Welcome to the

2013

BCAA Education

Conference

Our mission is to serve women and men in the community by providing easy access to support and information about breast cancer and to enhance the quality of life for survivors, family and friends.

Vaccines For the Treatment and Prevention of Breast Cancer

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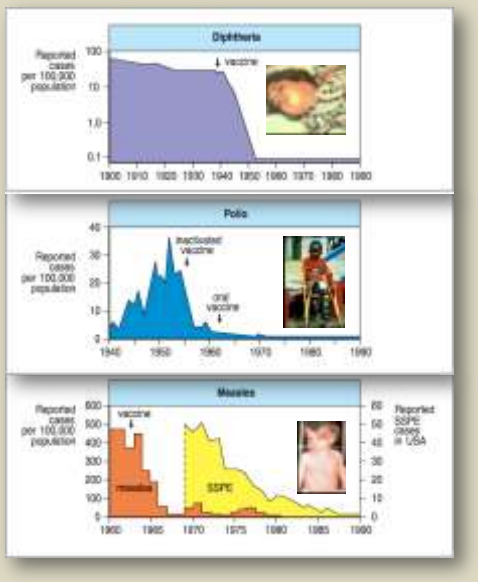
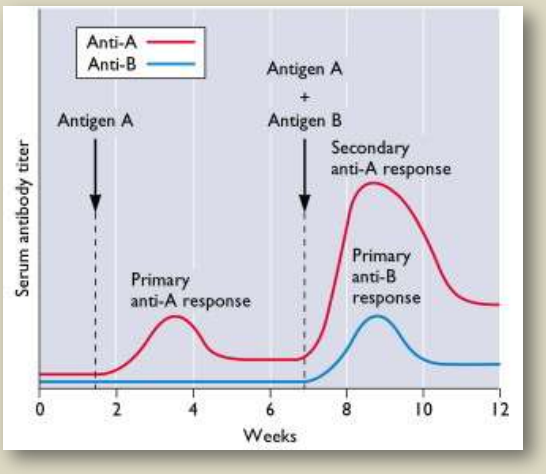
Rochester, MN; Jacksonville, FL; and Scottsdale, AZ



Disease Eradication

- Vaccines
- Clean water
- Sanitation

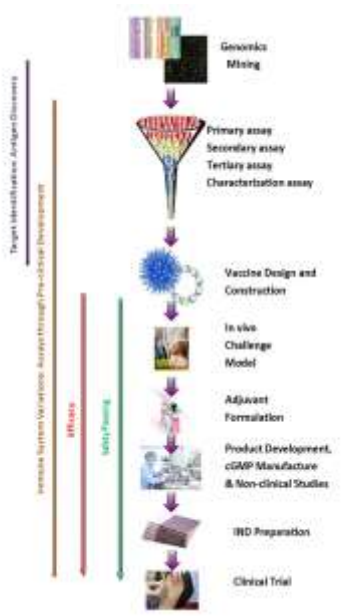
Why do we vaccinate?



27 diseases are now vaccine preventable

Disease	Year	Disease	Year
Smallpox	1798	Rubella	1969
Rabies	1885	Anthrax	1970
Typhoid	1896	Meningitis	1975
Cholera	1896	Pneumococcus pneumonia	1977
Plague	1897	Adenovirus	1980
Diphtheria	1923	Hepatitis B	1981
Pertussis	1926	H. influenzae type b	1985
Tetanus	1927	Japanese encephalitis	1992
Tuberculosis	1927	Hepatitis A	1995
Influenza	1945	Varicella	1995
Yellow fever	1953	Lyme disease	1998
Poliomyelitis	1955	Rotavirus	1998
Measles	1963	Human papillomavirus	2006
Mumps	1967		

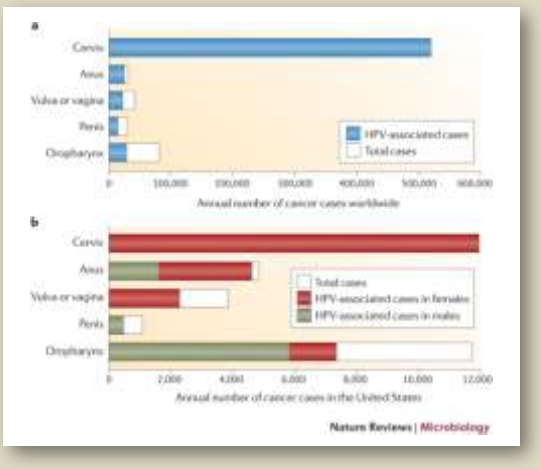
Adapted from CDC *MMWR* April 2, 1999; 48(12): 243-8



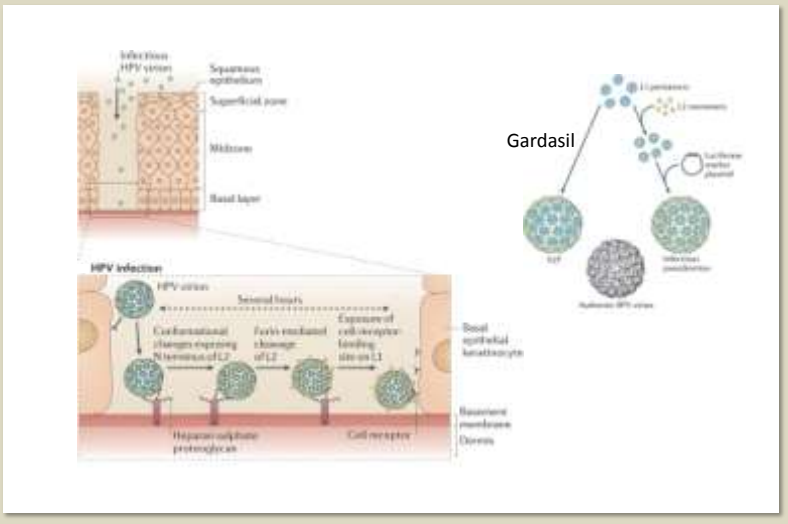
NBCC ARTEMIS PROJECT

- Bacterial/viral antigens
- Neoantigens
- Tumor associated antigens

Cervical Cancer



The Mechanism Challenge

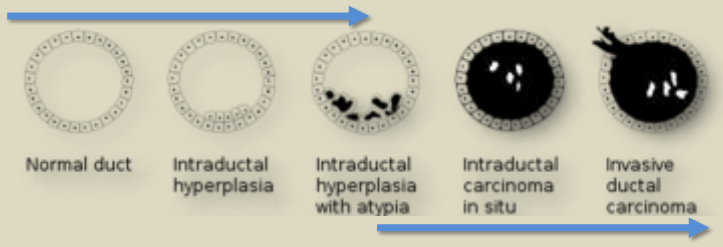


What is the Breast Cancer Mechanism?

