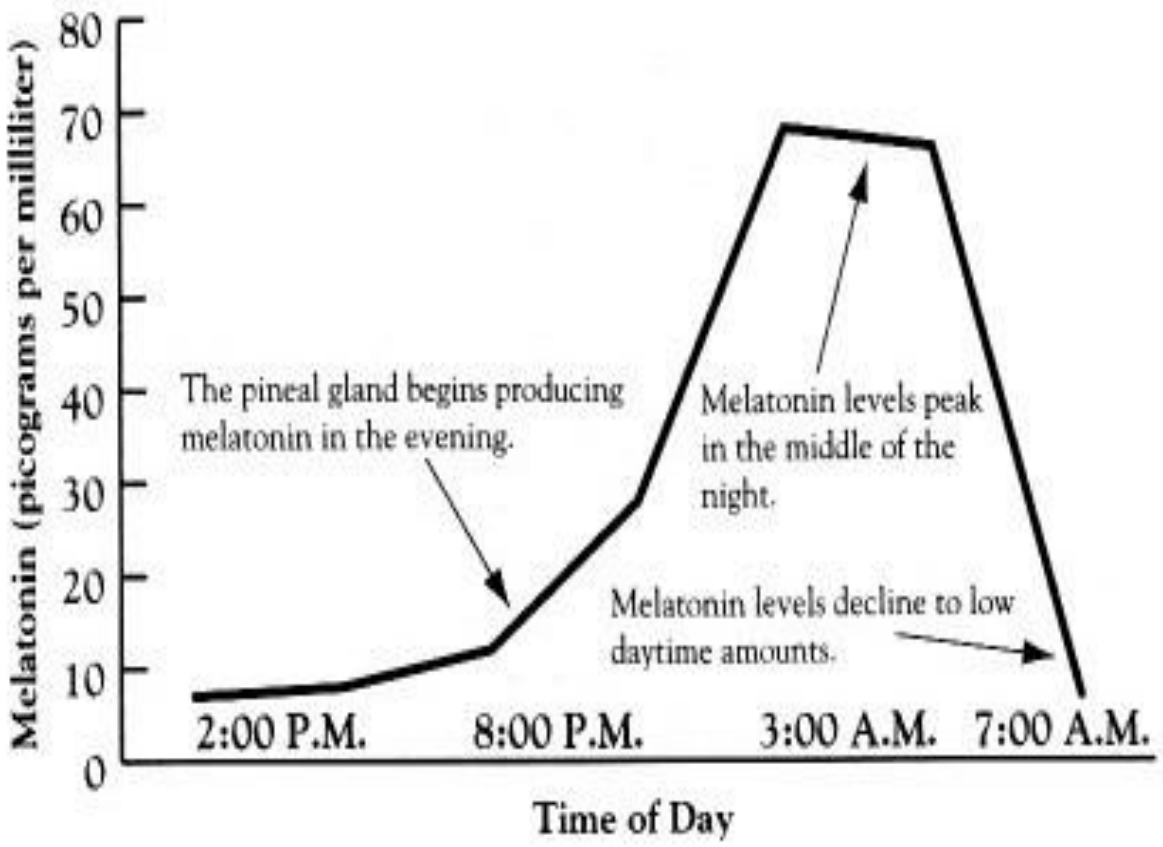
Darkness-induced Secretion of Melatonin



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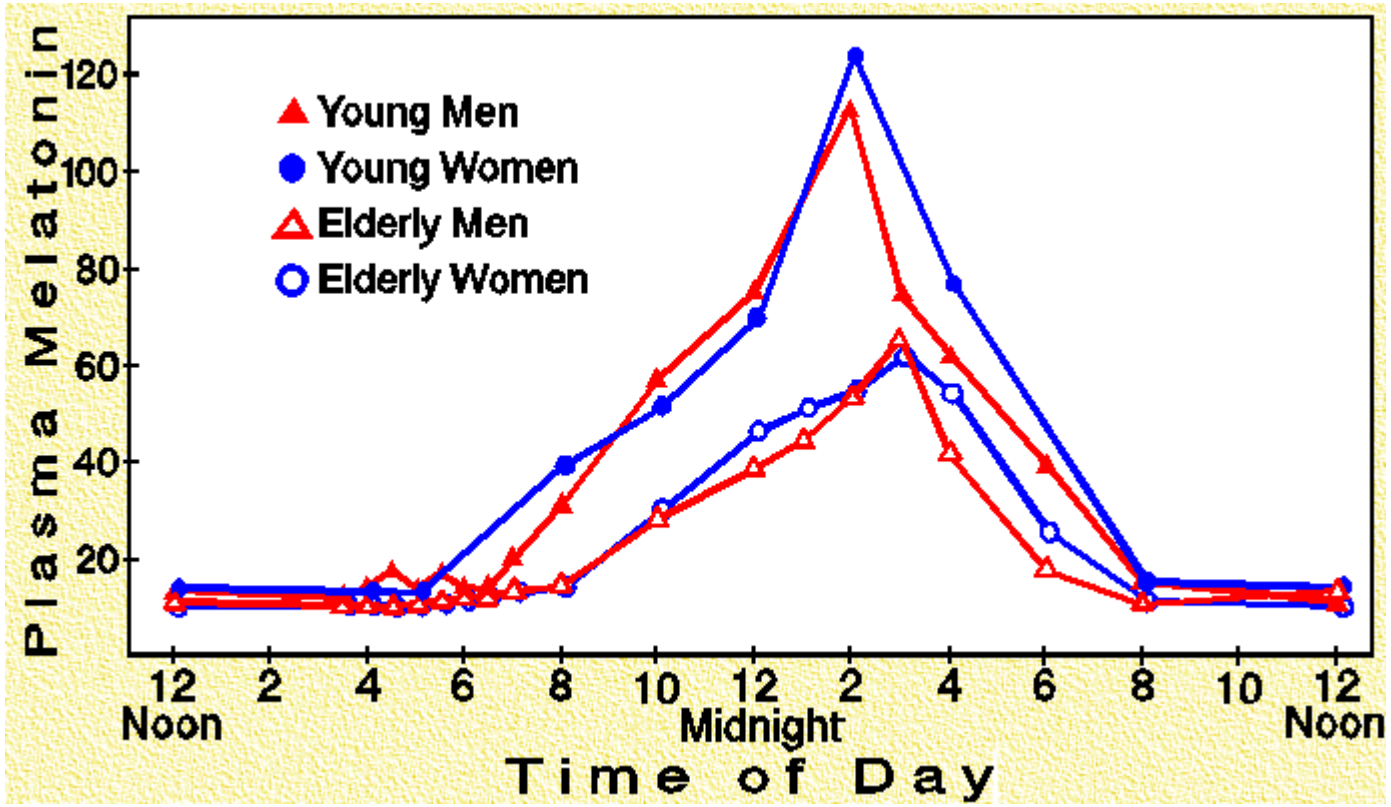
Reduced Night Time Melatonin in Aging



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Melatonin required for sleep, brain antioxidant and immune system modulator (low melatonin associated with breast and prostate cancers)

