Diet & Other Lifestyle Factors in Hereditary Breast & Ovarian Cancers

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Scientific Themes (Kumar Group/Lab)

- (1) Contribution of psychological, social and physiological basis of obesity, body composition and the resulting modulation of steroid hormones as it relates to cancer risk/survival;

- (2) The role of nutrients, nutrient-derived agents and other non-toxic agents in cancer chemoprevention, treatment and survival; &

- (3) Understanding the bio-behavioral etiology of cancer disparities and developing and testing the safety and efficacy of novel trans disciplinary interventions to reduce, and ultimately eliminate, these disparities.
Causes of Cancer

Estimate percentage of total cancer deaths attributable to established causes of cancer

- Tobacco: 30%
- Adult diet/obesity: 30%
- Sedentary lifestyle: 10%
- Occupational factors: 5%
- Family history of cancer: 3%
- Viruses/other biologic agents: 2%
- Perinatal factors/growth: 3%
- Reproductive factors: 3%
- Alcohol: 2%
- Socioeconomic status: 2%
- Environmental pollution: 1%
- Ionizing/ultra-violet radiation: 1%
- Prescription drugs: 1%
- Medical procedures: 1%
- Salt/other food additives/contaminants: 1%

Current Treatment Strategies for BRCA1 and BRCA2 Carriers

- Hormone Modulators
- Risk-reducing salpingo-oophorectomy
- Prophylactic mastectomy
- Genetic Counselling
- Surveillance
- Exploring other options ..Lifestyle Factors..?
Laboratory Studies
International Differences in Diet & Cancer Incidence

- Africa, South and Central America, Caribbean,
- Japan, China, India
- Europe, USA, Canada, Australia, New Zealand

<table>
<thead>
<tr>
<th>Region</th>
<th>Diet Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-90% fruits, vegetables, grains</td>
<td>50-90% fruits, vegetables, grains</td>
</tr>
<tr>
<td>10-25% meat, dairy, sugars, fats and other</td>
<td>25-55% fruits, vegetables, grains</td>
</tr>
<tr>
<td>45-75% meat, dairy, fats, sugars and other</td>
<td>25-55% fruits, vegetables, grains</td>
</tr>
</tbody>
</table>

- 50-90% fruits, vegetables, grains
- 10-25% meat, dairy, sugars, fats and other
- 25-55% fruits, vegetables, grains
- 45-75% meat, dairy, fats, sugars and other
## Migration Studies - Comparison of Cancer Incidence (Annual/million)

<table>
<thead>
<tr>
<th>Site</th>
<th>Japanese in Japan</th>
<th>Japanese in Hawaii</th>
<th>US Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>70</td>
<td>371</td>
<td>368</td>
</tr>
<tr>
<td>Rectum</td>
<td>95</td>
<td>297</td>
<td>204</td>
</tr>
<tr>
<td>Breast</td>
<td>335</td>
<td>1221</td>
<td>1869</td>
</tr>
</tbody>
</table>
Migration Studies

Incidence of Breast Cancer in Japanese Women Rate per 100,000

Japan  Hawaii (First Generation)  Hawaii (Second Generation)

[Bar chart showing incidence rates]
Secular Trends

- Seventh Day Adventists in the US
  - Vegetarian, no-pork
- 50% lower mortality rate for Breast Cancer
- Lower Colon Cancer/heart disease rates than the US Population
- African populations in the USA – disparity in cancer mortality and morbidity
  - (W Africans, Jamaica, Bahamas, etc)
Biological Plausibility

- Advances in Molecular Oncology/genetics
- Carcinogenicity of environmental factors
- Nutrients can alter genetic & epigenetic events
  - Essential Nutrients
  - Phytochemicals or allelochemicals
    (Bioactive secondary compounds in plants)
    - Zoochemicals – conjugated linoleic acid, n-3 fatty acids
- Obesity – hormonal changes
- Sun Exposure
- Tobacco/chronic alcohol intake
- Lack of Physical activity
Obesity & Cancer
Obesity Trends* Among U.S. Adults

BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data           <10%          10%–14%
Obesity Trends* Among U.S. Adults

**BRFSS, 1995**

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)*

No Data           <10%          10%–14% 15%–19%
Obesity Trends* Among U.S. Adults

