

Nutrition and Medicine, 2006
Tufts University School of Medicine
Nutrition and Cancer:
Learning Objectives

Margo N. Woods, D.Sc.

1. Identify three stages of cancer and discuss how diet may affect each stage.
2. Identify the four major dietary themes concerning nutrition and cancer. Discuss the specific types of cancer that are related to each of the themes and the proposed mechanism by which each of the dietary factors interact with cancer.
3. Describe three ways in which nutrition can have an effect on genetic mechanisms.
4. List the types of studies used to investigate the role of diet and cancer and identify the two that can demonstrate a causal relationship.
5. Discuss the Bradford-Hill criteria and how it is used to evaluate the literature on diet and cancer research.
6. Discuss cancers that have been studied with nutritional interventions using a double-blind design and their results.
7. List the recommendations made to the general public to decrease their overall risk of cancers.

Nutrition and Cancer: Answers to Learning Objectives

1. Identify three stages of cancer and discuss how diet may affect each stage.

Initiation – When the human organism receives exposure to a carcinogenic agent, carcinogen binds to DNA. Rapid and irreversible.

- a.) Dietary components may detoxify carcinogen so DNA is not damaged – induce P450 system with cruciferous vegetables (cabbage, broccoli, cauliflower, brussels sprouts)
- b.) Dietary components may increase DNA repair – selenium and isoflavones
- c.) Dietary components may protect DNA from damage – antioxidants Vitamin A, E, C, carotenoids and selenium

Promotion – The period between initiation and premalignancy – generally epigenetic (regulation of the expression of gene activity without alteration of genetic structure), generally reversible, may be very prolonged

- a.) Dietary fat has been seen as a promoter of hormone sensitive cancer by increasing hormone levels that are associated with cancer. Also dietary fat increases the production of bile acids, and secondary bile acids which are carcinogenic in the colon.

Progression – the period between premalignant and malignant disease – generally irreversible, genetic mechanisms involved, may be very prolonged

- a.) High fat diet increases progression
- b.) Increase differentiation: retinoic acid, omega 3-fatty acids, flavonoids. These nutrients can delay or reverse progression in animal cancer models.
- c.) Decrease angiogenesis (the development of capillaries and vessels to increase blood to the developing malignancy): soy, genistein can decrease this process

2. Identify the four major dietary themes concerning nutrition and cancer. Discuss the specific types of cancer that are related to each of the themes and the proposed mechanism by which each of the dietary factors interact with cancer.

a.) **Antioxidants:** Vitamins E and C, carotenoids, retinoids, flavonoids, and selenium. Protective because they deactivate “reaction oxygen species” (ROS) in the body, which are known to cause damage that can lead to cancer. ROS are “initiators” of the cancerous process. Sites of oxidative damage are proteins, DNA, and lipids.

Antioxidants help by:

- Detoxifying carcinogens via trapping ROS.
- Preventing the formation of carcinogens from procarcinogens by quenching the ROS
- Inducing cellular defense mechanisms to accelerate detoxification
- Increasing selective immune responses

Antioxidants are important in the prevention of cancer of the lung, stomach, bladder, colon, skin, and oral cavity. Fruits and vegetables are excellent sources of antioxidants and are associated with decrease of “all cancer” mortality.

b.) **Fat:** Studies have shown a correlation between fat intake and cancer of the breast, ovaries, cervix, uterus and prostate.

Breast cancer: Low fat/high fiber diets have been shown to increase the fecal excretion of estrogens due to a decrease in the enterohepatic circulation of estrogen. Estrogen has been shown to increase breast cancer and long-term use of oral contraception has shown to increase the risk of breast cancer. Data on the effect of fat on cancer of the endocrine organs is strongest for breast cancer. Type of fat may also be important when evaluating data on fat and breast cancer. Animal studies have reported that consumption of omega-3 fatty acids lead to decreased number of mammary tumors in rats. This may be related to the influence of the omega-3 fatty acids on the prostaglandin series (E_3 vs. E_2). Consumption of omega-3 fatty acids has been shown to decrease the number of mammary tumors in rats and suppress in-vitro tissue culture proliferation.

Colon cancer: A high fat diet has been associated with an increased risk of colon cancer. The mechanism of this effect has been attributed to the increased formation of bile acids with a high fat diet. The primary bile acids are converted to secondary bile acids in the intestines and have been shown to be carcinogens. However, there is evidence pointing to a specific protective role of the omega-3 fatty acids, which decrease the turnover (total labeling index) of rectal mucosal cells.

c.) **Fiber:** A diet high in fiber, especially insoluble fiber, has been found to protect against chemically-induced colon cancer in animal models. It is hypothesized that fiber decreases the risk of colon cancer in humans by a number of mechanisms:

- Increased fecal weight and bulk, which decreases the concentration of potential carcinogens in the intestinal lumen.
- Increased frequency of defecation and speed of transit through the intestines, which will decrease the time of exposure of potential carcinogens to the intestinal mucosa.
- Increases in microbial growth, which is considered beneficial since this increases the production of fatty acids shown to be beneficial to the intestinal mucosa.
- Decreased dehydroxylation of bile acids, which decreases production of secondary bile acids shown to be co-carcinogens by binding them to the fiber and thereby reducing access to conversion.
- Absorbs organic and inorganic substances, which may be irritants to the intestinal mucosa.
- Increased production of H_2 , CH_4 , CO_2 and short-chain fatty acids by bacterial action on the dietary fiber. These molecules affect the pH of the gut, which is considered protective.

d.) **Phytochemicals:** Our foods (fruits, vegetables, legumes, whole grains) have hundreds of compounds, some of which have been investigated concerning possible anti-cancer properties.