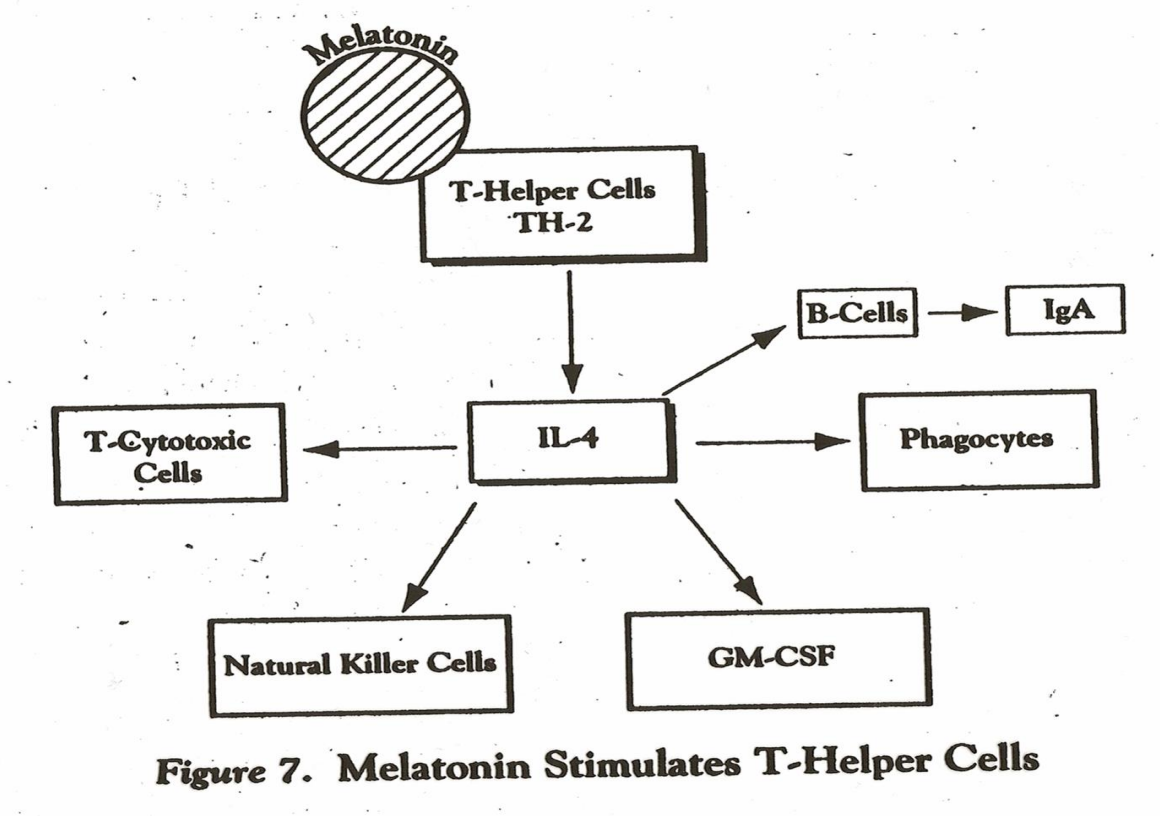

Figure 7. **Melatonin Stimulates T-Helper Cells**

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2010 Review: Natural Medicine Journal
An Overview of Melatonin and Breast Cancer. Kaczor T.

http://www.naturalmedicinejournal.com/journal/2010-02/overview-melatonin-and-breast-cancer

General Considerations:

- Melatonin binds to cell surface receptors (ML1, ML2), cytosolic sites (calmodulin), and directly to nuclear DNA binding sites (nuclear receptors RZR/RORα).

- Overall its effect on cancer cells is oncostatic at physiological levels, or cytotoxic at higher concentrations.

Well Documented Anti-cancer Effects Shown Experimentally

- Antioxidant
- Antimitotic
- Anti-estrogenic
- Pro-differentiating
- Anti-metastatic.
- Influences the hypothalamic-pituitary axis (HPA) and immune system, which confers anticancer effects through modulation of hormonal and immune-mediated pathways of proliferation/metastasis.

