STRATEGIES FOR PREVENTION OF CANCER IN HUMANS

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I. INTRODUCTION

The best and most effective treatment of cancer is its prevention. Most of the major human diseases of mankind have been controlled, not through aggresive treatment approaches, but via the application of basic science discoveries in support of preventive or public health strategies (Table 1). Pellagra, rickets, and scurvy, once common and poorly understood diseases, have been essentially eliminated in Western civilization by assuring adequate dietary intakes respectively of nicotinamide, vitamin D (via sunlight), and absorbic acid. Infectious diseases have been particularly well-controlled by preventive interventions. Rabies, small pox, and polio have all been controlled by the widespread application of vaccination and plaque by rodent and sewage control. Syphilis and tuberculosis have yielded substantially to the powerful combination of a basic understanding of the disease processes, design of targeted pharmacologic interventions, and application of the appropriate medical and public health measures.

Table 1
Control of Many Major Diseases of Mankind Using Prevention Strategies

Disease	Evidence for Prevention Role		Intervention
	Laboratory	Epidemiology	
Nutritional			
Scurvy	-	++	Vitamin C
Pellagra	+	++	niacin
Rickets	+	++	
Infectious			
Plaque control	-	++	sewage & rodent
Rabies control/vaccination	+	++	animal
Small pox	+	++	vaccination
Polio	+++	+++	vaccination
Syphillis medical	++	+++	sexual behavior,
Tuberculosis	+	++	quarantine, medical
Vehicular trauma	+++	+++	seat belts
Chronic diseases			
- cardiovascular	+++	+++	smoking cessation, lower blood pressure and cholesterol
- cancer	+++	+++	smoking cessation ? dietary

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Although generally acknowledged for some time that prevention strategies can reduce morbidity and mortality from a number of nutrition-based and acute and chronic infections diseases, an unanswered question has been whether prevention approaches can reduce morbidity and mortality in patients with chronic diseases, such as heart disease of cancer. The experience with cardiovascular diseases in the past two decades indicates that application of a few simple measures impacts on the outcome of this chronic disease. Lowering of blood pressure and cholesterol and cessation of smoking has significantly reduced both the incidence and the morbidity and mortality from cardiovascular disease in U.S. society in the past decade.

What about cancer? In our understanding of risk factors for cancer and the use of prevention strategies to alter the natural history of malignancy, we are about 15 years behind our scientific understanding of the biological and medical basis for cardiovascular disease prevention. Before discussing strategies for chemoprevention of human cancer, it is useful to consider those epidemiologic factors which are known to contribute significantly to cancer risk. Table 2 lists those risk factors which unequivocably contribute in a major way to the development of cancer. Reduction of exposure to these risk factors should lead to a rapid fall in the incidence of certain cancers. Exposure to tobacco, radiation, and certain chemicals (dyes, asbestos) represent a major risk to human beings. In the past two decades awareness of the contribution of these factors to cancer risk has increased. Nevertheless, smoking tobacco remains an unsolved societal problem, and radon, aniline dye, and asbestos is exposure continue at a substantial level. Clearly, reduction or abrogation of exposure to these key carcinogens should be possible and a marked decrease in incidence in the associated cancers should eventually occur. Whether this desirable goal is met however is more an educational and public health issue than biological or medical problem per se.

Table 2
Major Avoidable Risk Factors for Cancer Formation in Humans

Factor	Associated Cancers	Prevention Strategy
Tobacco		
- Cigarette	Lung, Oropharyngeal, Bladder, Esophageal Pancreatic, Cervix	Abstention, cessation
- Smokeless	Oral	Abstention, cessation
Radiation		
- Ionizing	Lung, Leukemia	Shielding
- Non-Ionizing	Skin Cancer	Sun screens, "sun sense"
Chemicals		
- Dyes	Bladder	Reduce exposure in work place
- Asbestos	Lung, mesothelium	Avoid contact, use alternative building materials
Viruses		
Sexually-transmitted		
- AIDS-related	Kaposi's sarcoma, Lymphomas	Abstinence, condom
- Papilloma	Cervix	Abstinence, condom
Endemic		
- Hepatitis	Liver	Vaccine
- Ebstein-Barr	Burkitt's lymphoma, Nasopharyngeal	?

A number of viruses also appear to play a role in cancer development including those from both DNA (papilloma, hepatitis, and Ebstein-Barr) and RNA (human immunodeficiency viruses) families. Abstinence and barrier contraception are reasonable, but difficult to achieve strategies, for sexually-transmitted viruses. The endemic nature of hepatitis virus suggests that only a vaccine or reduction in exposure to the major co-carcinogen (aflatomin) is likely to affect disease outcome.

