

CANCER PREVENTION 2009

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CANCER PREVENTION - LECTURE OUTLINE

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5. Radiation
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7. Medical procedures
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1. Tobacco

Evidence for Tobacco as a Carcinogen

Despite reports in the eighteenth century on the association of tobacco or smoking with different forms of cancer, it was not until about 1950 that there was sufficient epidemiological data to convince most individuals that use of tobacco was a risk factor for cancer, particularly lung cancer. Apparent inconsistencies in the data and the difficulty in identifying a predominant carcinogen in tobacco slowed the acceptance of this risk. The early studies of Wynder & Graham, Levin et al. and Doll & Hill were followed by other investigations which led to the Surgeon General's report of 1964. Subsequent reports of Surgeon Generals have emphasized that cessation of smoking is the single most important factor in decreasing cancer mortality. With respect to smoking, conclusions have been summarized by Novello et al. as follows:

- a. Smoking cessation has major and immediate health benefits at all ages.
- b. Former smokers live longer than continuing smokers.
- c. Smoking cessation decreases the risk of lung cancer and other cancers.

A worrying trend in recent years has been the increased use of smokeless tobacco, particularly by young people. It is ironic that the first reported association between tobacco and cancer in 1761 was for a smokeless tobacco product. The risk of oral cancer can be increased as much as 50-fold by smokeless tobacco.

Making Tobacco Less Carcinogenic

As noted by Wynder, there can be no safe cigarette. Efforts have been directed to decreasing the risk of smoking cigarettes by decreasing the tar content and encouraging the use of filters. It may be necessary to permit sufficient nicotine for the hopelessly addicted to refrain from compensating by increasing the number of cigarettes smoked. Less than 10 mg of tar and about 1 mg of nicotine has been suggested.

Although many potentially carcinogenic agents can be detected in tobacco smoke, they are generally present at low concentrations. In recent years attention has focussed primarily on tobacco specific nitrosamines. These include N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). It is encouraging that the metabolism of these compounds to ultimate carcinogenic forms can be inhibited by isothiocyanates in cultured rat oral and lung tissue. Isothiocyanates are found in cruciferous vegetables and are of interest as potential chemopreventive agents.

UMDNJ Tobacco Dependence Clinic

Dr. Michael Steinberg, Medical Director of the Tobacco Dependence Clinic at UMDNJ - School of Public Health is studying the use of varenicline (an $\alpha 4\beta 2$ nicotinic receptor partial agonist/antagonist) in the treatment of hospitalized smokers.

“By stimulating a partial dopamine release in the nucleus accumbens (partial agonist), this medication reduces cravings and withdrawal symptoms ... In addition, through its antagonistic , this medication can reduce the rewarding effects of smoking.”

UMDNJ Research, Spring 2007, page 10.

2. INFECTION

1. **Viruses**

Worldwide, the association of hepatitis B virus with liver cancer appears to be the greatest threat on a numerical basis. Other viruses for which there is a strong association with human cancer include the Epstein-Barr virus (Burkitt's lymphoma and nasopharyngeal cancer), human papilloma viruses (cervical cancer) and human T-cell leukemia virus (cutaneous T-cell lymphoma). The observation that only a small percentage of infected individuals eventually develop cancer suggests that additional factors are involved. In the case of liver cancer, the role of aflatoxins has been controversial. Doll concluded that it is difficult to believe that, in addition to hepatitis B virus, aflatoxin is not also an important factor in humans. Present data has given some evidence of a role for aflatoxin B1 on the basis of specific mutations in the P53 tumor suppressor gene.

2. INFECTION

1. **Viruses**

Key risk factors for cervical carcinoma including age at first intercourse, and history of a prior sexually transmitted disease have been found to be strongly associated with genital human papilloma virus infection. The use of the polymerase chain reaction in association with Southern blot hybridization has identified a large proportion but not all individuals who have been infected by human papilloma viruses. Furthermore, it appears that most individuals who are infected will not develop anogenital malignancies so the predictive power of this sensitive procedure is limited. Behavioral modification or immunization may be required if we are to decrease the incidence of cervical cancer that may be anticipated from the present spread of human papilloma virus infection.