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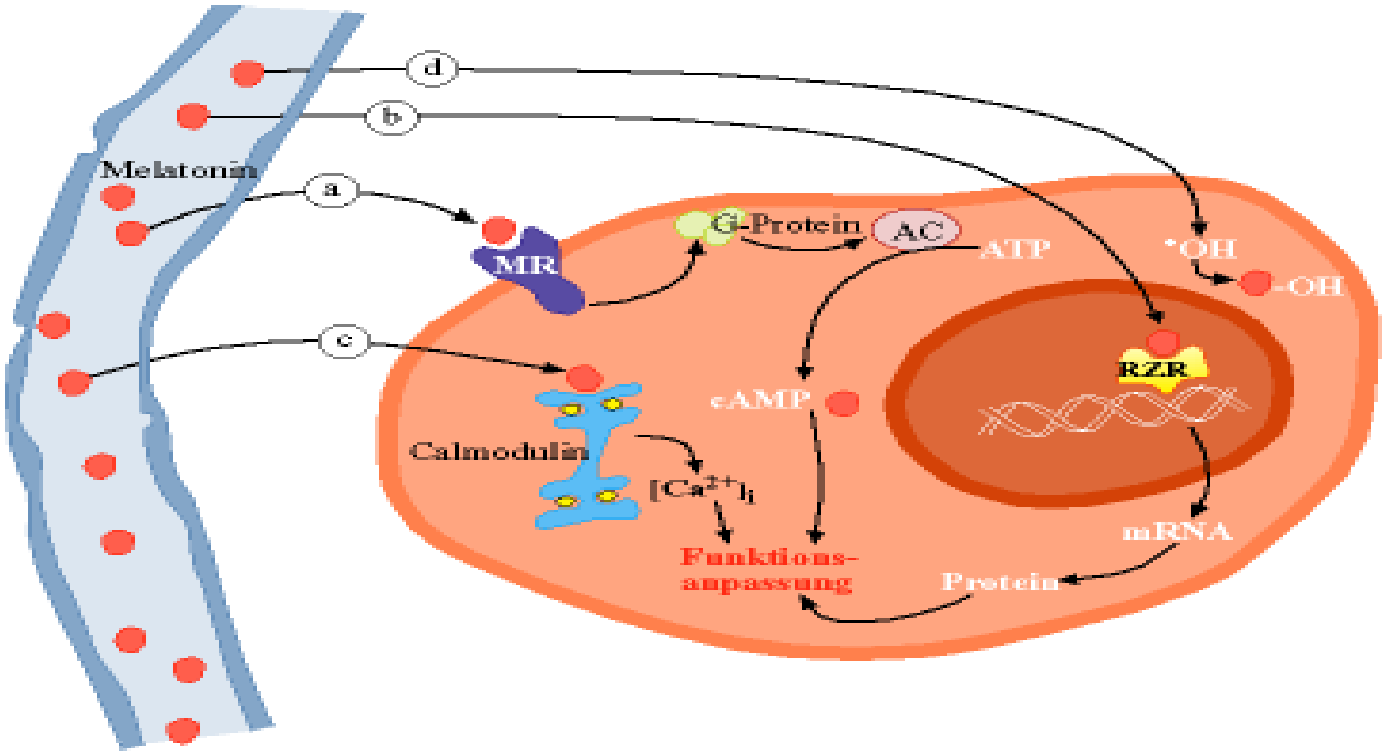
Melatonin diffuses easily through cell membrane of all cells and exerts physiological effect via:

a. Melatonin Receptor Binding (ML-1 ML-2)
b. DNA Retinoid Receptor Binding (RZR)
c. Calmodulin Binding (key signal transduction intermediate messenger modulating inflammation, apoptosis, immune function etc.)
d. Water and Fat-Soluble Antioxidant Effects



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Melatonin and Breast Cancer

- Best characterized oncostatic effect of melatonin results from the net reduction of estrogenic stimulation to breast cancer cells.

- Estrogens are involved in many aspects of the malignant process, including proliferation, angiogenesis, metastasis, immune evasion, and immortality.

- Melatonin has demonstrated attenuation of all of processes in the presence of estrogen.

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How Does Melatonin Reduce Breast Cancer Risk?

- **Reduces Estrogen and Progesterone Levels -** melatonin affects the hypothalamic-pituitary-ovarian (HP) axis, which results in lower circulating levels of estrogen and progesterone.

- **SERM Effects** - on a cellular level, melatonin acts as a selective estrogen receptor modulator (SERM) through decreased expression of estrogen receptor alpha and reduction in the ability of estrogen-estrogen receptor alpha (ERα) complex to bind to the estrogen response element (ERE) on DNA.

- **Aromatase Inhibitor**

- **Anti-Proliferative via Calmodulin Binding -** melatonin has demonstrated antagonist effects on Estradiol-induced-ERα-mediated transcription of proliferative genes through its binding to calmodulin in the cytosol. When the ERα-calmodulin complex is bound by melatonin **it is incapable** of binding to the promoter regions or the ERE of DNA. This reduces the transcription of many downstream genes that increase proliferation

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Reduces Invasiveness of Breast Cancer:

- **Preserves Adhesion Molecules** - Melatonin decreases motility and invasive capabilities of breast cancer cells (MCF-7) cells in vitro. This is partly due to melatonin stimulating expression of cell surface adhesion molecules such **as E-cadherin and β1-integrin,** which allow for attachment of the cells within the extracellular matrix as well as to each other. These adhesion molecules are down-regulated by estrogen, increasing the invasive potential of the cell. Melatonin has been shown to increase the expression of these adhesion molecules in MCF-7 cells.