Table 3
Suspected Major Dietary or Hormonal Associations with Cancer Formation in Humans

Factor	Associated Cancer	Proposed Prevention Strategy
DIETARY		
Fat	Endometrium, Breast Prostate, Colon	Lower intake
Fibre	Colon, Breast	Increase intake
Vitamins	Skin, Liver, Oropharynx, Cervix, Colon	Increase intake
HORMONAL		
Oestrogens	Breast	Decrease calorie intake, antioestrogen
Androgens	Prostate	Antiandrogen

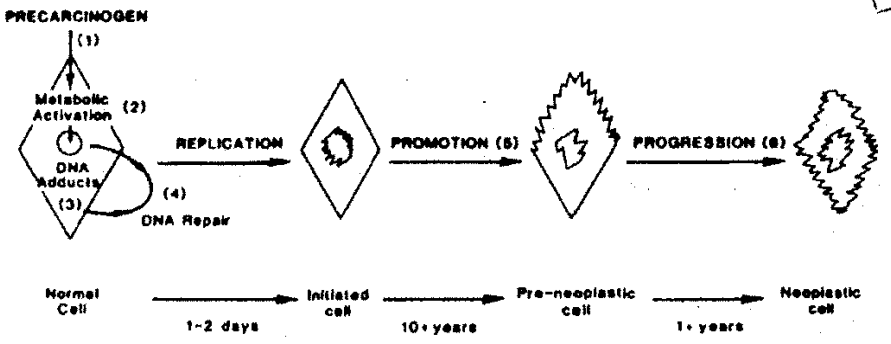
Table 3 lists those hormonal and dietary factors for which there is considerable reason to believe that they are associated with cancer development, and that appropriate modification in intake or exposure will reduce risk. However more confirmatory data is needed before strong preventive recommendations can be made. Rigorous clinical trials need to be performed to refute or confirm the value of dietary changes in modifying cancer outcome.

In this review we discuss the scientific basis for chemoprevention intervention strategies to cancer, the role of the biologist and physician in participating in chemoprevention trials, and prospects for future development in this area with an emphasis on dietary interventions.

II. BIOLOGICAL BASIS OF CANCER PREVENTION

Logical application of prevention strategies depends on general and detailed knowledge of the biological basis of cancer causation and early transformation events. Over the past 30 years there has been a large number of laboratory studies which have been performed in order to understand the mechanistic basis of cancer formation (carcinogenesis). A general scheme which outlines our understanding of the process of carcinogenesis which has evolved is presented in Figure 1. Tumor development can be results in irreversible genotypic damage, promotion represents altered phenotypic expression, and progression is evolution of this process from a classically preneoplastic to neoplastic state. The essential elements are detailed on the next page.

Figure 1
Steps in the Induction of Cancer and Loci for Intervention
(Adapted with permission from Bertram et al., 1987)



Initiation

Initiation produces damage to the DNA of the cell and consequently an altered genetic message potentially exists. There are three key steps identified so far in the process of initiation: conversion of the chemical or physical agent to an active carcinogen, interaction of the carcinogen with DNA to produce a lesion in the genetic material, and fixation of that damage. Not all carcinogens require activation but among those that do the liver or kidney is the usual site of metabolism and the event is rapid. Interaction of the active carcinogen with DNA may be direct or indirect. Many initiators produce activated lipid (oxidized) species which secondarily produce genetic damage. This step is also generally regarded as rapid although ongoing damage to DNA from oxidized lipid species may occur over long periods of time. After nucleotides in the DNA are altered the cell may attempt to correct the damage. Under certain conditions, particularly when accompanied by cellular quiescence, the genetic aberrations can be corrected. A number of agents can serve as initiators. These include: viruses, physical agents, and chemicals.

Viruses

In animals, viruses are a causative agent for many cancers. In humans, viruses suspected to have etiologic roles for cancer include: T-lymphotropic virus, Ebstein-Barr virus, human papilloma virus (HPV) and hepatitis virus. Associations respectively with T-cell lymphomas and leukemias, nasopharyngeal, cervical, and liver cancers have been convincingly demonstrated. Causative functions of these viruses in vivo remain however to be shown.

Human immunodeficiency virus, type 1, produces an aggresive T-cell lymphoma/leukemia. This virus is probably transmitted largely through homosexual contact among affected individuals and therefore represents a tough public health problem.