2. INFECTION

1. **Viruses**

During the last two decades, malignancies associated with acquired immunodeficiency syndrome (AIDS) have caused the largest increases in cancer incidence in men between the ages of 20 and 44. These types of cancer are non-melanoma skin cancer and non-Hodgkin's lymphoma. The former includes Kaposi's sarcoma which does not relate to all populations with AIDS and may be declining in importance. On the other hand, the situation with respect to non-Hodgkin's lymphoma is a more general one whose prevention may be linked to efforts to combat HIV infection.

2. INFECTION

2. **Non-viral infections**

Non-viral infections do not appear to constitute a significant cancer risk in the United States. In less developed countries, associations have been noted of bladder cancer with infections by *Schistosoma hematobium* and hepatic angiosarcoma with infection by the liver fluke *Clonorchis sinensis*. An association of *Helicobacter pylori* infection and gastric cancer has been reported. Chronic infectious processes that result in a cellular proliferative response may be a cancer risk factor in affected tissues.

2. INFECTION

3. **Vaccination and Immunostimulation**

The clearest cases for immunization against cancer-related viruses can be made for vaccines against hepatitis B virus and the human T-cell lymphotropic viruses 1 and 2. In 1991, the National Cancer Institute solicited proposals for research leading to the development of vaccines for human cancers of known, or strongly suspected, viral etiology, including cancers associated with human papillomaviruses, Epstein-Barr viruses and hepatitis C virus.

A vaccine against hepatitis B has been available since the early 1980s and more recently a recombinant vaccine has been developed. If a large proportion of liver cancer in the world is attributable to chronic infection with hepatitis B virus, there is the potential to achieve a major reduction of this malignancy, particularly in those parts of Asia and Africa where liver cancer is more prevalent.

2. INFECTION

4. **Sexual Transmission**

A positive association of cervical cancer with multiple sexual partners has long suggested a transmissible factor. Suspicion regarding the etiological agent has shifted in recent years from herpes simplex type 2 to human papilloma viruses, particularly HPV 16 or 18.

2. INFECTION

Gardasil is a new vaccine being made by Merck & Co., Inc. and which has been approved by the FDA to prevent cervical cancer in females between the ages of 9 and 26 years of age.

Gardasil is a vaccine against the HPV or Human Papillomavirus. The Gardasil vaccine protects recipients against 4 types of HPV, including the two types that cause most cervical cancers and the two types that cause the most genital warts. HPV is a sexually transmitted disease that causes genital warts, abnormal Pap tests, and **cervical cancer**.

About 20 million people are infected with HPV in the United States and almost 3,700 women die of cervical cancer in the US each year. Since many people have no symptoms and not even know that they are infected with HPV, they can pass on their HPV infection to their sexual partners without knowing. There is no cure for HPV infections. It has been recommended that Gardasil be routinely given to girls when they are 11 or 12 years old.

http://pediatrics.about.com/od/immunizations/p/06_gardasil.htm

3. OCCUPATION

1. **Epidemiologic Surveillance**

Estimates of the contribution of occupational exposure to cancer incidence have ranged from 1 to 20% with consensus figures of 4-5%. There are a great variety of occupations that have increased risk for cancer and this reflects the widespread exposure to chemicals in agriculture and industry. The industries most seriously affected include mining, construction, chemicals, petroleum and metal processing.

Higher estimates for the contribution of occupational exposure to cancer risk have come from studies in which the contribution of asbestos exposure appeared to be particularly high. In addition to other pulmonary problems, exposure to asbestos has been associated with increased incidence of some cancers, most notably bronchogenic carcinoma and pleural and peritoneal mesotheliomas.