- **Telomerase Inhibitor** – prevents cancer cells from preserving telomere length with each cell division

- **Inhibits 15 Lipoxygenase thus reducing 13 HODE Synthesis** – Melatonin binds to membrane receptors, ML1 and/or ML2, leading to a decrease in cellular uptake of linoleic acid, reducing availability of linoleic acid. This results in an antiproliferative effect through the resultant decrease in its metabolite **13-hydroxyoctadecadienoic acid (13-HODE),** which serves as an energy source and growth-signaling molecule for proliferative pathways such as epidermal growth factor receptor (EGFR)/mitogen-activated protein kinase (MAPK) pathway.

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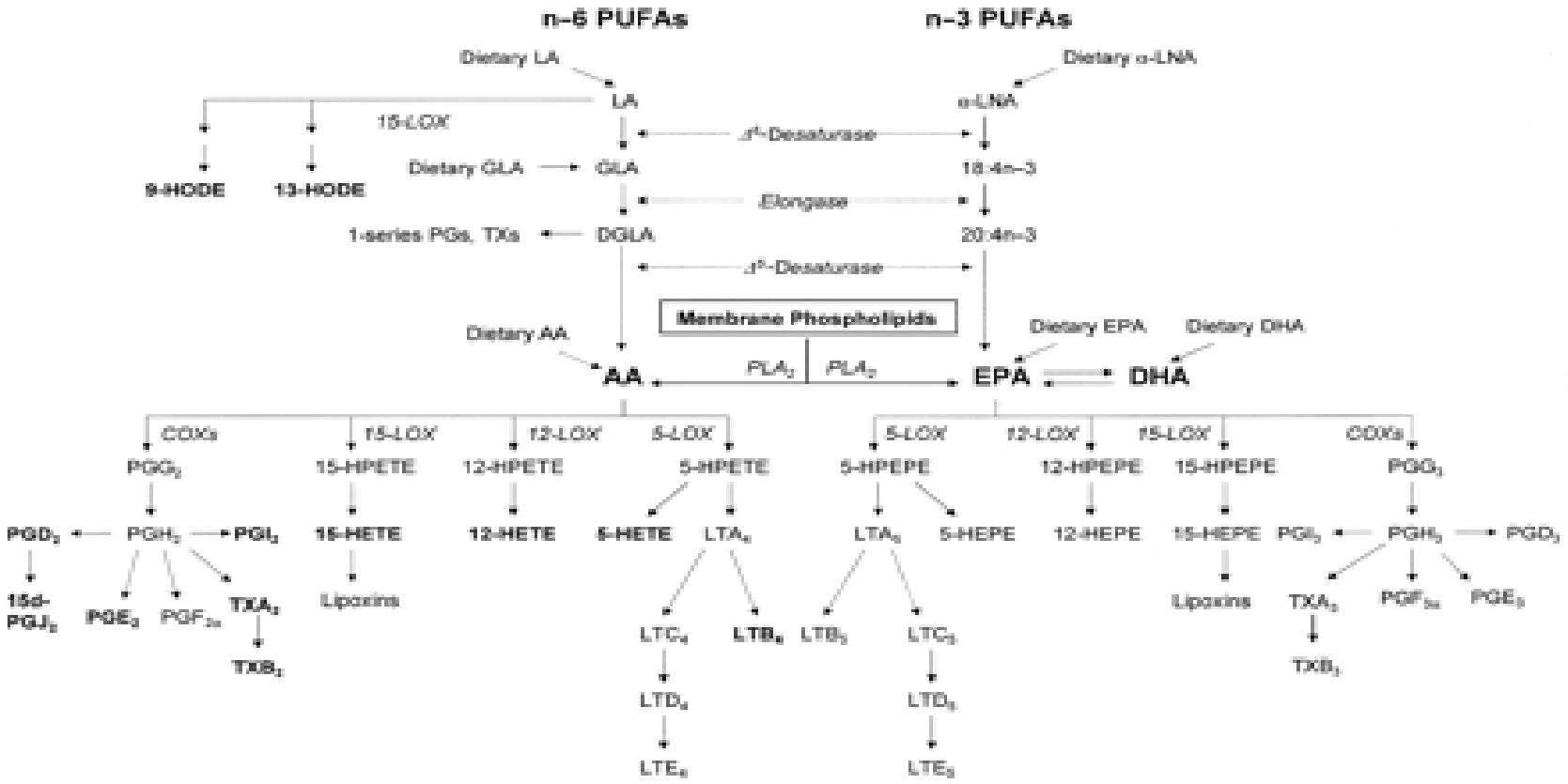
13 HODE: LA becomes HODE via 15 lipoxygenase (promotes cancer growth)



- **Binds to Retinoid Receptors (RZR/RORα steroidal region of DNA)** - which leads to altered transcription of several genes involved in cellular proliferation, such as tumor suppressor gene p21 and pro-inflammatory 5-LOX. Separately, melatonin has been shown to potentiate the proapoptotic effect of retinoic acid.

