Nutrition and Cancer

• In 1999, cancer replaced heart disease as the leading cause of death among men and women in the U.S. aged 85 years and younger
• Between 1990/1991 and 2007, cancer death rates decreased by 22.2% in men and by 13.9% in women; however, 1 in 4 deaths in the U.S. is currently due to cancer
• Over 12 million persons in the U.S. are cancer survivors, and 65% of Americans diagnosed with cancer now live more than 5 years

Stages of Cancer Development

• Initiation
• Promotion
• Conversion
• Progression

Nutrition and Cancer

• Cancer etiology is multifactorial – both genetic susceptibility and a variety of environmental factors determine risk
• Accumulated evidence suggests that approximately 30-40% of cases are potentially preventable by modifying food choices and nutritional factors
• Disentangling effects of various foods, specific dietary constituents and associated lifestyle factors is challenging
Diet, Recurrence and Survival

- Biological evidence suggests that nutritional factors may influence cancer progression.
- Epidemiological studies suggest that many of the nutritional factors associated with risk for primary cancer may affect survival following diagnosis.
- For breast cancer, clinical trials examining whether diet modification can affect risk for recurrence and survival have been conducted, and more are ongoing.

Nutrition and Cancer Research

- Epidemiological studies: Ecologic, case-control, prospective, clinical trials.
- Animal models.
- Cell culture studies.
- Clinical studies, feeding studies.

Bioactive Food Components and Cancer Risk and Progression

- Nutrients: Vitamins, minerals.
- Carotenoids.
- Flavonoids.
- Organosulfur compounds.
- Isothiocyanates.
- Indoles.
- Ellagic acid.
- Polyphenolics.
- Resveratrol.
- Melatonin.

Diet May Influence Genetic and Epigenetic Events Associated with Several Cancer Processes

- Carcinogen Metabolism.
- DNA Repair.
- Hormonal Regulation.
- Differentiation.
- Apoptosis.
- Cell Cycle.

Limitations of Observational Studies

- Confounding: The possibility that an observed association between intake and disease is actually due to other differences in the groups being compared.
- People eat food, not nutrients, and foods are consumed in a pattern that is characterized by several factors.
- Clustering of behaviors: Dietary pattern, physical activity, other behaviors.

Emerging Evidence from Observational Studies

- Dietary patterns, rather than specific nutrients: For example, evidence suggests that a prudent/healthy dietary pattern (vegetables, fruit, poultry, fish, low-fat dairy foods and whole grains) is associated with lower risk for cancer and greater likelihood of survival after diagnosis.
- Current patterns of overweight and obesity in the U.S. could account for 14% of all deaths from cancer in men and 20% of those in women.
Obesity and Cancer Risk and Progression

- Overweight/obesity is associated with mortality from cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, kidney, non-Hodgkin’s lymphoma, multiple myeloma; stomach and prostate (men); breast, uterus, cervix and ovary (women)
- Cancer-related biomarkers respond to even a modest degree of intentional weight loss, suggesting a reduction in cancer risk even with latencies as short as a few years

Obesity and Cancer: Mechanisms

- Several biologically-plausible mechanisms may link obesity to cancer progression (especially cancers of the breast, colon and prostate)
- Mediators may be specifically responsive to weight loss (reduced adiposity) or to a change in behaviors that promote weight loss and weight loss maintenance (e.g., increased exercise)

Reproductive Steroid Hormones

- Adipose tissue is an important extragonadal source of estrogens from precursor adrenal androgens
- Endogenous circulating estrogens are 50-100% higher in postmenopausal obese (vs. normal weight) women
- Obesity is associated with decreased sex-hormone binding globulin (SHBG)
- Circulating estrogen levels are strongly associated with risk and progression of breast cancer

Insulin, Growth Factors, and Inflammatory Cytokines

- Insulin exhibits mitogenic effects that influence both premalignant and cancerous stages of cell growth, stimulates the synthesis of sex steroids and inhibits the synthesis of SHBG
- IL-6, IL-8, TNF-α, and vascular endothelial growth factor (VEGF) are consistently associated with the development of breast and other cancers
- Obesity is characterized by chronic mild inflammation, and weight loss promotes a reduction in inflammatory factors
- Levels of C-reactive protein and serum amyloid A have been associated with reduced overall survival in breast cancer patients

Randomized Clinical Trials (RCTs)