VIRUSES

ENVIRONMENTAL ESTROGENS

OTHER INFLAMMATORY MEDIATOR

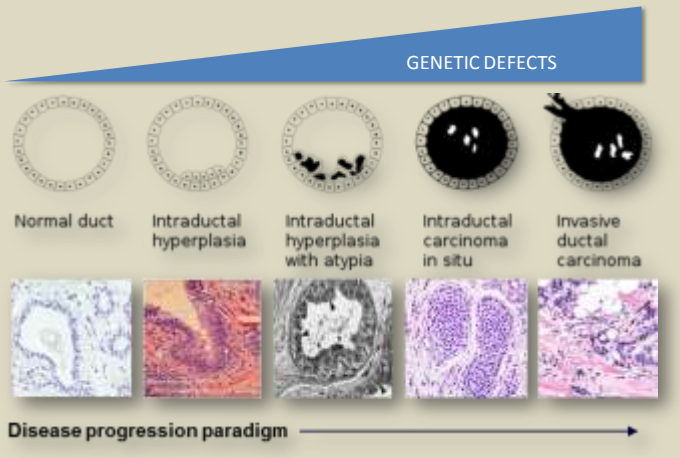


OTHER SELF ANTIGENS (SURVIVIN, HTERT)

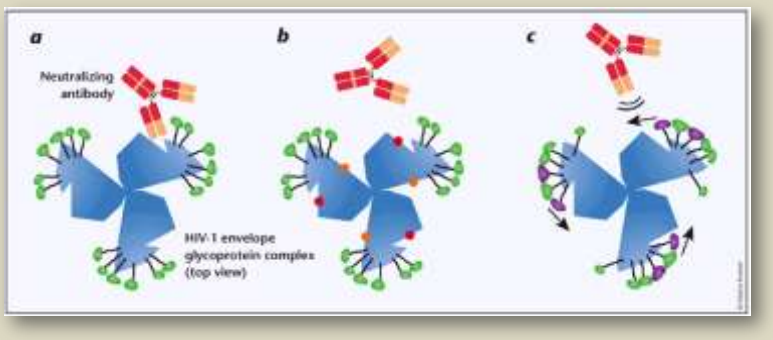
NEOANTIGENS (FUSIONS / FRAMESHIFTS)

ONCOGENIC PATHWAYS (E.G. HER-2, E7)

The earlier the better

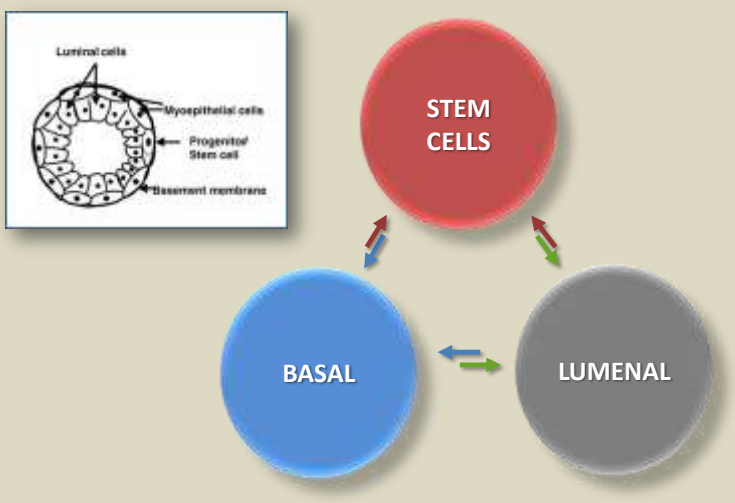


Mutation

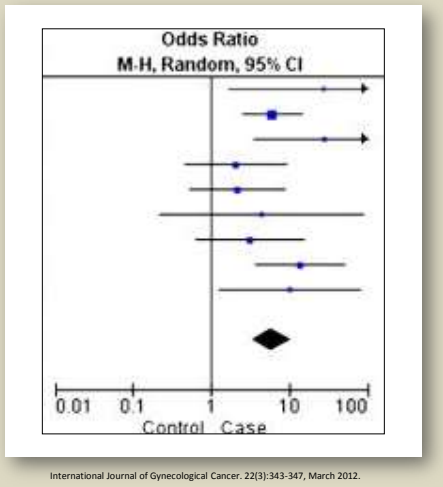


Nature Medicine **9**, 393 - 394 (2003)

Stem Cells – Multiple Targets



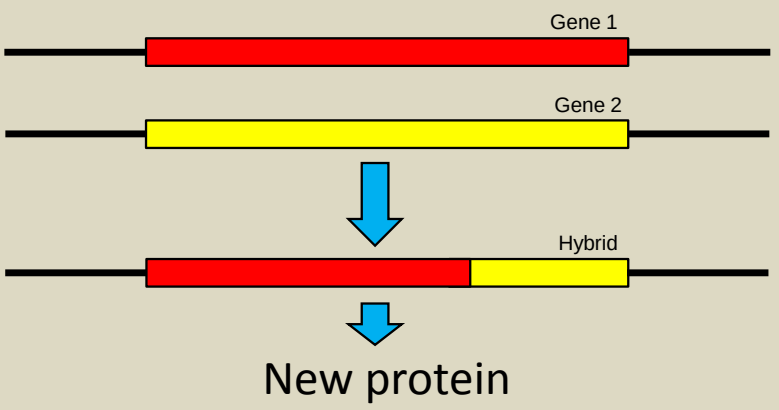
HPV is associated with increased risk of developing breast cancer



- HPV
  - 25% of B Ca
  - HMEV transformation
  - Portends 6-fold increased risk
- EBV
  - 30% of B Ca
  - Chronic inflammation
  - 6-fold risk of ovarian cancer
  - No interest in vaccines

International Journal of Gynecological Cancer. 22(3):343-347, March 2012.

Tumor cells change DNA to make new proteins!