- **Immune Modulation** - One study showed extrapineal production of melatonin by lymphocytes increased the activity of interleukin-2 (IL-2) and IL-2 receptor system – provides major immune boost in fighting cancer (e.g. drug Proleukin). Clinically, many trials have shown a synergistic effect with therapeutic IL-2 administration in various cancers.

- **Suppress Inflammatory Cytokine Release** - melatonin exerts systemic anti-inflammatory effects, as demonstrated in lower circulating levels of IL-6 and erythrocyte sedimentation rate (ESR) in patients taking melatonin, which may affect both tumorogenesis and proliferative and metastatic pathways that are otherwise stimulated by inflammatory cytokines.

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12. Green Tea Catechins - 400-600 mg per day or 5 cups per of green tea per day – (70-80 mg of EGCG per cup)

EGCG= Epigallocatechin-3 gallate (polyphenol)

Polyphenolic compounds (catechins) found in green tea show multi-modal effects on reducing breast cancer risk and have been used in the adjunctive management of breast cancer with impressive results (https://www.karger.com/Article/FullText/369170)

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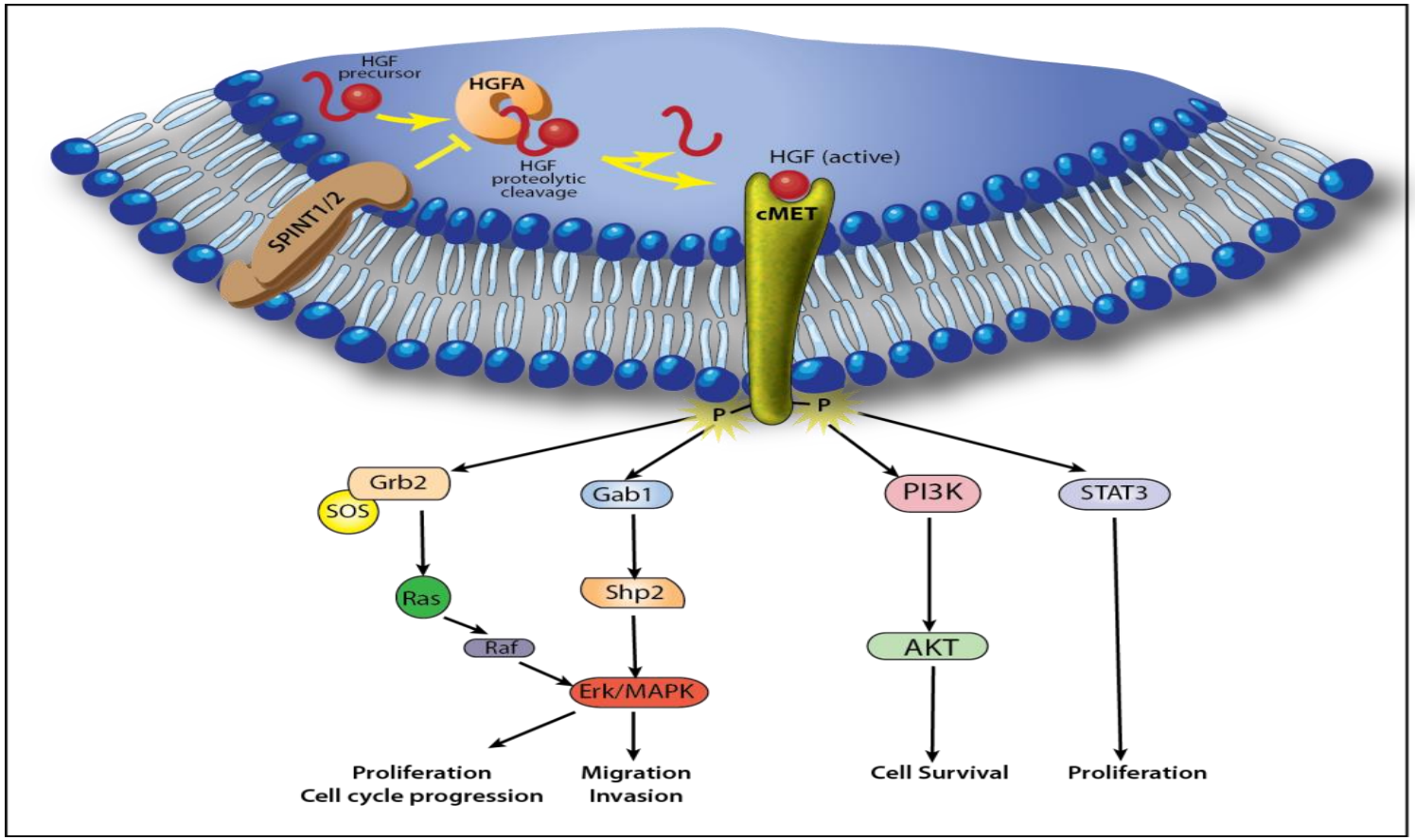
Catechins reduce secretion of Hepatocyte Growth Factor in the HGF/Met C Signaling Pathway