BRFSS, 2000

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults

BRFSS, 2003

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults

BRFSS, 2005

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults

BRFSS, 2008

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
(*BMI ≥ 30, or about 30 lbs. overweight for 5’4” person)
Disease Risk/Consequences of Obesity = Rising Health Care costs

- Hypertension
- Stroke
- Renal Disease
- Gallbladder Disease
- Diabetes mellitus
- Pulmonary Diseases
- Osteoarthritis
- Gout
- Breast & endometrial Cancer

- Abnormal plasma lipids and lipoproteins
- Impaired cardiac function
- Problems during surgery with anesthesia
- Sleep apnea
- Inflammation
Weight Gain in Adult Years and Risk of Hereditary Cancers
Progressive Weight Gain Through Adulthood

22.5  24  32  35
Body Fat Distribution

"Apple" vs. "Pear"

Above the waist
Below the waist
“Perils of Portliness”-Consequences of android/abdominal obesity

- Breast Cancer-Risk x5 fold
- Endometrial cancer
- Polycystic ovary syndrome
- CVD/CAD/Hypertension
- Gallbladder Disease
- Adult onset Diabetes
- Insulin resistance
- Metabolic Syndrome
- Adult weight gain
- Highly correlated with
  - visceral fat
- **Weight gain in the 30’s**

(Kumar et al)
Potential Mechanisms Proposed

- Mechanisms proposed –
  - adipose tissue-induced increased concentrations of estrogens and insulin, thyroid dysfunction,
  - bioavailable insulin-like growth factors, leptin, and cytokines.
- Reduced immune functioning,
- Chemotherapy/Other preventive therapy dosing
- Differences in diet and physical activity in obese and nonobese patients
Body Composition/Hormones in Breast Cancer Survival (Kumar et al., Cancer, 2002)

- Android Obesity - risk and for survival
- Obesity at diagnosis - adverse prognostic indicator
- Abdominal Obesity at diagnosis - Hazard ratio of 2.5
- Risk of recurrence - 1.33-1.5 times higher - obese vs non-obese
- 1.6 times greater risk of death in gainers vs non-gainers
## Android Obesity at Diagnosis and Risk of Breast Carcinoma Survival

### Proportional Hazards Regression Analysis Body Mass Indices and Breast Carcinoma Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suprailiac: thigh ratio</td>
<td>2.61</td>
<td>(1.63–4.17)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight at age 30 yrs</td>
<td>1.15</td>
<td>(1.01–1.28)</td>
<td>0.036</td>
</tr>
<tr>
<td>Quatelet index</td>
<td>0.92</td>
<td>(0.87–0.98)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

CI: confidence interval.
Android Obesity- What do we know?

- Central/Android Obesity is an independent powerful predictor of disease, including Breast Cancer
- Central/android obesity is highly correlated to visceral obesity
- Waist:Hip Ratio >0.8-Android Obesity
- Alters steroid hormone profile
- Genetic- similarities w/first-degree relatives-significance
- Weight loss in early adult life (age 18 to 30) protects against early-onset BRCA-associated breast cancers.
- Weight gain should also be avoided, particularly among BRCA1 mutation carriers who elect to have at least two pregnancies.
Change in Body Composition with weight loss – Yes, There is Hope!
It is not all Gloom & Doom!

- Carcinogenesis is a complex biological process, genetically determined and environmentally modulated.

- Nutrition, Physical Activity and other lifestyle factors may play a Critical Role in modulating carcinogenesis.

- Variations in penetrance between individuals who are carriers.

- Factors other than gene mutation may influence the risk in susceptible women.
Nutrients as “Chemoprevention Agents” - The promise

- A Diet-Derived agent that can prevent the induction and inhibit the development of preinvasive and invasive cancer and its progression.