- Primary cancer prevention
  - Women’s Health Initiative (WHI)
  - Selenium and Vitamin E Cancer Prevention Trial (SELECT)
  - Physicians’ Health Study II (PHS II)
- Secondary cancer outcomes (recurrence, survival)
  - Women’s Intervention Nutrition Study (WINS)
  - Women’s Healthy Eating and Living (WHEL) Study
- Relevant previous clinical trials
  - Polyp Prevention Trial (PPT)
  - Nutrition interventions and preinvasive lesions

WHI Low-Fat Diet and Colorectal Cancer

- 48,835 postmenopausal women, 8.1-yr follow-up
- Diet intervention: Reduced fat intake (20% of energy), increased vegetables and fruits (5/day) and grain (6/day) servings
- No difference in risk of colorectal cancer
- Considerations:
  - Intervention did not achieve a large difference: Few intervention women met fat goal, only 5.7% increase in serum carotenoids (dietary biomarker of vegetable/fruit intake)
  - Relatively short duration, long latency of colorectal cancer
- WHI calcium + vitamin D supplement trial also found no effect on risk of colorectal cancer

**WHI Low-Fat Diet and Breast Cancer**

- 48,835 postmenopausal women, 8.1-yr follow-up
- Diet intervention: Reduced fat intake (20% of energy), increased vegetables and fruits (5/day) and grain (6/day) servings
- Breast cancer incidence was 9% lower (NS) in the intervention group; longer, planned nonintervention follow-up may yield a more definitive comparison
- Similar considerations: Few intervention women met fat goal, only 5.7% increase in serum carotenoids (dietary biomarker of vegetable/fruit intake) at year 3
- Women with higher baseline fat intake showed greater evidence for reduced risk


**SELECT Trial**

- 35,533 men aged 50 years and older (African-American) or 55 years and older (all other men) followed for 5.5 years (planned for 7 years)
- Intervention: Selenium (200 ug/day) and/or vitamin E (400 IU/day) vs. placebo
- No significant differences in prostate cancer risk or any other prespecified cancer endpoints
- Increased risks of prostate cancer in the vitamin E group and type 2 diabetes in the selenium group (NS)

**Physicians' Health Study II (PHS II)**

- 14,641 male physicians initially (in 1997) aged 50 years and older; followed for up to 8 years
- Intervention: Vitamin E (400 IU/day) and/or vitamin C (500 mg/day) vs. placebo
- No significant differences in risk for prostate cancer risk or total cancer or total mortality
- A greater number of hemorrhagic strokes was observed in those assigned to vitamin E
- Beta-carotene component of the trial was terminated in 2003; multivitamin component is continuing

**WINS**

- 2437 postmenopausal women who had been diagnosed and treated for early stage breast cancer, 5-yr follow-up
- Diet intervention: Reduced fat intake, with the goal of 15% energy from fat but expected 20%
- Primary analysis was of borderline significance; exploratory analysis showed a significantly reduced risk in the intervention group, especially in women with ER- cancer
- Considerations: Greater weight loss, and higher frequency of mastectomy, in the intervention group


**WHEL Study**

- 3088 pre- and postmenopausal women who had been diagnosed and treated for early stage breast cancer, 7.3-yr follow-up
- Diet intervention: 5 Vegetable servings plus 16 oz vegetable juice or equivalent, 3 fruit servings, 30 g fiber, 15-20% energy from fat, each day
- No significant differences in breast cancer recurrence or survival; secondary analysis found women without hot flashes (indicative of higher circulating estrogens) had 31% fewer events in the intervention group
- Considerations: Average intake of vegetables and fruit at baseline was 7.3/day, higher longitudinal exposure to carotenoids was associated with greater recurrence-free survival

**Polyp Prevention Trial (PPT)**

- 2079 men and women 35 years and older with a history of colorectal adenomas, 4-yr follow-up
- Diet intervention: Reduced fat intake (20% energy), high fiber (18 g/1000 kcal), 3.5 servings/day fruit and vegetables
- No significant differences in risk of recurrence of colorectal adenomas (Schatzkin et al. N Eng J Med 2000;342:1149-1155)
- Considerations: The group difference in self-reported fruit and vegetable intake was 1.13 per 1000 kcal; plasma carotenoids (a dietary biomarker) increased by only 5% in the intervention group

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RCTs Targeting Preinvasive Lesions and Supplement Trials

- Systematic review of nutritional interventions and outcome in cancer or preinvasive lesions provides little evidence for benefits or harm, although most trials had methodologic limitations.
- A 2007 systematic review and meta-analysis of 68 randomized trials for primary and secondary cancer prevention concluded that supplemental beta-carotene, vitamin A and vitamin E may actually increase mortality (Bjelakovic et al. JAMA 2007;297:842-857).