Summary of Fusion Transcripts

- **131 novel fusion transcripts in 24 EARLY primary tumors**
- **Every tumor has at least one fusion transcript**
- **Median fusion transcripts/tumor**
  - ER+ -- 24/tumor
  - TN -- 32/tumor
  - HER2+ -- 16/tumor
- **45 redundant transcripts (two or more tumors)**
  - 7 restricted to ER+
  - 8 restricted to TN
  - 0 restricted to HER2

Cancer Res 2012

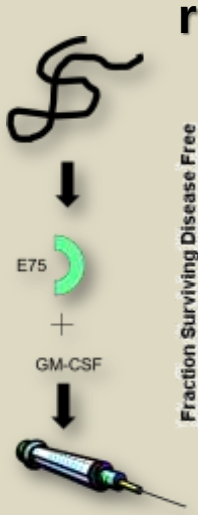
Self Antigen Vaccines

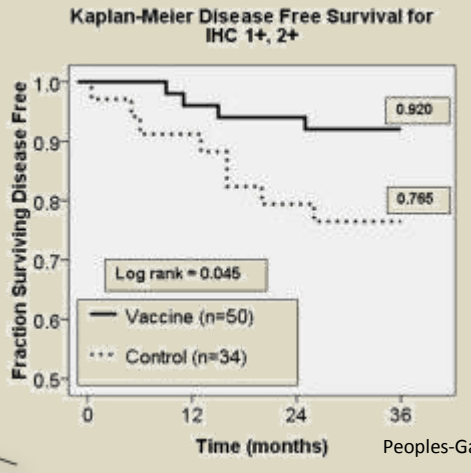
Vaccines for Prevention of Recurrence Ag-Specific
HER-2/FRα/CEA/IGFBP2

- Ag Express – Phase III HER2 CD4 MD Anderson
- TapImmune – Phase I HER2 CD4 VGTI Mayo
- VaxOnco – Phase I FRα VGTI Mayo
- Galena – Phase III E75 MD Anderson
- TapImmune – Phase I HER2 CD4/8 VGTI Jupiter/Martin
- UPenn – Phase III ICD Czernieki
- iImmune – Phase I HER2 - HERCEPTIN VGTI

JCI 2001
JCO, 2002
Clin Cancer Res, 2002
Clin Cancer Res, 2010
CII, 2010
JCO, 2007
J Clin Immunol, 2004
JCO, 2004
Blood, 2004

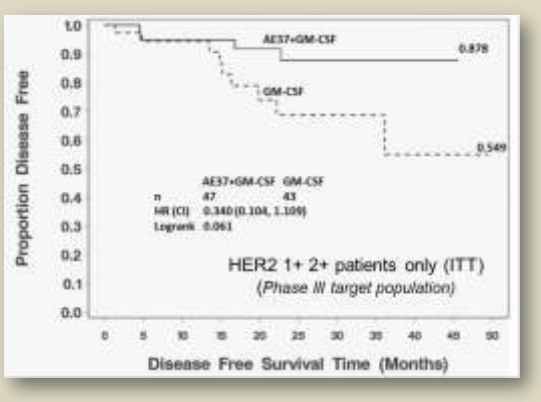
HER-2 vaccines prevent recurrence





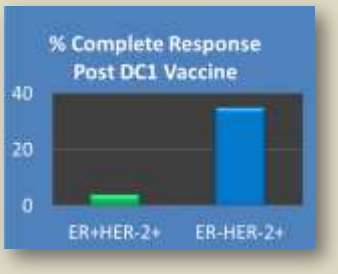
Peoples-Galena

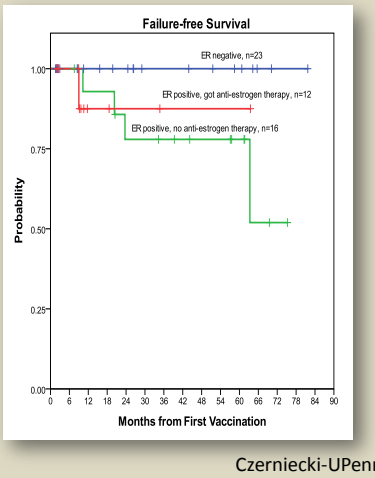
HER-2 vaccines prevent recurrence



Von Hofe-Antigen Express

HER-2 vaccines induce regression in DCIS patients





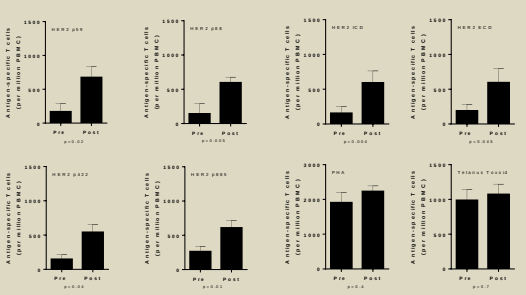
Czerniecki-UPenn

NEW GENERATION HER-2/NEU VACCINES

- **Phase I Clinical Trial**
  - Four helper T cell epitopes w/GM-CSF
  - One arm:
    - 2+(FISH+) and 3+
  - Three mos. following last dose of trastuzumab
    - Disease-free.
  - Objectives
    - Immunogenicity (i.e. proof of principle)
    - Safety
    - Feasibility

- Advantages of this HER-2 vaccine
- Targets helper T cell lymphocytes which help to coordinate the immune response and to generate long-term immunity
- Can be given to women regardless of HLA status, ie available to all eligible women

NEW GENERATION HER-2/NEU VACCINES



The *Challenging* Road Ahead for a Prevention Vaccine

- **Feasible – *YES* – Some things more than others.**
  - Hard to definitely prove that a virus causes a cancer.
  - Studying Gardasil/Cervarix starting now.
- **Determine what antigens.**
  - More than one / mutation / escape - The earliest targets
- **How many vaccines do we launch?**
  - $1-2 million per phase I - $10 million per phase II
  - $50 – 100 million for a phase III
- **Early discussions with the FDA.**
  - If a self antigen – will be a FIRST – Safety
  - How do we show protection in a disease that takes decades to develop?

Conclusions

- **Vaccination for the prevention of breast cancer, secondary and primary are a reality.**
- **There are three possible choices of antigens that could be targeted.**
  - *Self antigens*
  - *Mutated proteins*
  - *Microbial antigens.*
- **Vaccination against self antigens is already underway and showing great promise.**

Thank you!

George Institute
612-863-3333

Five "Need to Know" Supplements for Breast Health

Gregory A. Plotnikoff, MD, MTS, FACP
Penny George Institute for Health and Healing

"The Precautionary Principle"

"Where there are significant risks of damage to the public health,

We should be prepared to take action to diminish those risks,

Even when the scientific knowledge is not conclusive, if the balance of likely costs and benefits justifies it."

Richard Horton, MD, editor-in-chief, The Lancet
"The *new* public health of risk and radical engagement."
Lancet. 1998;352(9124): 251-2.

Five Supplements

- Vitamin D
- Omega-3 Fatty Acids
- Vitamin E
- Iodine
- Probiotics

3 Myths

- Vitamin D is a vitamin activated in the kidney.
- Vitamin D has no relevance to health outside of bone health.
- North Americans, with few exceptions, have sufficient vitamin D.