- **Anti-promotion and Anti-progression agents** that prevent the growth and survival of cells, already committed to become malignant
  - **Phytochemicals** or allelochemicals
    - (Bioactive secondary compounds in plants)
  - **Zoochemicals** – conjugated linoleic acid, n-3 fatty acids
Cell Fate: Rationale for Chemoprevention

APOPTOSIS (Programmed Cell Death)

MATURATION/DIFFERENTIATION

CHEMOPREVENTION:
- Mutagenesis
- Programmed Death
- Maturation/
- Differentiation
- Proliferation

PROLIFERATION
Chemoprevention - Opportunity

- In most epithelial tissues –
  - Accumulating mutations (i.e., genetic progression) and loss of cellular control functions →
  - Progressive phenotypic changes from normal histology →
  - Early pre cancer (intra epithelial neoplasia - IEN) →
  - Increasingly severe IEN →
  - Superficial cancer and finally →
  - Invasive cancer.
Carcinogenesis: A Multi-step Process

NORMAL → DYSPLASIA → CARCINOMA \(\text{in situ}\) → MALIGANT CARCINOMA

- Normal tissue
- Dysplasia: Cells with condensed nuclei
- Carcinoma \(\text{in situ}\): Cells with condensation and invasion
- Malignant Carcinoma: Invasion of connective tissue

**Key Terms:**
- Basal layer
- Connective tissue
- Basal lamina
- Differentiating cells with condensed nuclei
Epidemiological Evidence on Diet Cancer

- Dietary factors-used alone or in combination to prevent
  - Occurrence of cancer
  - Metastatic progression
  - Treatment of Cancer
- May be able to produce chemotherapeutic effects with a relatively lower toxicity
Opportunity and need for identification of Nutrients as agents for chemoprevention

- Long Latency
- High Incidence
- Significant Morbidity & Mortality
- Several promising nutrients
- Current agents- high toxicity
- Screening complexity (When? How? What? Effectiveness?)
Antioxidants

**Figure 9-8**
Vitamin E functions as an antioxidant that protects the unsaturated fatty acids in cell membranes from damage by neutralizing reactive oxygen compounds.
Antioxidant Nutrients

- STABILIZATION OF CELL MEMBRANE
- REGULATION OF OXIDATION REACTIONS,
- CRITICAL FOR CELL STRUCTURE
- Critical for Cell FUNCTIONs
- -> Systems function
- Oxidative stress loads maybe
- elevated in carriers
- Need to meet increased needs
- Structure is critical for Function
Angiogenesis → Carcinogenesis
Nutrients—pro or anti-angiogenic
Nutrients that are promising in preventing Cancer, ageing and other diseases

- **Soy Isoflavones** (Breast, Prostate, Lung)*
- **Carotenoids** (lycopene, ß-Carotene)(Prostate)*
- **Green tea** polyphenols *
- Calcium(Colon)
- Indole-3-carbinol(Breast)
- Curcumin(Colon)
- Allylic sulphides –garlic,onion(oral)
- Folate (Colon)
- **Tannic Acid***
- Selenium/Vitamin E
- **N-3 fatty acids***
- Resveratrol/anthocyanins*
- B Vitamins/C, Vitamin E
Fruit & Vegetable Consumption of adults and Children in the US (CDC 2009)

- The challenge

- 50 states & DC 50 have not achieved national objectives for fruit and vegetable consumption of 5 a day for better health

- 32.6% of adults consumed fruit two or more times per day and 27.2% ate vegetables three or more times per day

- Potato is the #1 vegetable of choice!

- Vegetables were also cooked with high fat meats
<table>
<thead>
<tr>
<th>CONVENTIONAL/ORTHODOX Paradigms of Health Care Delivery</th>
<th>Nutrients for Chemoprevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Popular Demand/Epidemiology</td>
</tr>
<tr>
<td>Cellular, in-vitro</td>
<td>Political Support/Advocacy groups</td>
</tr>
<tr>
<td>Animal models</td>
<td>Clinical Trials, Phase II, III</td>
</tr>
<tr>
<td>Clinical Trials, Phase I, II, III</td>
<td>[Cost-Effectiveness/Health Service]</td>
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<td>Cost-Effectiveness/Health Science</td>
<td>[Basic Science/Animal/in-vitro]</td>
</tr>
<tr>
<td>Health Policy/Reimbursement/Politics</td>
<td>[Scientific Acceptance]</td>
</tr>
<tr>
<td>Change Healthcare Delivery</td>
<td>Health Policy/Reimbursement/Politics</td>
</tr>
<tr>
<td></td>
<td>Change Healthcare Delivery</td>
</tr>
</tbody>
</table>

(Eisenberg, 2003-modified)
Where do we go from here?
What can you Do?
Recommendation #1: Reduce Caloric Intake

- Japanese in Okinawa island
- “hara hachi bu”- “belly 80% full”
- Doubled the number of functional Centurions
- Relatively longer life spans -consistently
- Quantities / “Portion Distortion”
Cheese is a garnish/appetizer - not food!