The cultural epidemiology of Ebstein-Barr virus and its association to nasopharyngeal cancer has not been sufficiently worked out that preventive intervention strategies can be proposed.

HPV subtypes 6, 8, 16 and 18 are strongly associated with risk for cervical cancer and this malignancy clearly belongs in the realm of sexually-transmitted diseases. Appropriate barrier contraception (condom) as a preventive strategy for prevention of cervical cancer is likely to block transmission of HOV, but direct proof for this assertion does not currently exist.

Hepatitis virus presents a more complex problem since the biologic agent is endemic in some societies (e.g.Taiwan, southern China, and South Africqan blacks) and is also transmissible through both sexual contact and intravenous routes. Additionally, aflatoxin B, a potent chemical mutagen found in fungi which contaminate foodstuffs, which has a predilection for the liver plays a major co-factor role by damaging hepatocytes. This results in enhanced cellular hepatocellular proliferation and subsequent fixation of genetic damage caused by the virus. Several prevention strategies therefore appear relevant to control of liver cancer: a virus vaccine (being tested), altered cultural habits (barrier contraception, abstinence from shared needles, reduction of aflatoxin B in food stuffs), and screening of blood products.

Radiation

A second major group of cancer causing agents important in initiation include physical disturbances such as ionising (x-rays) and non-ionizing radiation (ultraviolet). Exposure to ultraviolet light largely occurs through outdoor contact with sunshine and is confined to the skin. Nevertheless, at high doses sunlight may produce a genetalized immunosuppresion as well. The world-wide incidence of both non-melanoma and melanoma skin cancer has doubled in each of the last three decades and has risen more rapidly in sunny climes. Cutaneous malignant melanoma is in incidence the fastest increasing cancer in the U.S. and in the Southwestern and Western regions the rise has been even sharper. The reasons for this change are probably now understandable and relate to changing cultural habits with increased exposure of skin to sunlight.

The ultraviolet (UV) light spectrum of sunlight is divided by length of wavelength into three major regions; UV-A (320-400 nm), UV-B (290-320 nm) and UV-C (<290 nm). UV-C is germicidal and highly mutagenic but fortunately these shorter wave lengths of light are effectively filtered out by the ozone layer in the upper stratosphere. Although the role of ozone in blocking UV-C has been appreciated for some time, only in the last few years has it been understood that man-made fluorcarbons released to the atmosphere inactivate ozone via a simple chemical reaction. This depletion has been of sufficient magnitude to deplete the ozone layer to dangerously low levels. Fortunately, the problem has been recognized and almost all countries have adreed to stop the manufacture of these compounds. Since however flurocarbons are integral to plastic manufacture and a phase-out period is required, the incidence of skin cancer is

will allow correction of the lesion in situ remains to be seen. The next major step in carcinogenesis is called promotion. Cellular and tissue changes take years to unfold and in experimental systems early and late stages have been identified. A progressive accumulation of phenotypic alterations occurs, although in general no further genotypic changes are evident. A number of common exogenous factors unequivocably play a role as enhancers of the process of promotion (Table 5). Less certain is the role of specific natural dietary factors (Table 6).

Table 5
Established Promoters of Human Cancer Formation

Agent	Exposure	Cancer
Alcohol	Social	Esophagus, larynx, oropharynx, liver
Estrogens	Medical	Endometrium, vagina*
Immunosuppressive drugs	Medical	All sites (esp, marrow)
Overnutrition	Social	Breast, endometrium, gallbladder
Reproductive History**	Physiologic	Breast, ovary
Parasites	Environment	
Chloronchis simensis		Liver (cholangioma)
Schistoma hematobium		Bladder (squamous carcinoma)
Steroids:	Medical, cultural	
Anabolic		Liver
Contraceptives		Liver (benign hamartoma)

* Transplacental synthetic estrogen
**Breast - late age at first pregnancy; ovary - zero or low parity.

Established promoters of human cancer formation include alcohol, hormones, and drugs. Alcohol alone does not produce cancers in animal models although when associated with primary hepatic damage from almost any cause it can serve as a potent promoter. Epidemiologic associations of human cancers with alcohol alone have been weak, although recent data suggests that high daily alcohol ingestion may be associated with an increased incidence of breast cancer. In contrast, epidemiologic studies have clearly shown that alcohol is a potent co-carcinogen and markedly enhances cancer risk in the oropharyngeal cavity, larynx and esophagus in association with smoking.

