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ROLE OF CHEMOPREVENTION IN CANCERS

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Summary

Chemoprevention of cancer is a means of cancer control in which the occurrence of this disease, as a consequence of exposure to carcinogenic agents, can be entirely prevented, slowed, or reversed by the administration of one or several naturally occurring or synthetic agents. Thus, the chemoprevention of cancer differs from therapy in that the goal of prevention is to lower the rate of cancer incidence. Such chemopreventive agents are also known as anticarcinogens. The use of specific nutrients other chemical compound in the prevention of cancer is referred to as chemoprevention. The aim of cancer chemoprevention is to circumvent the development and progression of precancerous cells through the use of non-cytotoxic nutrients and/or pharmacologic agents. Although decreasing cancer incidence and mortality is the ultimate goal of chemoprevention, much effort is being devoted towards identifying specific steps in the carcinogenesis process that are amenable to intervention and that can serve as surrogate endpoint biomarkers for possible modulation by chemopreventive agents. There appear to be at least two basic mechanisms by which chemical agents with relatively low toxicity may inhibit carcinogenesis. Chemopreventive agents can also identified by systematic evaluation of agent that acts at specific molecular targets with respect to cancer by using laboratory assay. The present article highlights epidemiologic evidence with selected mechanism of action for various agents and potential chemopreventive activity.

Keywords: Chemoprevention, Cancer, Carcinogenesis, epidemiology

Introduction

Cancer chemoprevention is defined as the use of pharmacological, natural or dietary agents to inhibit the development of invasive cancer by blocking DNA damage caused by carcinogens or by arresting the progression of premalignant cells after damage has already occurred. Angiogenesis inhibition blocks carcinogenesis by preventing progression to the invasive phenotype. A number of well-known chemopreventive agents have antiangiogenic properties in vivo and in vitro. These include retinoids, tamoxifen, oltipraz, curcumin, linoleic acid, ellagic acid and celecoxib [1, 2, 3]. Cancer chemoprevention, as first put forward by sporn in 1976 is use of natural and synthetic chemical agent to reverse, supressness or prevents carcinogenic progression to invasive carcinoma for understanding of rationale for cancer chemoprevention. One of the most impressive findings in the field of cancer chemoprevention is the very number of compounds that have been demonstrated to over 20 different classes of chemicals have been shown to have chemopreventive capabilities [4].

Epidemiologic evidence for chemoprevention

Fortunately, several types of evidence indicate that a major fraction (50-80%) of human cancer is potentially preventable, because its causation i.e. the factors that determine incidence are largely exogenous. This evidence comes mainly from epidemiological studies including:

- Time trends in cancer incidence and mortality.
- Geographic variations and the effects of migration.
- The identification of specific causative factors like cigarette smoking, occupation and environmental chemicals, radiation, dietary factors, socio economical factors , specific viruses etc.
- The fact that the vast majority of human cancers do not show sample patterns of inheritance.

Chemoprevention of cancer means of cancer control in which the occurrence of the disease is prevented by the administration of one or more chemical or biologic substances [5].

From the point of view of primary prevention of the initial development of a neoplasm or its precursor, the external factors are probably the most operable optimistic message since it means that the development of several forms of cancer is not in an inherent consequence of the aging process and that the human species is not destinated to suffer a high incidence of cancer [6].

The second encouraging message is the fact that early detection of at least some forms of cancer saves lives. Therefore, increased efforts in secondary prevention inducing the development of new diagnostic method to detect early lesions and the development of more effective method of intervention including chemoprevention, hold great promise. The third reason to be optimistic about prevention relates to the spectacular advances in basic research which are providing powerful new approaches to identifying specific causes of human cancer (through molecular epidemiology), highly sensitive tools for early diagnosis by using molecular probes and novel strategies for cancer chemoprevention.

Both prospective and retrospective epidemiologic studies indicate that high intake of carotenoids rich foods and dark green leafy vegetables, yellow and orange vegetables and fruits etc. are related to reduced risk for lung cancer, consumption of vegetable fruit also appeared. They may be associated with reduced risk for stomach, head, neck, breast, skin, prostate and bladder cancer.

Chemoprevention of skin cancer

Chemopreventive agent should have (i) little or no untoward or toxic effects, (ii) high efficacy against multiple sites, (iii) capability of oral administration, (iv) a known mechanism of action, (v) low cost, and (vi) human acceptance. With regard to naturally occurring agents, fruits, vegetables, and

common beverages, as well as several herbs and plants, have been identified as rich sources of cancer chemopreventive agents. While a wide range of laboratory studies has identified many compounds, including several polyphenols, as cancer chemopreventive agents, in this article our main emphasis is on the cancer chemopreventive potential of a polyphenolic fraction isolated from green tea and silymarin, a flavonoid present in artichoke, against different stages of mouse skin multistage carcinogenesis [7].