3. OCCUPATION

Asbestos

There are several types of naturally occurring silicate that are classified as asbestos of which the most commonly used mineral has been chrysotile. Although chemically inert, asbestos may be genotoxic through inducing the formation of active oxygen specie or through interference with chromosome segregation. An important feature of asbestos may be the type of fiber with evidence existing for increased risk with long thin fibers. Recognition of the health threats from asbestos has halted the use in construction but continued exposure arises from repair and maintenance and in the removal of previously installed asbestos.

There has been debate on whether different types of asbestos should be subject to the same stringency in regulation, with some investigators considering that chrysotile does not present a health risk in the non-occupational environment. Occupational exposure would seem to merit monitoring and control and debate will no doubt continue on the relative wisdom of removal or covering of asbestos in schools and offices.

Man-made vitreous fibers may serve as substitutes for asbestos in some applications. However, the carcinogenic potential of these materials will require careful monitoring as their status is not well documented. In view of the association of cancer with non-asbestos mineral fibers such as erionite it would seem advisable to minimize inhalation of all such materials.

OCCUPATION

2. Screening for Mutagens and Carcinogens

Much evidence for carcinogenicity of compounds in humans has been derived from **epidemiological studies** but such information arrives late and often in a form that does not permit an accurate assessment of exposure levels. It would obviously be preferable to screen compounds for carcinogenicity and prevent exposure to hazardous agents.

Tests on animals are notoriously expensive. In part this is a consequence of the long latency that is a feature of chemical carcinogenesis. Short term screening for mutagenicity offers a speedier and more economic guide to carcinogenesis. Variable metabolic activation by different cell types would require a battery of test cells and might still give false negative and positive results for the human situation. Bacterial cells fortified with mammalian microsomal enzymes, as in the **Ames test**, can provide a relatively inexpensive method to survey mutagenic and potential carcinogenic activity. However, with such systems not all mutagens can later be shown to be carcinogens and not all demonstrated carcinogens have been shown to be genotoxic.

Epigenetic factors may have a role in the development of cancer, particularly in the action of tumor promoters through such postulated mechanisms as the activation of protein kinase C. Even in the case of animal studies there is debate on the degree to which one can extrapolate to human risk. This is particularly true when using the estimated maximum tolerated dose in cancer bioassays .

OCCUPATION

3. **Industrial Hygiene and Legislation**

Materials that were once used with little caution, such as benzene and formaldehyde, are now known to be potentially carcinogenic in animals and/or humans. There are different levels of confidence in our knowledge of the cancer risk posed by different compounds and this is recognized in the classification of the International Agency for Research in Cancer. There is increasing legislation to limit the exposure of workers during manufacture and to restrict the disposal of carcinogenic compounds. The lists of agents that require legislative control is long and growing.

4. ALCOHOL

There is considerable evidence that alcoholic drinks increase the risk for certain types of cancer but there is uncertainty with respect to the role of **ethanol** itself. Cottrell noted that whether the risk is due to ethanol or to congeners is deeply controversial as only a question devoid of clear evidence can be. This poignant comment might be applied to a number of issues in cancer prevention.

From a long-term prospective study, Hirayama observed that alcoholic drinks are associated with cancer of the **digestive tract, liver and prostate**. For cancer of the upper digestive tract and liver, this risk occurs in association with cigarette smoking, whereas for the lower digestive tract and prostate the interaction with smoking was absent. Doll concluded that alcohol was responsible for a high proportion of all cancers of the **mouth, tongue, pharynx, esophagus and larynx** and, via the production of cirrhosis, a small proportion of cancers of the liver.

Rogers and Longnecker found that in 3 of 3 follow-up studies and 8 of 11 case-control studies there was a positive association between **alcohol consumption and breast cancer**. Users of mouthwashes may be unaware of the ethanol concentration of these products which can be comparable to alcoholic beverages. Risks of oral cancer were found by Winn et al. to be elevated by 40% among male and 60% among female mouth wash users. The increased risks were confined to users of mouth wash containing ethanol at a concentration of 25% or greater. If mouth washes are used, it appears advisable to use one with a low ethanol content.