Hormones are potent promoters of cancer in individuals at risk. One of the most dramatic instances of promoter enhanced cancers in humans was the "epidemic" of endometrial cancer which occurred in the late 1950s. The rapid rise in the incidence of thia malignancy was traced to the use of unopposed estrogen (diethylstilbesterol) in women for the management of osteoporosis. The incidence of this cancer promptly fell after this practice decreased. Old style high dose oral contraceptives produced benign liver tumors with fair regularity as well. Fortunatgely modern contraceptives use lower doses of estrogen and are combined with progesterone, producing a hormonal effect which is more physiologic. Both these properties should obviate tumor development. Most worrisome is the popular use of anabolic steroids by athletes since this drug produces many undesirable side effects including hepatomas.

The role of dietary substances as modulators of cancer risk has been intensively discussed over the past few decades. For the most part these compounds probably extend their major effects at the promotional stage of carcinogenesis, although as discussed below, they may have a broader effect. A substantial number of epidemiologic studies support the notion that fat, fiber, vitamins, and micronutrients play a role in the expression of cancer risk. Likewise laboratory investigations have shown that these substances can serve to affect the process of carcinogenesis. The contribuition of dietary factors to cancer risk is discussed separately below.

Changes in the phenotype of the cell leads to progressively increased molecular and biochemical alterations. At some point protein changes occur which affect the antigenic presentation of the cells and its interaction with host cells. Surprisingly little is known about the

early "tumor"/host cell interactions. This is particularly striking when one considers the large number of studies which have examined the interaction between fully transformed or late cancer cells and the host immune response. A study of host cell function and cytokine expressions with the early preneoplastic cell is likely to provide new insights into the process of cancer formation and its control.

Preneoplasia and Progression

Conventionally the premalignant state is regarded as synonymous with histologic alterations identified at the clinical and/or light microscopic level. With a newer understanding of the process of carcinogenesis the point of transition from promotion to progression has become more nebulous. Nevertheless, identifiable clinical changes which are microscopically definable and result in measurable lesions provide a useful benchpost for study. In most tissues in man preneoplastic precursor lesions have been identified. Some of the better known conditions include actinic keratoses (skin), leukoplakia (orophargyngeal cavity), dysplasia (cervix), and polyps (colon). Surprisingly very little is known about the biology of preneoplasia and what changes occur as preneoplastic tissue progresses to neoplasia, nor are the factors which enhance or inhibit this transition well understood. Part of the problem has been the limited nature of good model systems in which to study preneoplasia but equally prominent has been investigator disinterest in this important step in tumor formation.

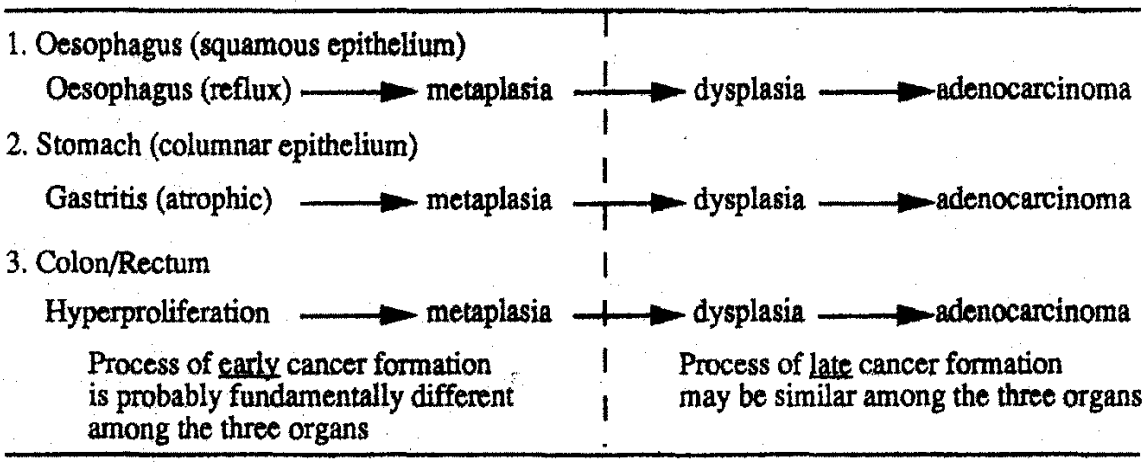
Several important observations about progression of preneoplasia have been made in animal model systems. These include (a) many of the same factors which affect initiation also influence progression, (b) new genetic changes occur and progressive accumulation of genetic damage results, (c) spontaneous regressions occur and the basis for this event is largely unknown, and (d) progression is surprisingly infrequent.