RCTs: Lessons Learned

- With diet intervention trials, the intervention effort itself is being tested, in addition to cancer outcomes; degree of change may not be sufficient to have a biological effect.
- Time frame of the intervention: The intervention may be too late in the cancer continuum, and the length of trial, relative to the long latency of most cancers, may be too short.
- Effect modification by baseline status.
- Reductionist approach, testing specific dietary constituents as causal or beneficial, has clearly not proven to be useful: The alternative is to focus on and test effects of dietary patterns and/or whole foods.

Reducing Breast Cancer Recurrence with Weight Loss: A Vanguard Trial

- Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) Trial
- A randomized controlled study with the primary endpoint of clinically significant weight loss in 800 overweight or obese breast cancer survivors, with demonstration of improvements in quality of life and co-morbidities.
- Sets the stage for a larger cancer outcome study that has sufficient statistical power to assess the effects of weight loss on cancer outcomes in overweight or obese breast cancer survivors.
- Supported by NIH/NCI: R01 CA148791.

Intervention Group

- Cognitive-behavioral closed group sessions
  - First 4 months: sessions every week
  - Next 2 months: sessions every other week
  - Month 6 onward: session every month
- Tailored newsletters.
- Individual participant contacts (by email and/or telephone).
- Intervention components: Diet, emphasis on increased physical activity, behavioral strategies, cognitive restructuring, social support, self-nurturing and alternative behaviors, body image and self-acceptance, issues specific to cancer survivors.

ENERGY Research Team

- ENERGY Study investigators (in alphabetical order): Tim Byers, MD, MPH, Graham Colditz, MD, DrPH, Wendy Demark-Wahnefried, PhD, RD, Patricia Ganz, MD, James Hill, PhD, Bilge Pakiz, EDD, Barbara Parker, MD, Cheryl Rock, PhD, RD (PI of parent grant and coordinating center), Rebecca Sedjo, PhD, Kathleen Wolin, ScD, Holly Wyatt, MD
- NCI: Catherine Alfano, PhD (program officer) and Julia Rowland, PhD, Office of Cancer Survivorship; also Robert Croyle, PhD, Division of Cancer Control and Population Sciences

Transdisciplinary Research in Energetics and Cancer (TREC)

- A cooperative agreement initiative that explores the relationship between obesity and cancer, funded by the National Cancer Institute.
- Integrates the study of diet, weight, and physical activity and their effects on energy balance and cancer.
- Projects range from the biologic and physiologic mechanisms of energy balance to the behavioral, sociocultural, and environment influences on nutrition, physical activity and weight in cancer survivors and other populations at high risk.
TREC Consortium

- Coordinating center: Fred Hutchinson Cancer Research Center (PI: M. Thornquist, PhD)
- Four research centers:
  - UCSD (PI: R. Patterson, PhD): Insulin resistance, inflammation, mammary carcinogenesis
  - Harvard University (PI: F. Hu, MD, PhD): Behavioral and physiologic determinants of obesity
  - University of Pennsylvania (K. Schmitz, PhD): Exercise and weight loss interventions in cancer survivors
  - Washington University (G. Colditz, MD, DrPH): Informing policy and practice to prevent obesity and reduce burden of cancer due to obesity

Emerging Evidence for Weight Management Across the Cancer Continuum

Issues specific to cancer survivors:
- Body image issues related to cancer and cancer treatments
- Enduring psychosocial symptoms, such as depression and fatigue, affect efforts to make changes in behaviors
- Changes in family dynamics and social support
- The importance of physical activity, due to the relationship between lean body mass and resting energy expenditure, and effects of treatments

Strategies in Weight Management for Survivors

- Diet and weight loss studies aimed toward survivors need to address issues specific to cancer survivors
- This target population is motivated and able to make diet and lifestyle modifications
- Individualized counseling (in person or by telephone), group sessions, and mailed material can promote weight reduction
- More intensive interventions produce greater weight loss