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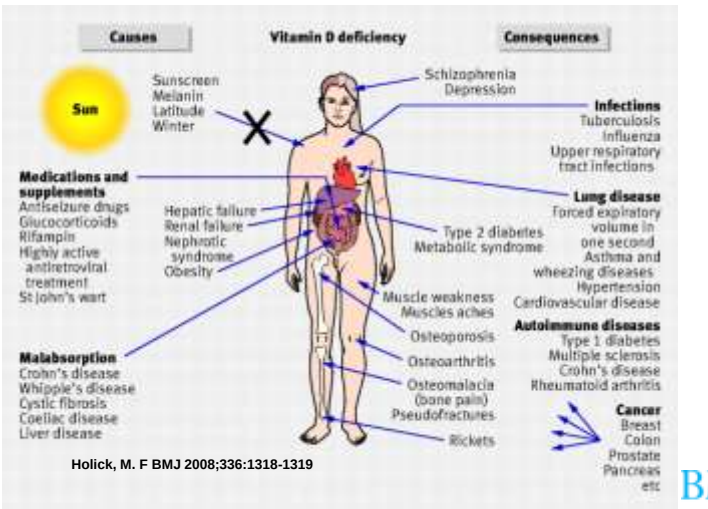
Causes and Consequences of Vitamin D Deficiency



Holick, M. F BMJ 2008;336:1318-1319

BMJ

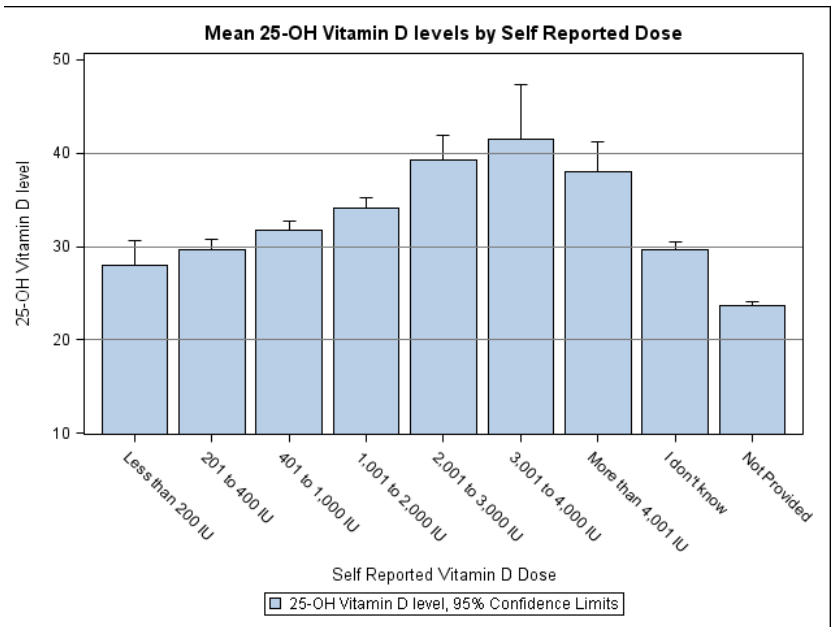
3 Myths

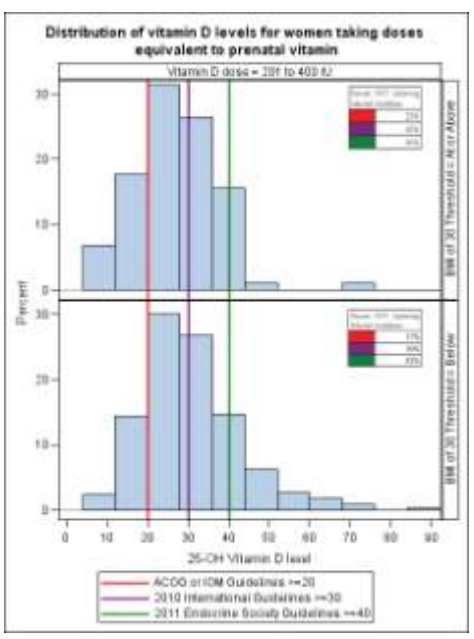
- Vitamin D is a vitamin activated in the kidney.
- Vitamin D has no relevance to health outside of bone health.
- North Americans, with few exceptions, have sufficient vitamin D.

Springtime 2010 prospective observational study of 10,646 Allina employees

Vitamin D sufficiency was defined by the three existing standards:

1) The 2010 Institute of Medicine/American College of Obstetrics and Gynecology definition of ≥ 20 ng/ml
2) The 2010 International Consensus definition of ≥ 30 ng/ml
3) The 2011 Endocrine Society definition of 40-60 ng/ml.



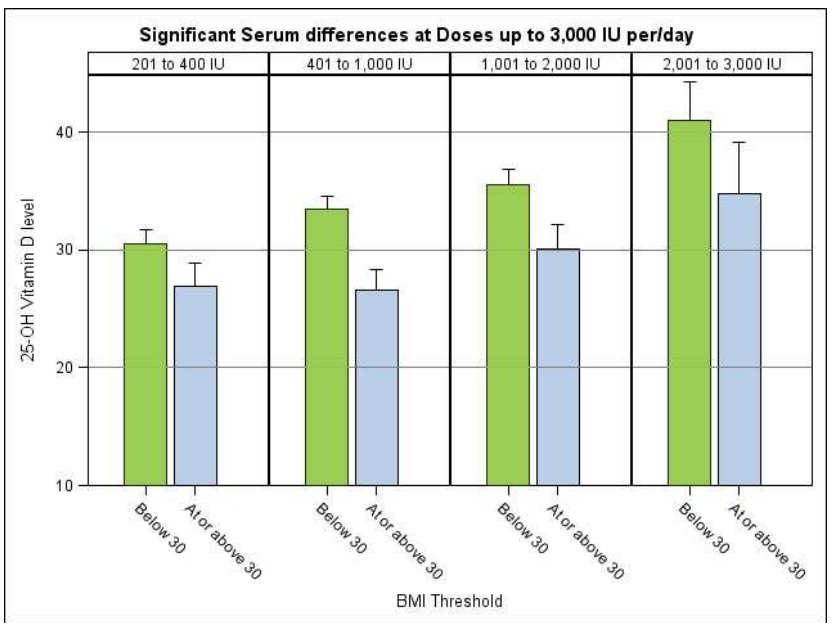


1,710 (32.4%) did not meet 2010 IOM vitamin D guidelines for vitamin D sufficiency (≥ 20 ng/ml),

3,684 (65.5%) did not meet 2010 international guidelines (≥ 30 ng/ml),

4,874 (86.6%) did not meet 2011 Endocrine Society guidelines (40-60 ng/ml).