5. RADIATION

Ionizing radiation and **ultra violet radiation** were considered earlier in the course.

Early alarm about **electromagnetic fields** (EMF) was raised by the study of Wertheimer and Leeper on EMF exposure of 344 children in Colorado who had died of cancer. It was concluded that children from high exposure homes were 2-3 times as likely to develop cancer especially leukemia, lymphomas and nervous system tumors. Additional studies have generally given risk ratios of 1-2 but a consistent pattern has not emerged. On the other hand, an odds ratio of 6.0 with a 95% confidence interval of 1.7-21 has been reported for the risk of breast cancer in U.S. men employed as electricians, telephone linemen and electric power workers.

It has been traditionally felt that the low energy involved in the exposure to EMF such as from electricity transmission lines would be unlikely to have significant biological effects. However, there is a literature on the biological effects of EMF, and there is a need for more experimental data. Even if one does not subscribe to a stated opinion that there is no evidence of carcinogenic effects from any of the EMF epidemiological studies, avoidance of external EMF must be rated as one of the lesser priorities in cancer prevention.

6. POLLUTION

Pollution as a risk factor for cancer looms large in the mind of the public but small in the estimations of epidemiologists. Potential carcinogens may be found in the air, ground and water of our environment. Although polycyclic aromatic hydrocarbons can be created by industry and automobile exhausts, a study in New Jersey found that the major contributor was residential wood combustion. Much public attention has been directed to chlorinated organic compounds in drinking water and pesticides in soil and water.

A series of papers by **Ames** and colleagues have suggested that naturally occurring pesticides pose a much greater danger than synthetic pesticides. These views have been vigorously debated. In an attempt to assess the risk from different carcinogens, Ames and coworkers have proposed an index (HERP) which looks at the ratio of human exposure to a carcinogen and the potency of the carcinogen in animal tests. The objective in this work is to establish priorities for removal from the environment. This requires a balance between financial cost, carcinogenic potential and the magnitude of human exposure. It is to be hoped that analysis of these parameters will replace the emotional approach which has prevailed historically.

6. POLLUTION

One of the most extensively studied environmental contaminants is 2,3,7,8 - tetrachlorodibenzo- *p* - dioxin (TCDD). Although highly toxic to some mammalian species, there has been considerable uncertainty about the carcinogenic potential of TCDD for humans. A retrospective study by Marilyn Fingerhut and coworkers at the National Institute for Occupational Safety and Health indicated that workers with with more than 1 year exposure to TCDD had cancer death rates after 20 years that were 46% higher than for the general population. It is difficult to extrapolate from this data to the sort of exposure that caused such consternation at Times Beach, MO in 1983. There is a common feeling that less drastic action would be taken today with the same level of exposure.

Other chlorinated organic compounds including polychlorinated biphenyls, DDT and trichloroethylene have aroused concern. Chlorination of drinking water which contains organic molecules must be done in a judicious manner because of the danger of creating carcinogenic compounds. Water chlorination and manufacturing by-products have been described as the major contributors to water pollution..

7. MEDICAL PROCEDURES

1. **Drugs**

It is unfortunate that the largest category of drugs with a carcinogenic potential are compounds that are useful as chemotherapeutic agents. Many of these are genotoxic agents and/or immunosuppressants. Other substances that have been used as drugs and which are potentially carcinogenic include phenacetin and arsenic. Hormonal agents, notably diethylstilbestrol, may promote carcinogenesis in target tissues. In the case of phenacetin and diethylstilbestrol, the danger has been considered too great for continued use, but for many cancer chemotherapeutic agents, such as cyclophosphamide, the potential benefit in many cases has been held sufficient to outweigh the risk.