Ahh, the power of Cheese.
BAGEL

20 Years Ago

140 calories
3-inch diameter

Today

350 calories
6-inch diameter

Calorie Difference: 210 calories
CHEESEBURGER

20 Years Ago

333 calories

Today

590 calories

Calorie Difference: 257 calories
SPAGHETTI AND MEATBALLS

20 Years Ago

500 calories
1 cup spaghetti with sauce
and 3 small meatballs

Today

1,025 calories
2 cups of pasta with sauce
and 3 large meatballs

Calorie Difference: 525 calories
Choose Lean Meats, Chicken or Sea Food
Beef/Pork

- Limit intake of Beef & Pork
- Rich source of Cholesterol & LDL
- Trim off visible fats (Triglycerides)
- Select leaner cuts

$$$$$
<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Amount Per Serving</th>
<th>% Daily Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories</td>
<td>150 Calories</td>
<td>120</td>
</tr>
<tr>
<td>Total Fat</td>
<td>13g</td>
<td>21%</td>
</tr>
<tr>
<td>Saturated Fat</td>
<td>5g</td>
<td>23%</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>30mg</td>
<td>9%</td>
</tr>
<tr>
<td>Sodium</td>
<td>450mg</td>
<td>19%</td>
</tr>
<tr>
<td>Total Carbohydrate</td>
<td>1g</td>
<td>0%</td>
</tr>
<tr>
<td>Protein</td>
<td>5g</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

Not a significant source of dietary fiber, vitamin A and vitamin C.

*Percent Daily Values are based on a 2,000 calorie diet.
Good Fats with protein

- Fats found in seafood, especially the redder fish, is rich in **Omega 3– fatty acids**.
Watch those Desserts & “empty Calories”

- Apple pie and Carrot Cake don’t count as Fruits!
- Ice milk/yogurts - in place of Ice Cream
- **Dove bars - they stand alone!**
- Fresh Fruits make great Desserts
- Avoid “empty calories”
  - Sodas, Beers, fruit flavored juices
Limit Alcohol - Alcohol and Cancer Risk

Mechanism:
- Genetic Vulnerability/susceptibility
- Alcohol metabolizing enzymes – variations among individuals
- Other confounders – diet/smoking
- Increased oxidative stress
- Chronic alcohol use impairs not only gut and liver functions, but also multi-organ interactions, leading to persistent systemic inflammation
- Depletes folic acid, riboflavin, Zinc and retinoic acid
## Fast Foods - Sudden Foods - SUPERSIZING!

<table>
<thead>
<tr>
<th>Item</th>
<th>Calories</th>
<th>Fats</th>
</tr>
</thead>
<tbody>
<tr>
<td>BK Db Whopper w/Cheese</td>
<td>950</td>
<td>63</td>
</tr>
<tr>
<td>BK Whopper</td>
<td>630</td>
<td>39</td>
</tr>
<tr>
<td>Mc Big Mac</td>
<td>510</td>
<td>26</td>
</tr>
<tr>
<td>Mc ¼ pounder w/Cheese</td>
<td>520</td>
<td>29</td>
</tr>
<tr>
<td>OM ¼ pound Hot Dog</td>
<td>360</td>
<td>34</td>
</tr>
</tbody>
</table>
#2 Improve Bone Strength

- **Approach - HRT, Nutrition & Physical Activity**
- **Anti-osteoporotic minerals & vitamins**
  - Calcium, phosphorous, Magnesium, Vitamins A & D
  - Vitamin D 700-800 IU/day for prevention of bone loss
- **Physical Activity**
  - Resistance Training
- **Hormone replacement**
- **Long term interventions**
- **Timing**
  - Early start - 30-50’s
Osteoporosis- Declining spinal curvature