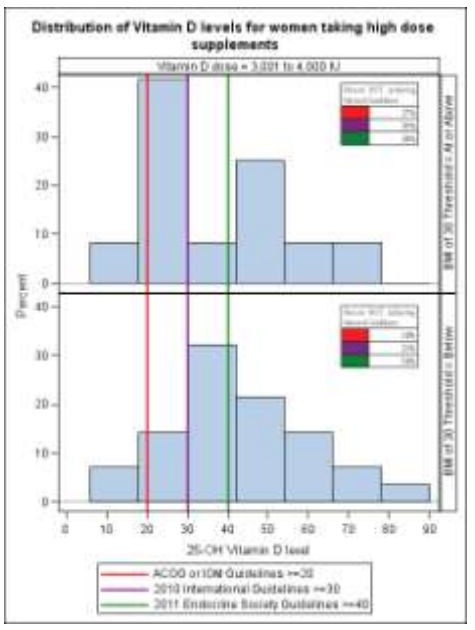
N = 5,628



Higher Doses are not Toxic

Mean 25-OH-vitamin D serum levels and standard deviations for higher reported vitamin D3 daily intakes were:

- 3,001-4,000 IUs 38.57 ng/ml (17.06)
- >4,000 IUs 37.98 ng/ml (16.40)



Take Home Points

- By any definition, female healthcare workers of child bearing age demonstrate a high incidence of vitamin D deficiency.
- Daily prenatal or multivitamin supplementation does not ensure adequate 25-OH-vitamin D levels.
- A BMI ≥30 represents a substantially increased risk of suboptimal 25-OH-vitamin D status.
- Reported daily intake of >4,000 IUs did not result in elevated serum levels of vitamin D.

Shocking Fact #1

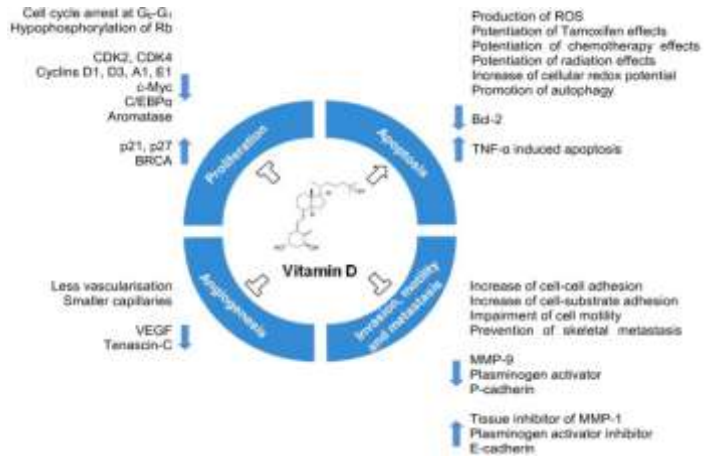
- Vitamin D has chemopreventive effects on the development and progression of several cancers including breast cancer.

Vitamin D and Cancer

- Proliferation
- Differentiation
- Apoptosis

- Anti-inflammatory
- Potentiator of anti-tumor actions
- Anti-thrombotic

Vitamin D and Breast Cancer



Shocking Fact #2

- BC patients with a more aggressive molecular phenotype (basal-like) and worse prognostic indicators (ER- and triple-negative) have lower mean 25-OH vitamin D levels.

Ann Surg Oncol. 2012 Aug;19(8):2590-9

Shocking Fact #3

- Vitamin D status may affect breast cancer treatment results.

Potentiates Anti-tumor Activities

- DNA-damaging:
  cisplat, carboplat, doxorubicin
- Anti-metabolites:
  5-FU, ara-C, gemcitabine ,hydroxyurea
- Microtubule-disturbing agents:
  paclitaxel, docetaxel

Ma Y, et al. Vitamin D in combination treatment. J Cancer. 2010;1:101-107.

Potentiates Anti-tumor Activities

- Gamma irradiation (Prostate, Breast, SCC)
- Cyclooxygenase inhibitors
- Vitamin K2
- Carnosic acid
- Bryostatin-1
- Iron deprivation agents
- Dexamethasone
- RRR-alpha-tocopherol
- Genistein
- Phosphorylated prolactin

Ma Y et al. Vitamin D in combination cancer treatment. *J Cancer*. 2010; 1;101-7

Optimal Vitamin D

"The Precautionary Principle"

"Where there are significant risks of damage to the public health,

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2013 Annual BCAA Education Conference
October 12, 2013

Carolyn Torkelson MD MS
- Breast Specialists
  Breast Center U of MN
- Medical Director of Integrative Health at Women's Health Specialists
- Associate Professor
  Family Medicine & Community Health
  University of Minnesota
  tork0004@umn.edu

Breast Specialist – Breast Center – U of MN

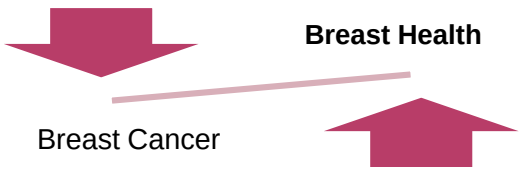
- Women with breast concerns:
  - Lumps/pain/discharge
- Women at high risk for breast cancer:
  - Family history
  - Gene mutation
- Breast cancer survivors:
  - >5 years
- Integrative Consults:
  - Conventional + complementary options

Breast Health: Objectives/Goal

Provide a framework for “Breast Health” and risk reduction using prevention, screening, early detection and lifestyle modification strategies.

Breast Health vs. Breast Cancer

- In 2013, an estimated 232,340 new cases of breast cancer will be diagnosed in the US.
- 85% of women diagnosed with breast cancer now survive for five years or more.
  - Early detection with screening
  - Identification of High Risk
  - Prevention



Breast Cancer Screening

- American Cancer Society:
  - Yearly mammograms starting at age 40 and continuing for as long as a woman is in good health.
  - Yearly CBE after age 40.
  - Every three years CBE and breast awareness age 20-39.
- ACOG
  - Women in their 40s continue mammography screening every one to two years and women age 50 or older continue annual screening. Routine mammographic screening should continue to the age of 75.
- USPSTF guidelines (11/2009):
  - Routine breast cancer screening guidelines recommend “biennial screening mammography for women starting at age 50.
  - Screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient's values regarding specific benefits and harms.

Breast Risk stratification/category

Average Risk (Low Risk)

- The NCI Surveillance, Epidemiology, & End Results (SEER) database = Lifetime risk in the US at **12.7 %** or “1 in 8," yet the chance that a woman will never have breast cancer is 87.3%, or "7 in 8" women.

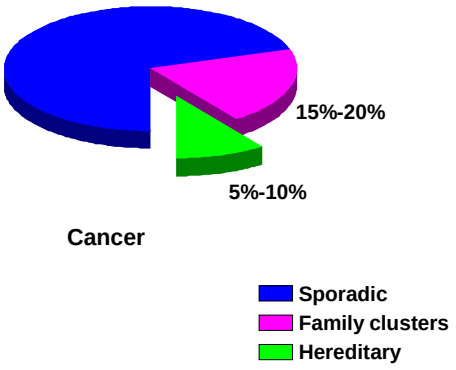
Moderate Risk (Higher Risk)

- **12-20%** lifetime risk.

High-Risk

- 5-year risk of greater than 1.66%.
- Lifetime risk of > **20%:**
  - **High risk screening**
  - **Treat with chemoprevention**
  - **Refer to genetic counselor**

How Much Cancer is Hereditary?