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Hormone Imbalance Issues In Younger Women

- PMS
- Fibrocystic Breast Disease
- Uterine Fibroids
- Endometriosis
- Polycystic Ovarian Disease

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General Protocol PMS etc.

1. Aerobic Ex – increase estrogen detoxification (liver)
2. Insoluble Fiber – Wheat bran eliminates estrogen via the enterohepatic route
3. Low Saturated Fat Diet – 36% decrease in circulating estrogens
4. Ground Flaxseed - (FBD) – 50 gm/d
5. Black Cohosh and Soy Extract - Black Cohosh increases progesterone as well
6. Prebiotics – prevent deconjugation of estrogen bound to glucuronic acid in large bowel (dysbiosis) – FOS, Insulin (1,000-5,000 mg) and probiotic functional food
7. Essential Fatty Acids – decrease PG-2 (anti-inflam and anti-prolif)
8. Vitamin E (400 IU, Mg -250 mg, Vit B6- 50 mg) Multi Vit

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Polycystic Ovarian Syndrome PCOS

PCOS - common female hormonal disorder affecting approximately 5%-10% of women of reproductive age (12–45 years old).

Pathophysiology: The cysts discovered in the ovaries upon ultrasound examination are actually **immature egg follicles, not cysts.**

Rather than one egg follicle maturing and ovulating during a normal menstrual cycle, in PCOS a number of egg follicles start to develop, but their development becomes arrested along the way (forming permanent cysts), due to hormonal imbalances of high testosterone, dihydrotestosterone, estrogen (made in the fat cells along with testosterone), insulin and LH, as well as low amounts of FSH (follicle stimulating hormone)

(being overweight and lack of aerobic fitness increases insulin resistance)

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While the causes are not completed understood, insulin resistance, diabetes, and obesity are all strongly correlated with PCOS.

Common Findings:

- Obesity
- Irregular menstrual cycles or amenorrhea
- Acne and related effects of masculinizing hormones, such as excessive hair growth.
- Ovarian pain and cyst rupture can occur spontaneously, in severe cases
- The symptoms and severity of the syndrome vary greatly among women.

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Treatment Options

Medical treatment aimed at controlling insulin levels through the use of diabetic drugs, as well trying to balance female hormones with birth control pills, and attempting to lower testosterone with androgen blocking agents.

None of these methods have proven to provide consistent amelioration of PCOS and many of these drugs are associated with undesirable side effects.

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Natural Treatments For PCOS:

1. Weight Reduction (exercise, low glycemic diet) to reduce insulin and estrogen levels). High estrogen also blocks release of FSH. Thus, weight loss helps balance the LH:FSH ratio

2. Phytoestrogens to tone down effect of body's estrogens (black cohosh, soy isoflavones; gamma-oryzanol decreases release of LH).

3. Supplements to block conversion of testosterone to dihydrotestosterone (e.g. Prostate Supplements)

4. Soy Product, Cruciferous vegetable, ground flaxseed – block estrone synthesis in fat cells

5. Indole-3 carbinol and milk thistle (silymarin) increase estrogen detoxification in liver

6. Essential Fatty Acid Supplement (flaxseed, fish, borage oils) to reduce inflammatory prostaglandins