- 3 million osteoporosis-associated fractures
- Bone within the vertebral column, the hip, and the forearm near the wrist.
- Affects Physical Function
  Fractures with minimum Trauma
  80% are women
- Teeth- (Bone w/enamel)
- Current or former smokers and those on hormone deprivation therapies-more vulnerable
Choose low fat Dairy Products - Excellent for Bone Health

- Milk/-cheeses/-yogurts
- Lactose intolerance-
- Probiotics
- Get your Bone Mineral Density Checked
High Fat Dairy Products
#3 Prevent Muscle Loss - Sarcopenia

- **Sign of physical ageing**
- 22% -23% decline between ages 30-70 without purposeful exercise (NIA)
- **Loss of steroid hormones**
- **Just as important as preventing bone loss**
  - Purposeful Physical Activity
  - Resistance Training
    - Endurance
    - Flexibility
    - Cardio-respiratory
  - **Protein status-Quality of nutrients must not be compromised**
  - **Hormone Replacement Therapy**
Benefits of Purposeful Physical Activity

- Increased blood volume
- Strengthened heart muscle
- Lowered resting heart rate
- Increased stroke volume
- Improved VO$_2$ max
- Improved circulation
- Lowered blood glucose levels

- Increased energy expenditure
- Reduced stress
- Improved mental health
- Strengthened immune system
- Improved cardiovascular fitness
- Reduced body weight
- Increased bone mass
- Improved blood lipids
#4 Select a minimum 8-10 Fruits & Vegetables/day
#5 Select whole grain breads/cereals

- 20-30 grams of fiber intake is recommended/day
- Americans consume less than 50% of fiber
- **Americans spend the most on laxatives**
- Highest incidence of diverticulosis in the US
#6. Food vs. Vitamins???

Multivitamins/Minerals

- Most reliable way to make sure that you are getting your minimum
- Look for USP label -
- Take with a meal for maximum utility
- Use a mainstream label
- No megadoses recommended (x10 times USRDA)
#7 Select a fat that is a mono-unsaturated?

- Unsaturated fats
- Saturated Fats
- Trans fats (margarine)
- Mono unsaturated fats
  - Olive Oil
  - Canola Oil

Fats found in canola and olive oil are called monosaturated fats or omega-9 fatty acids. These oils have been shown to protect against heart disease and cancer.
Low fat dressings and mayonnaise- Best Option- Olive Oil & Vinegar
#8 Stop Smoking (exposure to second-hand smoke & tobacco products)

- Cigarette smoking causes 87 percent of lung cancer deaths and is responsible for most cancers of the larynx, oral cavity and pharynx, esophagus, and bladder.

- Secondhand smoke is responsible for an estimated 3,000 lung cancer deaths among U.S. nonsmokers each year.

- Tobacco smoke contains thousands of chemical agents, including over 60 substances that are known to cause cancer.

- “Snus”

NIH 2005
#9 Avoid Sun Exposure & Tanning beds

Do not sunbathe & Avoid unnecessary sun exposure, especially between 10:00 a.m. and 4:00 p.m., the peak hours for harmful ultraviolet (UV) radiation.

- When outdoors, use **sunscreens rated SPF 15 or higher**. Apply them liberally, uniformly, and frequently.

- When exposed to sunlight, wear **protective clothing** such as long pants, long-sleeved shirts, broad-brimmed hats, and UV-protective sunglasses.

- Wrinkles/skin cancer/eyes
- 75% increased risk of skin cancer
#10 Skin – the largest organ in the body – indicator of health and Disease

- Nutrition
- Hydration
- Sun exposure
- Exercise
- Tobacco
- Alcohol
- Stress
- Diseases
- Age……
- Cherish & Preserve it!
Most chronic diseases including Cancer result from:

- Genetic endowment
- Social & environmental conditions
  - Including advances in Medicine
- Individual behaviors
In Summary....Promise

- Biologically feasible to prevent cancer
- Body Composition & Obesity contribute to the progression of certain cancers
- **Physical activity and weight reduction** modulates cancers
- Populations that consume a predominantly **plant-based diet** have the lowest incidence of cancers
- **Nutrients and Nutrient-derived agents** have a significant role in Cancer Prevention
- The best data appears with wholesome, fresh, variety of foods in a daily diet- not supplements.