Clinical observations of preneoplastic conditions have been recorded for quite some time. Two major themes emanate from these clinical observations.

1. The process by which different tissues evolve from normal to neoplasia varies among organs. An examination of the types of progression which occur in the gastrointestinal tract is instructive (Figure 2).

Figure 2

Evolution of Preneoplastic Lesions of the Gastrointestinal Tract into Cancer



To evolution from normal to neoplastic tissue in the gastrointestional tract seems to occur via several different pathways although a common end pathway may be in effect. The initial damage in the esophagus occurs from reflux of acid from the stomach with inflammation being a prominent early change. Subsequently, in some cases the stratified squamous epithelium tissue

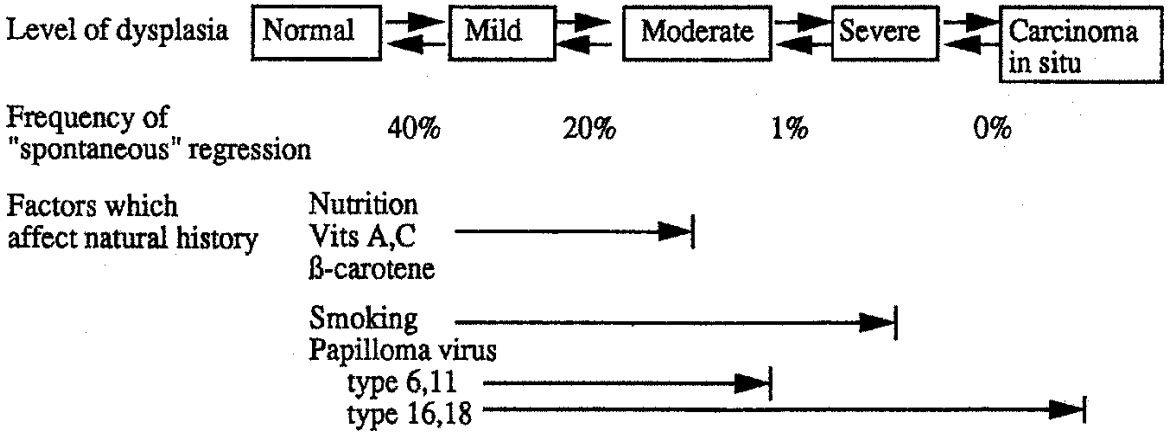
undergoes transition (or metaplasia) to a columnar epithelium. In the stomach the initial damage also appears to be inflammation, but before further progression an atrophic state frequently occurs. In contrast to the esophagus, the stomach uniformly evolves to precursor lesions via the native columnar epithelium pathway. Early events in the colon appear quite different from the esophagus and stomach as hyperplasia followed by polyp (adenoma) formation are the initial abnormalities.

These three pathways likely represent fundamentally different strategies in the early evolution of preneoplasic lesions. In contrast metaplasia in the esophagus, abnormal stomach columnar epithelium, and polyps in the colon all seems to later evolve through as common step of dysplasia before frank carcinoma appears.

2. The process of preneoplastic evolution and the factors which affect progression are complex. This is no better illustrated than for cervical dysplasia (Figure 3). In the cervix the process of progression is complex. The transition from mild to moderate to severe dysplasia is not inevitable and a real/spontaneous remission rate is evident, which decreases in frequency as the lesion progresses. Both human papilloma virus and mutagenic products from tobacco (e.g. cigarette smoking) play a role in progression. Likely also involved are inflammation, other viruses and nutrition.

Figure 3

The Natural History of Cervical Dysplasia and Factors which Affect this Process



The exact point at which a preneoplastic lesions becomes neoplastic has become increasingly hard to define as more is learned about the process. Nevertheless preneoplastic tissues becomes functionally neoplastic when cells are locally invasive and/or produce metastatic deposits. This transition stage is accompanied by a series of changes in which the tumor cells becomes less and less responsive to both host immunological and cell and tissue regulation. Additionally, the cells gradually accumulate genetic alterations and acquire an independent biological mandate.