Risk Factors for Breast Cancer

- Family history of breast cancer
- Gene mutation (family/self)
- Chest/mantle field radiation treatment
- Previous breast biopsies
- Pre-malignant lesions – ADH/ALH/LCIS
- Dense breasts on Mammogram
- Ashkenazi Jewish ancestry
- Increasing age
- Nulliparity
- Early menarche – late menopause
- 1st child > 30
- Post menopause HT > 5 years
- Postmenopausal obesity
- Alcohol intake of >1/day
- High fat, low fiber, low intake of fruits and vegetables
- Night shift work

Intake Questionnaire: U of MN Breast Center

Identify high, medium and low risk?

↓

Notify the patient and MD

↓

Refer to a genetic counselor or a breast specialist

High-Risk Guidelines

Annual MRI and mammogram: (alternating every 6 mo.)

- BRCA 1 or BRCA 2 mutation.
- A first-degree relative with a BRCA1 or BRCA2 mutation, even if they have yet to be tested themselves.
- Radiation to the chest between the ages of 10-30.
- A lifetime risk of breast cancer has been scored at > **20 %,** based on a risk assessment tools.

Risk calculation Tools: Identification high risk

- Gail Model http://www.cancer.gov/bcrisktool/
- Claus Model (Family History)
- IBIS Model *www.ems-trials.org/**risk**evaluator/*
  - *Women who would benefit from high risk screening*
  - *Women who would benefit from chemoprevention*

Chemoprevention Strategies

SERMS: Selective estrogen receptor modulators

- Premenopausal
  - Tamoxifen X 5 years: NSABP (National surgical Adjuvant Breast and Bowel project) enrolled 13,000 women at high risk. (BCPT)
    - Reduce the risk of invasive breast cancer by 49%
    - Reduce the risk of non-invasive breast caner by 50%
    - Reduce the risk of Atypical Hyperplasia by 85%
      - **1998,** FDA approved
- Postmenopausal
  - Raloxifene X 5 years: (STAR Trial) 20,000 **postmenopausal** women, high risk & compared to Tamoxifen.
    - Reduces the risk of invasive breast cancer 37%
    - Reduces the risk of non invasive breast cancer by 50%
    - Retains 76-78% of Tamoxifen's chemoprevention benefits with fewer side effects
      - **2007**, FDA approval for use in postmenopausal women at high risk for IBC.

Risk Reduction Strategies

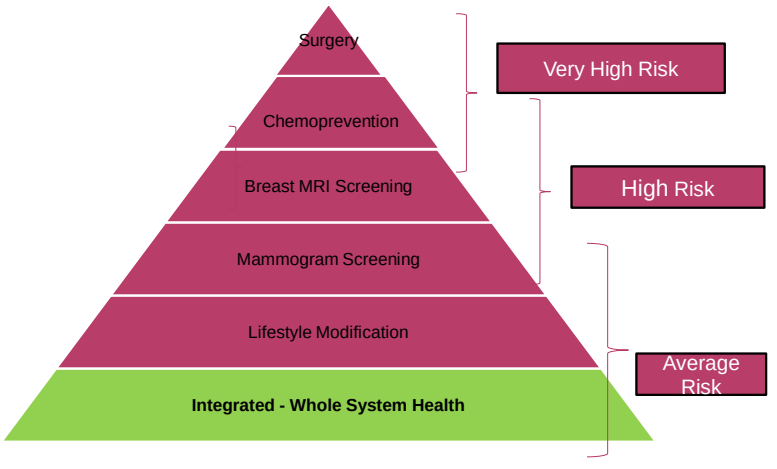
Chemoprevention

- SERMS: selective estrogen receptor modulators
  - Tamoxifen
  - Raloxifene
- An estimated 2 million premenopausal women are candidates for Tamoxifen – only 4% on the drug!
  - Lack of knowledge of the benefits
  - Side effects
  - Medication avoidance

Surgical Intervention [BRCA positive]

Lifestyle modification

Integrated Individualized Care Model



Lifestyle risk modifiers
(non-pharmacological)

Guidelines from American Cancer Society and WCRF/AICR

http://www.cancer.org/acs/groups/cid/documents/webcontent/002577-pdf.pdf

- Weight management
  - BMI in normal range (18.5-25)
- Healthy diet
  - Food as prevention/medicine
  - Diet rich in vegetables, fruits and whole grains
- Exercise
  - 30 minutes daily

Percentage Of Cancers That Could Be Prevented Via Healthy Diet, Regular Physical Activity And Healthy Weight

	US	UK	Brazil	China
Endometrium (lining of the uterus)	70	56	52	34
Esophagus	69	75	60	44
Mouth, pharynx & larynx	63	67	63	44
Stomach	47	45	41	33
Colon	45	43	37	17
Pancreas	39	41	34	14
Breast	**38**	**42**	**28**	**20**
Lung	36	33	36	38
Kidney	24	19	13	8
Gallbladder	21	16	10	6
Liver	15	17	6	6
Prostate	11	20	n/a	n/a
These 12 cancers combined	**35**	**37**	**30**	**27**

The table shows estimates for each cancer for the four countries. Totals are given for the 12 cancers (common cancers) studied as well as for all cancers.

Exercise as Medicine

At least 30 minutes of moderate to vigorous physical activity, above usual activities on 5 or more days of the week.

Physical activity among cancer survivors show positive and consistent effects on the following:

- Vigor and vitality
- Cardio respiratory fitness
- Quality of life
- Depression
- Anxiety
- Fatigue/tiredness

(*Knols 2005; Pinto, 2005).*

Resistance training:

•May counteract side effects of cancer treatment (bone and muscle loss)

•Improve survivors' physical function and quality of life. *Galvao and Newton,2005).*

Fat or Fit: The Joint Effects of Physical Activity, Weight Gain, and Body Size on Breast Cancer Risk.

(McCullough, Cancer 2012)

Results: Large Case Control Study

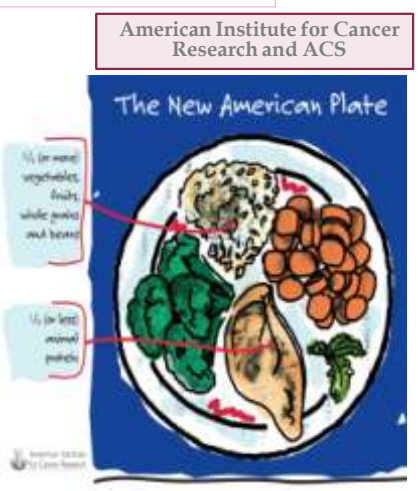
- Women with frequent episodes of RPA (10-19 hours/week experienced the greatest benefit with an approximate 30% risk reduction in the reproductive (odds ratio=0.67;95% CL=0.48-0.94) and postmenopausal years (odds ratio=0.70;95%CL=0.52-0.95).
- Postmenopausal weight gain may eliminate the benefits of regular RPA
- Women can reduce their breast cancer risk later in life by maintaining healthy weight and engaging in moderate amounts of activity.