2. **Radiation**

The dangers of ionizing radiation were considered previously. Ionizing radiation has both diagnostic and therapeutic use in medicine. Studies of dose-response relationships with respect to radiation and cancer induction have not always conformed to a linear model. Nevertheless, it is generally assumed that there is no threshold for the effect of ionizing radiation and that exposure should be minimized.

7. MEDICAL PROCEDURES

3. **Implants**

The phenomenon of implant-induced carcinogenesis seen in rats has not been noted in humans. However, there may be situations in which an implant causes a hyperplastic response in surrounding tissue that might be promotional for neoplasia.

4. **Immunosuppression**

The concept of immune surveillance as a general control mechanism for cancer has received little support in recent years. However, in individuals with either hereditary or induced immune impairment there is increased risk of a limited number of malignancies. Non-Hodgkin's lymphoma is the most notable of these conditions and increased risks of skin cancer and melanoma have been recorded. The risk of malignancy in organ transplant recipients is well recognized.

8. PSYCHOGENIC FACTORS

There is a popular feeling that the induction and progression of cancer can be influenced by psychological factors. Since stress can influence the hormonal and immune status of a person and there is data to suggest that these factors can influence cancer, it may be anticipated that stress will have some bearing on the disease. Such relationships have been observed in experimental animals but the evidence for humans has been conflicting. Even in animals, there is evidence that stress may have either a positive or a negative influence on carcinogenesis.

Lovestone and Fahy have suggested that, although some studies have failed to show a relationship between stressful events and the onset of cancer, most studies have shown at least a weak association. One of the more plausible mechanisms for such a relationship is an effect on the immune system. Using bereavement as a model for stress, a suppression of lymphocyte stimulation has been observed and it has been suggested that this may be related to the increased mortality that has been recorded following the loss of a spouse.

The advice to avoid stress is easy to give and hard to follow. Present data suggest that conforming to the advice may be beneficial but the effects will be small.

9. Exercise

Although the Multiple Risk Factor Intervention Trial did not reveal an effect of physical activity on cancer death rate, the majority of studies have suggested an inverse relationship between physical activity and cancer. The data is most extensive for breast and colon cancer. These malignancies have also been associated with caloric intake and fat consumption and the data suggest a complex interaction between these variables.

Early studies with animals involved involuntary exercise and might have been influenced by hormonal changes resulting from stress. On the other hand, voluntary exercise has also reduced tumor incidence when rats were treated with carcinogens that induce neoplasia in the breast or colon. In contrast, the work of Thompson and coworkers has indicated that moderate intensity treadmill exercise can stimulate mammary tumorigenesis in rats. Critical differences in this work were considered to be the short duration of the exercise and the fact that carcass fat content was not decreased. The stimulation could be observed on either low or high fat diets.

9. Exercise

Leisure-time activity has been considered in the Harvard alumni study which suggests that consistently higher levels of activity protect against colon cancer but not against rectal cancer.

Where inverse relationships between physical activity and colon cancer have been detected, the association has been stronger for males than females.

In a prospective study, Wu et al. found colorectal cancer to be inversely associated with physical activity and positively associated with the body mass index.

9. Exercise

A lower prevalence of breast cancer and cancer of the reproductive system was reported by Frisch et al. for women who were former college athletes. The possibility of a J-shaped response between cancer and physical activity has been raised. Subjects who exercised heavily and died of cancer of the lung, colon-rectum and pancreas had 20% to 37% higher standardized mortality ratios than men and women who reported moderate exercise although these differences were not statistically significant. The data suggested that, with respect to cancer mortality, moderate exercise is better than both inactivity or heavy exercise.

The colon is the site where there is the strongest evidence for an inverse relationship between cancer and exercise. If there is danger in heavy exercise, this may arise from the increase in free radical production which has been detected systemically. In these circumstances, dietary supplementation with antioxidants such as vitamin E may have a protective action.