III. DIETARY CONTRIBUTION TO CANCER RISK

A vast amount of laboratory and epidemiological data implicates dietary factors as important in determining the incidence of certain human cancers, particularly those of lung, breast,

likely to rise at least until the year 2025. Also, UV-B wavelengths are not completely filtered out by ozone and exposure of the skin integument results in sunburn and tanning. The role of UV-A in producing skin damage and cancer is not completely clear, but these wavelengths probably contribute to overall skin damage and cancer risk as well.

There are a number of prevention strategies which can be used to decrease overall exposure to sunlight. Gradual exposure to sunlight over short time periods and the use of sunscreens and sunblocks should result in lowering the incidence of skin cancers. However these acculturations involve long term personal, cultural and societal changes and maintenance of new behavior patterns even with constant educational reinforcement is difficult.

Significant exposure to ionizing radiation was until recently thought to be confined to diagnostic medical procedures, radiation accidents, or nuclear warfare. The amount of radiation exposure in diagnostic procedures has steadily fallen and is of minor concern if appropriate safeguards are followed. Also, radiation exposure in the medical work place has decreased markedly with appropriate shielding and precautions, and improvement in equipment. The one group for which special vigilance is warranted is the pregnant female since low dose exposure of the getus to ionizing radiation results in a demonstrable increase in leukemia during childhood.

A highly significant issue which has been identified in the past few years is the discovery of radon gas in many homes and its relationship to lung cancer. Radioactive materials are found in most rocks and without foundation shielding the level of radon gas in a home may rise to 100 times sage levels. This problem is a serious one and excessive exposure to radon may offer an etiologic explanation for up to 20,000 cases yearly of lung cancer not associated with cigarette smoking as well as lowering the carcinogenic threshold for tobacco. The control of residential radon has profound legal, economic, and public health implications and effective strategies for managing the quality of indoor air have not yet been firmly established.

Table 4
Chemicals which are Established Major Carcinogens in Humans

Agent	Exposure	Cancer
Aflatoxin	Foodstuffs (e.g. cotton, milk)	Liver (hepatoma)
Aromatic amines (e.g. benzidine)	Work place (dyes)	Bladder (transitional cell carcinoma)
Asbestos	Work place, buildings	Lung (squamous), pleura (mesothelioma)
Benzene	Work place	Bone marrow (aplasia, leukemia)
Vinylchoride	Work place (plastics)	Liver (angiosarcoma)

Chemicals

The list of chemicals which have been associated with causation of various cancers is long. However, only a few of these compounds have a major role (Tables 2 and 4); most of these substances probably act predominantly at the initiation stage of carcinogenesis. Aflatoxin, as a food contaminate, plays a major contributory role in the development of liver cancer. Although uncommon in the U.S. hepatoma is the number two cause of death from cancer in the world. Exposure to aromatic amines have been directly linked to bladder cancer and account for at least 50% of the 40,000 cases diagnosed in the U.S. in 1988. Likewise asbestos is an important carcinogen, contributing to 10% of the risk for lung cancer (16,000 cases/year) and greater than 90% of the risk for mesothelioma, of which there were 3,000 cases in the U.S. in 1988. Many other chemicals have been etiologically linked to cancer causation including benzene (bone marrow) and vinyl chloride (liver).

Promotion

After initiation and fixation of nucleotide changes in DNA has occurred, genotypic damage to the cell is generally regarded as irreversible. Whether in the future advances in genetic technology

colon/rectum and prostate origin. These sites are particularly relevant today since these cancers are common, are increasing as the population ages, and our therapeutic adventures for these tumor types remain less than optimal.

Table 6
Major Dietary Factors and Common Cancers

	Evidence for Association			
	Laboratory	Epidemiological		
Cancer		Ecologic	Analytic	Comment
FAT				
Breast	Strong	Strong	Weak	Role of total calories vs fat unresolved
Colon	Strong	Strong	Moderate	Complex interaction with fiber
Prostate	Little available	Little evidence	Moderate	Needs more study
FIBER				
Colon	Strong	Very strong	Mixed	Complex interaction with fat
Green vegetables	Protease inhibitors very potent	Consistent	Consistent	Vegetables are complex chemical factories
VITAMIN A				
Lung	Strong	None available	Strong	Complex, beta-carotene probably major factor
Oral	Little available	None available	Moderate	
Cervix	None available	None available	Moderate	

There has been a great deal of discussion about the role of diet in cancer causation but to date only preliminary trial results are available. The laboratory and epidemiologic information has accumulated sufficiently to suggest that far, fiber, green vegetables, and "vitamin A" play important and perhaps generic roles in cancer causation (Table 6). My reading of the enormous literature on this topic suggests at this time:

1. The amount of fat ingestion plays a role in the expression of postmenopausal breast, colon, and prostate cancers. The role of fat in cancer risk remains hotly debated and whether the "fat effect" or total calories is the culprit still remains to be determined. Nevertheless, increased "fat" intake has been associated with increased risk for breast, colon, endometrial and prostate cancers. Whether a subtype - polyunsaturated /saturated - of fat plays a distint role also remains to be determined.