Food As Medicine

Whole Food Diet:

- Rich in a variety of plant-based foods and less animal basedd protein.
- At least 2/3 of your plate filled with vegetables, fruit, whole grains and beans.
- Lower dietary fat to between 10% - 20% of calories.
- Alcohol in moderation
- Water intake 8-10 eight ounces/day
- Limit salts, nitrates and cured foods

American Institute for Cancer Research and ACS



Nutritional Components

- Polyunsaturated Fatty Acids:
  - Omega 3 fatty acids including EPA and DHA:
  - Fatty fish such as salmon, sardines and mackerel; Flax seed, walnuts.
    - The Vitamins and Lifestyle (VITAL) Study demonstrated that fish oil reduced the risk of ductal but not lobular breast cancers.
    - High doses of omega-3 fatty acids markedly reduces breast tissue hyperplasia and key biomarkers in pre-and post menopausal women (AACR).
    - (Small Study): The combination of EFA and Raloxifen as a feasible strategy that may be recommended in future breast cancer chemoprevention trials.
    - Contraindications: If any bleeding occurs, stop fish oil immediately. Stop one week prior to surgery.
- Monounsaturated Fatty Acids:
  - Oleic acid (omega 9 fatty acid) found in olive oil, avocados, hazelnuts, and cashews
    - 3/5 studies found significant decrease in risk of breast cancer.
- Carotenoids:
  - Specifically lycopene (tomatoes) have been found to be effective in reducing a women's risk of breast cancer; specifically risk reduction in ER-negative tumors. JAMA Jan 16, 2013 http://tinyurl.com/brqff5A

Cruciferous Vegetables

- Group of Glucosinolates that break down into biologically active compounds in the metabolism of selected estrogens:
  - Indole 3 carbinol (I3C)
  - Diindolylmethane (DIM)
- These compounds have shown anticancer effects in cells and animals, but the results of studies with humans have been less clear.

- Arugula
- Bok choy
- Broccoli
- Brussel sprouts
- Cabbage
- Cauliflower
- Collard greens
- Horseradish
- Kale
- Radishes
- Rutabaga
- Turnips
- Watercress
- Wasabi

Rich in nutrients: carotenoids, vitamins C, E, K, folate & minerals.

Vitamin D Supplementation

- Evidence for breast cancer reduction:
  - Three observational cohort studies had inconsistent results:
    - One found an inverse association
    - One found no association
    - Another, no overall trend but an inverse association in one subgroup
  - High incidence of hypovitaminosis D in cancer (colon, breast, prostate) patients compared to a healthy control group (Pazdiora et al, 2011).
- Levels:
  - Draw 25(OH)D
  - Optimal level (30-80 ng/ml). 1000-2000 IU daily
  - Sources: sunlight, fortified foods, animal products, & supplements
  - Benefits: Support bones, immune function, calcium absorption, etc.
- IOM recommended dietary allowance (RDA) for women is 600 IU daily and 800 IU if over 70.

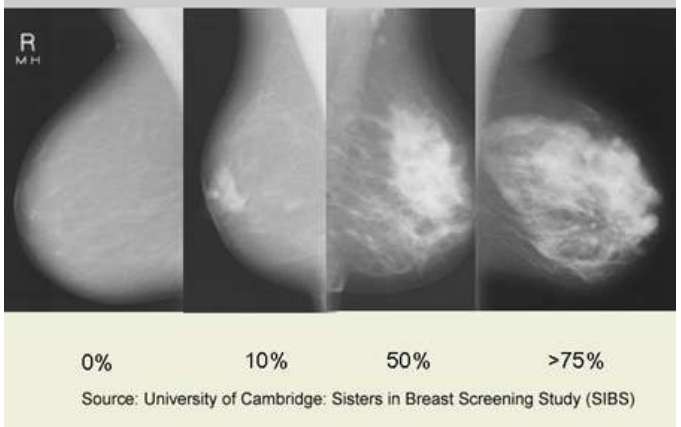
Green Tea Study and Reduction of Breast Cancer Risk

U of MN – NIH funded Study:

- 5 year randomized, double blind placebo controlled trial
- Randomized > 1000 women
- Determine effects of 12 mo green tea supplementation.
  - Mammographic density
  - Biomarkers of breast cancer risk: IGF-1; urinary estrogen metabolites; Estrone, Estradiol, SHBG.
  - COMT genotype.

The polyphenols - catechins are thought to be responsible for the health benefits that have traditionally been attributed to green tea. The most active and abundant catechin in green tea is epigallocatechin-3-gallate **(EGCG).**

Breast Density



Source: University of Cambridge: Sisters in Breast Screening Study (SIBS)

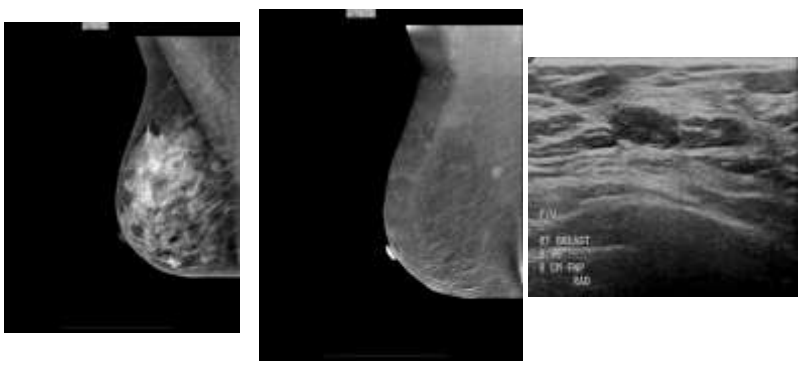
Mammogram Density

- About 40 % of women have dense breast tissue –it is not abnormal. It is a mammographic reading.
  - **Significance:** strongly associated with the risk of breast cancer:

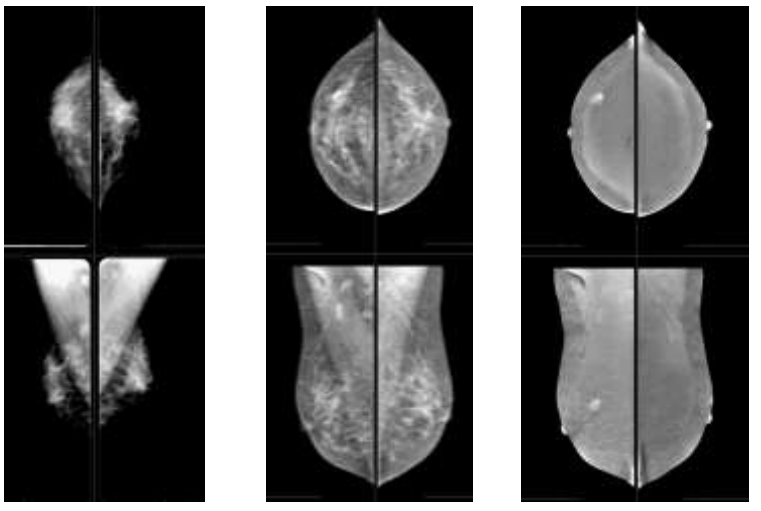
  A meta-analysis of 42 studies (McCormack):
  - Highest quartile of density have a 4-6 times higher risk.