9. Exercise

From a study of Harvard alumni, it has been estimated that, by the age of 80, adequate exercise can add one to more than two years to life. The evidence is somewhat equivocal that a decrease in cancer will contribute to this longevity but the advice to engage in exercise is reinforced by the epidemiological data with respect to life expectancy.

10.DIET

Dietary factors were considered earlier in the course. A number of compounds shown in the table below and in the following slide have potential cancer preventive activity and have been identified in fruits and vegetables.

<u>Compound</u>	<u>Food source</u>
Cinnamic acid	Fruit, vegetables, coffee beans
Flavonoids	Vegetables, fruit
Flavones	Fruit, celery, parsley
Flavonols	Vegetables, grains, onions, tea
Catechins	Tea
Flavanones	Citrus
Isoflavones	Soybean
Anthocyanidins	Grapes, cherry, raspberry
Indoles	Cruciferous vegetables
Isothiocyanates	Cruciferous vegetables
Lignans	Grains, flax
Organosulfur	Garlic and onions
Terpenes	Citrus, spices

Reference: J.A. Milner. Nonnutritive components in foods as modifiers of the cancer process. In Preventive Nutrition: The Comprehensive Guide for Health Professionals, 2nd ed. A. Bendich and R.J. Deckelbaum eds. Humana Press, Totowa, NJ, p. 131-154, 2001