2. Ingestion of fiber appears protective against colon cancer, although the details remain to be elucidated. The amount of fiber ingested is inversely proportional to colon cancer incidence above

a certain baseline incidence. The type of fiber seems to be important with protective roles for wheat bran and vegetable fibers and probably an adverse effect of oat bran. Protection probably is afforded by the fiber through a combination of complexing with bile acids (potential mutagens), absorption of harmful fat and lipid substances decreased and transit time of stool and will be discussed in more detail later. The effect of fiber seems to vary on different segments of the colon and rectum. The best protective effect occurs when fat is low but high fiber ingestion seems to protect against a high fat intake to a considerable extent.

3. Ingestion of green leafy vegetables is protective against cancer development in general and colon and lung cancer in particular. The exact chemical(s) responsible is unclear, but protease inhibitors are prominent candidates. There is considerable evidence that such common compounds as the Bowman-Brik Inhibitor asre highly effective in vitro and in animal models.

4. A potential for "vitamin A" as a cancer chemopreventive agent has a history over 70 years old. Currently, the data suggests the following. In the usual circumstance the "vitamin A" protective effect is due to beta-carotene. Both serum levels of beta-carotene and dietary intake seem to provide protection against lung, oral and cervical cancer. Very low levels of vitamin A (retinol) intake probably produce an increased risk for cancer and in this setting the effect of vitamin A per se may be greater than that of beta-carotene. Investigations of the potential role of other carotenoids in cancer prevention should also be informative.

5. Beta-carotene itself seems to have anti-carcinogen effects against many cancers. The mechanism of action of the compound may explain its broad spectrum effect. Cellular and genomic damage is frequently introduced via oxidant damage and beta-carotene serves as a strong antioxidant, protecting particularly against free radicals. Unfortunately, solubility issues related to beta-carotene have limited the number of in vitro cellular studies. Nevertheless, the evidence for an anticancer effect of beta-carotene is persuasive from the animal and epidemiological data (Table 7). Beta-carotene seems to have particular promise for prevention of lung and cervical cancer.

IV. INTERVENTION STRATEGIES

An understanding of the events which contribute to cancer causation and its biological evolution into progressively more malignant states provides one with a rational approach to the prevention of cancer. The management of cancer spans the therapeutic continuum from simple applied prevention to aggressive chemotherapy. For the most part the major medical emphasis to date has been on the treatment of late cancer and the early management of cancer has not been systemically approach.

Primary Prevention

Modern advances in molecular biology have clearly identified both deletions (tumor suppressor genes) and activators (proto-oncogenes) of genetic material as important in the evolution of cancer. The best studied of the neoplastic conditions are hereditary retinoblastoma in which a portion of chromosome 13p is consitutively deleted or lost. Recently this abnormality has been corrected in vitro by the delivery of the gene via retroviral vectors. Since deletions are being identified as a critical early change in many common cancers, (e.g. colon cancers), refinement of delivery technology of genes for in vivo use is an important goal. This type of approach may well have a major preventive role in the control of cancer in the future.

It will be important to be determined whether subtle constitutive changes are produced early on in individual nucleotides of certain genes in individuals at high risk for a cancer. With the identification of changes in specific genes closely related to various cancers, exploration of this goal will both be an important and attainable one for the future. For example if one knew that constitutive changes existed in one's genes that raised the risk considerably for a particular type of cancer, selected and specified screening and early detection as well as health promotion advice could be directed toward that organ in an individual. Once genetic change has occurred, repair unsuccessful, and the damage fixed, a cell is essentially irreversibly initiated. Although correction of lesions may be possible in vitro in the near future, this goal seems distant in the clinical arena at the current time and primary prevention strategies need to be considered.

The application of a number of conventional primary prevention strategies may impact enormougly on cancer incidence. Most prominent among these practices include elimination of smoking and use of sunscreens. Currently, the effect of inhibitors of initiation (anti-initiators) is being actively investigated as well. Some well known dietary anti-initiators include ß-carotene, alpha-tocopheral (vitamin E), selenium and soybean extract (protease inhibitors). Improving the cellular tissue microenvironment by providing reducing agents (ascorbate) may also be quite important as the number of harmful oxidized species should be reduced.