  Boyd et al, reported:
  - increased risk of breast cancer is not only because of a masking effect of the breast density, but also because of a biologic connection between breast density and breast cancer.
- Laws requiring the disclosure have been passed in Connecticut, Texas and Virginia and most recently California and consider additional screening us US or MRI
  - Leads to additional – unnecessary screening=false positives
    - vs
  - **marker of increased risk** of developing breast cancer.

Contrast Enhanced Digital Mammography



Mammogram: analog-digital-contrast enhanced



Breast Health Summary

- Screen appropriately
- Identify your risk category:
  - If >20 % by ACS guidelines
    - Consider chemoprevention
- Engage in healthy life style
  - Exercise
  - Normal BMI
  - Whole Foods Diet/vegetables
  - Avoidance of ETOH
  - Normal Vitamin D levels
- Evolution of knowledge in Breast Health

WE CONNOT DIRECT THE WIND BUT WE CAN ADJUST THE SAILS

~Author Unknown

Thank You

Q & A

References

Costanza ME and Chen WY. Epidemiology and risk factors for breast cancer. UpToDate www.uptodate.com Updated October 5, 2010.

Boyd NR, Lockwood GA, Byng JW, Tritchler DL, Yaffe MJ. Mammographic densities and breast cancer risk. Cancer Epidemiol Biomarkers Prev 1998;7:1133-1144.

Doyle C, Kushi LH, Byers T, et al. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. CA Cancer J Clin 2006;56:323-353.

Megdal SP, Kroenke CH, Laden F et al. Night work and breast cancer risk: a systematic review and meta-analysis. Eur J Cancer 2005;41:2023-2032.

Hanson J. Increased breast cancer risk among women who work predominantly at night. Epidemiology 2001;12:74-77.

Kushi LH, Byers T, Doyle C, et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 2006;56:254-281.

Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med 2001;344:276-285.

Lord RS, Bongiovanni B, Bralley JA. Estrogen metabolism and the diet-cancer connection: rationale for assessing the ratio of urinary hydroxylated estrogen metabolites. Altern Med Rev 2002;7:112-129.

Kabat GC, O'Leary ES, Gammon MD, et al. Estrogen metabolism and breast cancer. Epidemiology 2006;17:80-88

Bentz AT, Schneider CM, Westerlind KC. The relationship between physical activity and 2-hydroxyestrone, 16 alpha-hydroxyestrone, and the 2/16 ratio in premenopausal women. Cancer Causes Control 2005;16:455-461.

Terry P, Wolk A, Persson I, et al. Brassica vegetables and breast cancer risk. JAMA 2001;285:2975-2977.

Brasky TM, Lampe JW, Potter JD, et al. Specialty supplements and breast cancer risk in the vitamins and lifestyle (VITAL) cohort. Cancer Epidemiol Biomarkers Prev 2010;197:1696-708. BMC Cancer 2009:9216.

Kim J, Lim SY, Shin A, et al. Fatty fish and fish omega-3 fatty acid intakes decrease the breast cancer risk: a case-control study. BMC Cancer 2009;9:216.

Spencer L, Mann C, Metcalfe M, et al: The effect of omega-3 FAs on tumour angiogenesis and their therapeutic potential. Eur J Cancer 2009;45:2077-2086.

Sturgeon SR, Heersink JL, Volpe SL, et al: Effect of dietary flaxseed on serum levels of estrogens and androgens in postmenopausal women. Nutr Cancer 2008;60:612-618

References, cont.

Thompson LU, Chen JM, Li T, et al: Dietary flaxseed alters tumor biological markers in postmenopausal breast cancer. Clin Cancer Res 2005;11:3828-3835.

Circulating 2-hydroxy and 16-α hydroxy estrone levels and risk of breast cancer among postmenopausal women. Eliassen AH, Missmer SA, Tworoder SS, Hankinson SE. Cancer Epidemiol biomarkers prev. 2008 August 17(8) 2029-2035, doi: 10.1158/1055-9965.EPI-08-0262.

Ogunleye AA, Xue F, Michels KB. Green tea consumption and breast cancer risk or recurrence: a meta-analysis. Breast Cancer Research and Treatment 2010;1192:477-484.

Huang X, Holman CD. Dietary intakes of mushrooms and green tea combine to reduce the risk of breast cancer in Chinese women. International Journal of Cancer 2009;1246:1404-1408.

Smith-Warner SA, Spiegelman D, Yaun SS, et al. Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. *JAMA* 2001;285(6):769-776.

Bell MC, Crowley-Nowick P, Bradlow HL, et al. Placebo-controlled trial of indole-3-carbinol in the treatment of CIN. *Gynecologic Oncology* 2000;78(2):123-129.

Edlich R, Mason SS, Chase ME, et al. Scientific documentation of the relationship of vitamin D deficiency and the development of cancer. Journal of Environmental Pathology, Toxicology and Oncology 2009;282:133-141.

Blackmore KM, Lesosky M, Barnett H, et al. Vitamin D from dietary intake and sunlight exposure and the risk of hormone-receptor-defined breast cancer. Am J Epidemiol 2008;1688:915-924.

Garland CF, Gorham ED, Mohr SB, Garland FC. Vitamin D for cancer prevention: global perspective. Ann Epidemiol 2009;197:468-483.

Bischoff-Ferrari HA. Optimal serum 25 hydroxyvitamin D levels for multiple health outcomes. Adv Exp Med Biol 2008;624:55-71.

Ingraham BA, Bragdon B, Nohe A. Molecular basis of the potential of vitamin D to prevent cancer. Curr Med Res Opinion 2008;241:139-149.

Garland CF, Gorham ED, Mohr SB et al. Vitamin D and prevention of breast cancer: pooled analysis. J Steroid Biochem Mol Biol 2007;1033(5):708-711

Pazdiora P, et al. **Vitamin D in Colorectal, Breast, Prostate and Lung Cancer: A Pilot Study.** Anticancer Research October 2011 vol. 31 no. 10 3619-3621


Our mission is to serve women and men in the community by providing easy access to support and information about breast cancer and to enhance the quality of life for survivors, family and friends.