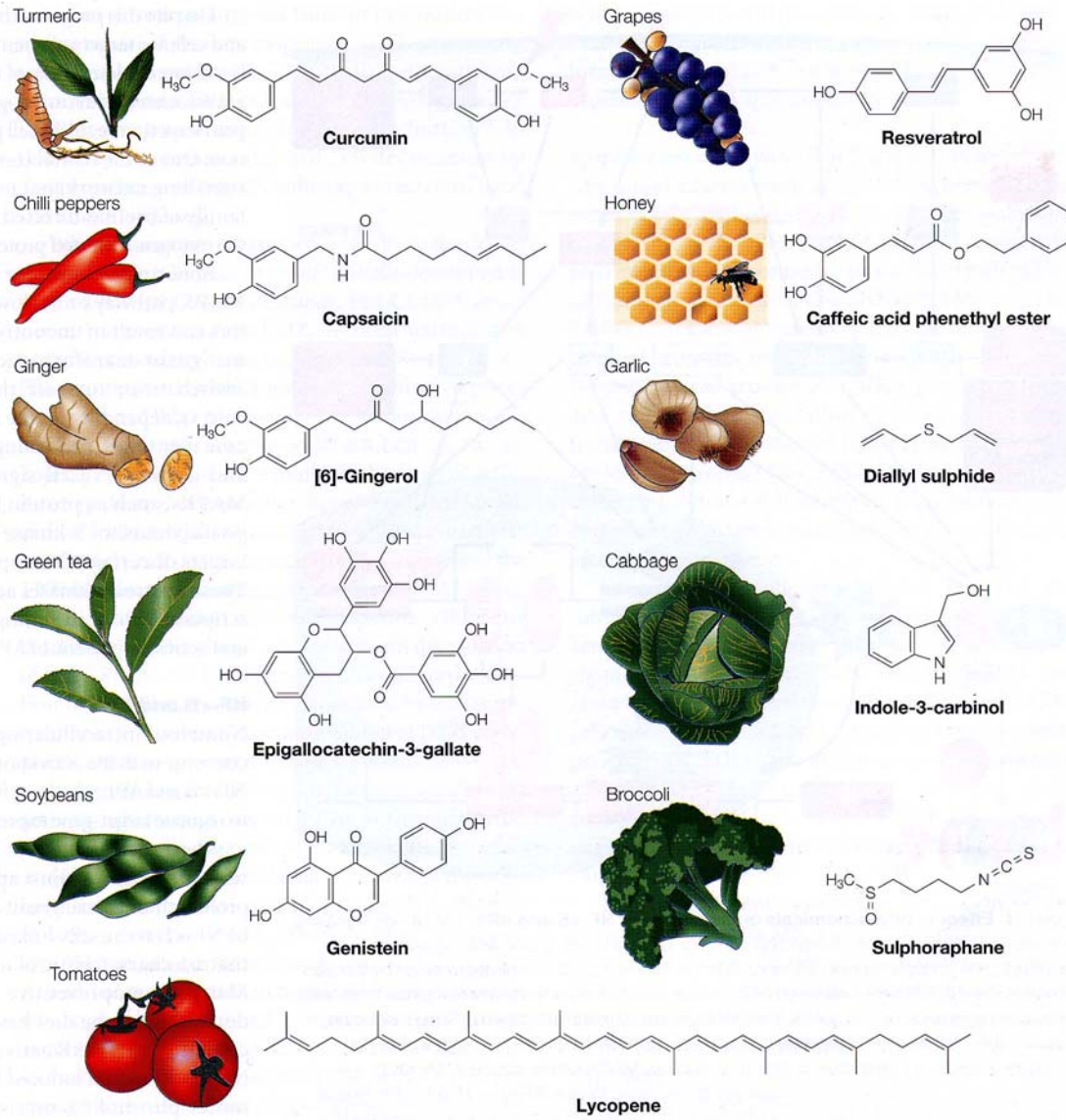


Figure 2 | Representative chemopreventive phytochemicals and their dietary sources.

10.DIET

A number of dietary factors are being examined as potential chemopreventive agents in trials. A feature of some of these trials is the use of biomarkers of tumors to monitor the effectiveness of the chemoprevention. Common biomarkers of solid tumors include the following; P53, EGFR, PCNA, RAS, Cox-2, Ki-67, DNA aneuploidy and DNA polymerase alpha.

Substances that have been positive in some but not all trials include:

Alpha-tocopherol

Ascorbic acid

Calcium carbonate

Cyclooxygenase inhibitors including aspirin, sulindac and celecoxib

Indole-3-carbinol

Retinoids including isotretinoin and vitamin A

CANCER PREVENTION-RECOMMENDATIONS

These ten recommendations for cancer prevention are drawn from the WCRF/AICR Second Expert Report

1. Be as lean as possible without becoming underweight.
2. Be physically active for at least 30 seconds every day.
3. Avoid sugary drinks. Limit consumption of energy-dense foods (particularly processed foods high in added sugar, or low in fiber, or high in fat).
4. Eat more of a variety of vegetables, fruits, whole grains and legumes such as beans
5. Limit consumption of red meats (such as beef, pork and lamb) and avoid processed meats.
6. If consumed at all, limit alcoholic drinks to 2 for men and 1 for women a day.
7. Limit consumption of salty foods and foods processed with salt (sodium).
8. Don't use supplements to protect against cancer.

Special Population Recommendations

1. It is best for mothers to breastfeed exclusively for up to 6 months and then add liquids and foods.
2. After treatment, cancer survivors should follow the recommendations for cancer prevention.

And always remember ~ do not smoke or chew tobacco.

CANCER PREVENTION -RECOMMENDATIONS

The following suggestions for minimizing cancer risk are largely derived from soft data but may also be appropriate for a virtuous life:

1. Eat moderately and have a plain but varied diet.
2. Avoid rich, fatty food.
3. When cooking, boil rather than fry.
4. Eat plenty of fresh fruit and vegetables with modest servings of bread, rice or pasta.
5. Do not become obese.
6. Do not smoke.
7. Drink little if any alcoholic beverages.
8. Keep out of the midday sun
9. Live where the air is fresh and the water is pure.
10. Maintain good hygiene.
11. Refrain from sexual promiscuity.
12. Exercise regularly and in moderation.
13. Adopt a cheerful disposition.