- a.) The foods most commonly cited as having possible anti-cancer properties are: Garlic, green tea, soybeans, citrus fruit, cruciferous vegetables (broccoli, cauliflower, brussel sprouts, cabbage), solonaceous vegetables (tomatoes and peppers), and cucurbitaceous vegetables (gourds, squash).
- b.) Compounds in these foods that have demonstrated anti-cancer properties in

animal models include:

Carotenoids, coumarins, flavonoids, lignans, phytates, phthalides, polyacetylenes, etc...

c.) Mechanisms of action attributed to these compounds include:

- Induce detoxifying enzymes
- Inhibit nitrosamine (a pro-carcinogen) formation
- Anti-angiogenic agent
- Block estrogen receptors
- Alter hormone metabolism
- Exhibit anti-oxidant effects

d.) Three most interesting at this time in animal models

- Genistein, in soy, acts as an anti-angiogenic agent
- Lycopenes (in tomatoes) decrease prostate cancer
- Green tea (EGCG is specific component) had anti-oxidant properties.

3. Describe three ways in which nutrition can have an effect on genetic mechanisms.

- a.) Protects DNA from oxidative damage and single strand breakage with antioxidants. Oxidative status can also affect signal transduction pathways.
- b.) Maintains methylation of DNA by adequate folate.
- c.) Omega-3 fatty acids in colon cancer animal models decreases RAS family proteins associated with development of cancer and increases protein kinase C.

4. List the types of studies used to investigate the role of diet and cancer and identify the two that can demonstrate a causal relationship:

- a.) **Animal Studies** - can determine *causation* (that the nutrient in question did or did not cause the formation of the cancer due to the ability to control dietary intake of the animals)
- b.) **International epidemiological studies** - only show association
- c.) **Migrant studies** - only show association
- d.) **Case control studies** - only show association
- e.) **Cohort studies** - only show association
- f.) **Metabolic studies** - can show causation (depends on study design). Uses secondary markers i.e. estrogen levels for breast cancers.
- g.) **Nutrition intervention studies** - can also prove *causation* in humans. However, because they are long-term, high cost studies, few are likely to be carried out.

5. Discuss the Bradford-Hill criteria and how it is used to evaluate diet and cancer research.

- a.) **Consistency of evidence** - Are the findings consistent across categories of studies, within type of study, across different populations and number of studies per category?

- b.) **Strength of association** - If the relative risk is significantly greater than 1.0 (i.e. ≥ 1.3), the greater the likelihood that the factor increases risk of cancer. If the relative risk is significantly less than 1.0 (≤ 0.7) the greater the likelihood that the factor is protective and causally related to protection.
 - c.) **Relationship in time** - Exposure preceded onset of disease.
 - d.) **Biological gradient** - Observations that the greater the exposure the greater the effect strengthens the inference that the association is causal.
 - e.) **Specificity** - Correcting for confounders has little effect. The more specific the effect the more likely it is to be causal.
 - f.) **Coherence of evidence** - Data is in one direction or “no effect”
 - g.) **Biologically plausible** - Fits existing biological and medical knowledge
 - h.) **Reasoning by analogy** - Other similar mechanisms or series of events have been shown in other diseases.
 - i.) **Experimental evidence** - Experimental data on mechanism is available.
6. **Discuss cancers that have been studied with nutritional intervention using a double-blind design and their results.**
- a. Intervention of 13-cis retinoic acid and secondary prevention in oral cancer – was effective. Also Vitamin E supplementation in regression of leukoplakia (a pre-cancerous lesion) – was effective.
 - b. Fiber intervention with adenomatous polyp recurrence – did not support a role for fiber.
 - c. Low fat diet (20%) for prevention of breast cancer – Womens Health Initiative (WHI) study – in progress.
 - d. Low folate levels and incidence of cervical dysplasia. Female patients who have been diagnosed with dysplasia from a PAP smear should be tested for folate status. Current research indicates that a local deficiency of folate may contribute to dysplasia. If serum levels are low-normal, prescribe folic acid and redo PAP in two months. No nutrition intervention to date.
7. **List the recommendations from the American Cancer Society and National Cancer Institute to the general public to decrease ones overall risk of cancers.**
- a.) Decrease or stop smoking
 - b.) Increase intake of fruits and vegetables
 - c.) Decrease intake of fat especially from animal products
 - d.) Increase fiber intake to >25 g/day
 - e.) Increase intake of cruciferous vegetables (broccoli, cauliflower, cabbage and brussel sprouts) which help detoxify many pro-carcinogens in the liver in the P450 system.
 - f.) Decrease alcohol intake
 - g.) Decrease intake of cured foods, especially those containing nitrites
 - h.) Decrease intake of charcoal grilled food

Useful Websites:

CancerNet:

http://www.cancer.gov/cancer_information

National Cancer Institute:

<http://www.nci.nih.gov>

Fruits & Veggies More Matters program:

<http://www.fruitsandveggiesmorematters.org>