Secondary Prevention

Once irreversible genotypic damage has occurred, efforts need to be addressed to repressing or altering the phenotypic expression of the abnormal genetic material. Secondary prevention management is directed toward decreasing exposure to promoters (e.g. aniline dyes, hormones and fat), providing substances (e.g. fiber) which reduce exposure to promoters, and/or improving the milieu in which the tissue is found so that proliferation is suppressed or differentiation enhanced (e.g. assure adequate vitamin A intake or synthetic retinoids).

Tertiary Prevention

Once phenotypic alterations have resulted in histologic changes clinical lesions can be identified and followed. Some of the more common approachable preneoplasia lesions include those of the skin, cervix, and oral cavity. Surgery and/or ablation has been used most frequently in the management of these conditions. These approaches are not always feasible (e.g. lung) or unpleasant (e.g. breast, colon) and lesions frequently recur even after removal. Secondary intervention such as improving the nutritional environment (increase in vitamins A and C, beta-carotene, decrease in fat) may place a beneficial role. Additionally, investigations now are being performed to determine whether active intervention with antiproliferactive (e.g. polyamine inhibitors) or differentiation agens (e.g. retinoids) can reverse preneoplasia or inhibit or suppress preneuplastic progression to a more malignant state.

Cells which are making the transition from preneoplastic to neoplastic status should be an active target for intervention. The cells at this stage are minimally transformed and probably still in dialogue with other like cells as well as with host immune cells and the tissue microenvironment within which they reside. Surprisingly little research has explored intervention at this stage. Advances in our understanding of host-preneoplastic-tissue interactions should allow rapid progress in this area in the future. Likewise certain malignancies in vitro and in animals appear peculiarly sensitive to differentiating agents. For example, human neuroblastoma cells in vitro and promyelocytic leukemia cells in vitro and in vivo terminally differentiate and mature in the presence of retinoic acid. Recently, several studies have shown that transpretinoic acid can induce terminal differentiation of acute promyelocytic leukemia with resultant clinical complete response. Further understanding of such phenomena may allow highly targeted and benign therapy of certain cancers in the future.

V. MAJOR PREVENTION TRIALS

Results from early small chemoprevention trials have shown many positive results and are summarized in Bertram et al. (1987). A summary of the major phase II, III and IV trials being conducted in the United States and elsewhere is provided in Table 8. Recently the results from two large trials were reported. In the first, Greenberg et al. (1990) conducted a randomized placebo-controlled trial of beta-carotene in patients who had had one or more prior non-melanoma skin cancers removed. There was no difference in the rate of recurrence of new skin cancers. In contrast, Hong et al (1990) showed that 13-cis retinoic acid in a large randomized placebo-controlled trial markedly and significantly reduced the recurrence of second regional malignancies in patients with a resected oral cancer. An understanding of the reasons for the results emanating from these trials will be important.

Chemoprevention as an approach to the management of human cancer holds tremendous promise and potential. The results from ongoing trials are eagerly anticipated.

Table 7
Evidence for Association of Beta-Carotene with Decreased Cancer Risk

	Evidence for Association		
Cancer	Laboratory	Epidemiologic	Comment
Lung	Moderate	Very strong	Consistent
Skin favours	Strong	Little available	Mechanism of action protection
Cervix	None available	Moderate	No good model
Breast	None available	Negative	No good model
Colon	Moderate	None available	Binding to fiber important
Prostate	None available	Moderate	Vitamin A model data negative

Table 8
Ongoing Major Phase II, III AND IV Chemoprevention Trials

Organ Site	Agents being tested
Skin (non-melanoma)	13-cis RA*, retinol, Beta-carotene, selenium
Lung	Retinol + Beta-carotene, 13-cis RA, Retinol + Vitamin E
Colon	Fiber, calcium, piroxicam, DFMO*, Beta-carotene + Vitamins C, E
Cervix	Folic acid, Beta-carotene + Vitamin C, RA*
Oral	13-cis RA, Beta-carotene
Breast	4-HPR*, Tamoxifen**
Esophagus	Multiple vitamins + Beta-carotene
All	Beta-carotene

*Abbreviations - RA, retinoic acid; DFMO, difluoromethylornithine; HPR, hydroxylphenylretinamide; **Tamoxifen - a major national prevention trial is being planned in the United States.

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