Chemoprevention of liver cancer

Despite significant advances in medicine, liver cancer, predominantly hepatocellular carcinoma remains a major cause of death in the United States as well as the rest of the world. As limited treatment options are currently available to patients with liver cancer, novel preventive control and effective therapeutic approaches are considered to be reasonable and decisive measures to combat this disease. Several naturally occurring dietary and non-dietary phytochemicals have shown enormous potential in the prevention and treatment of several cancers, especially those of the gastrointestinal tract. Terpenoids, the largest group of phytochemicals, traditionally used for medicinal purposes in India and China, are currently being explored as anticancer agents in clinical trials. Terpenoids (also called "isoprenoids") are secondary metabolites occurring in most organisms, particularly plants [8]. More than 40'20000 individual terpenoids are known to exist in nature with new compounds being discovered every year. A large number of terpenoids exhibit cytotoxicity against a variety of tumor cells and cancer preventive as well as anticancer efficacy in preclinical animal models. It was reported that the potential role of naturally occurring terpenoids, from diverse origins, in the chemoprevention and treatment of liver tumors. Both in vitro and in vivo effects of these agents and related cellular and molecular mechanisms are highlighted. Potential challenges and future directions involved in the advancement of these promising natural compounds in the chemoprevention and therapy of human liver cancer are also established.

Chemoprevention of breast cancer

High risk of breast cancer, you may be able to improve your odds of staying cancer-free by taking certain medicines, an approach known as chemoprevention or chemoprophylaxis. Medication options for breast cancer chemoprevention include tamoxifen or raloxifene (Evista) [9]. These medications currently used for breast cancer chemoprevention; as well as new medications that might be future chemoprevention options; are the subject of much ongoing research.

Chemoprevention of colorectal cancer

Colorectal cancer is the second leading cause of cancer-related deaths in the United States. It is estimated that this cancer will develop in 130,000 people in the United States in 2000 and that 56,000 will die from the disease. Surgical resection remains the only curative treatment, and the likelihood of cure is greater when the disease is detected at an earlier pathological stage. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely studied agents for the chemoprevention of colorectal cancer. These compounds exert their effects by a number of mechanisms. Recent observations suggest that aspirin and other NSAIDs, supplemental folate and calcium, and postmenopausal hormone-replacement therapy (estrogen) have a chemopreventive benefit. Since the value of such prophylactic strategies has not yet been confirmed in double-blind, placebo-controlled, randomized studies, chemoprevention cannot yet be accepted as standard medical practice. Chemoprevention should not replace periodic fecal occult-blood tests and endoscopic screening, as well as modification in known risk factors for colorectal cancer, such as reduction in the intake of red meat, appropriate exercise, smoking cessation, and weight control [10]. Any protective benefit must also be balanced against the potential side

effects of the long-term ingestion of any putative chemopreventive agent, including the gastric irritation and platelet dysfunction associated with aspirin and other NSAIDs, which are thought to be due to the inhibition of COX-1. More selective COX-2 inhibitors, such as celecoxib and rofecoxib, have already been evaluated in patients with familial adenomatous polyposis and are now being studied in patients with a history of sporadic polyps. In addition, other potential chemopreventive agents, such as ursodiol (a modulator of bile acid composition),eflornithine (which inhibits cellular proliferation by altering polyamine metabolism), and oltipraz (an inducer of the mutagen-detoxification enzyme glutathione S-transferase), are undergoing evaluation in studies in animals and clinical studies.

Chemoprevention of colon cancer

The non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, the anti-arthritis drug sulindac, and the newer, more selective drugs like Celebrex®, show great promise for the prevention of colon cancer. NSAIDs are effective chemoprevention agents in genetically predisposed and chemically-induced animal models of intestinal cancer, and high aspirin intake is associated with a 40-50% decrease in colon cancer mortality in humans. Although potent chemopreventive agents, some conventional NSAIDs can cause severe side-effects, including gastrointestinal (GI) bleeding, GI perforation, renal toxicity, and even death. NSAIDs are responsible for at least 100,000 hospitalizations and 10,000 to 20,000 deaths annually and are responsible for more serious adverse drug reactions reported to the FDA than any other class of drugs. These adverse effects are generally dose-dependent, with higher doses more likely to cause toxicity [11].

It was also reported that to minimize toxicity and increase efficacy of NSAIDs is to use very low doses of these drugs in combination with other chemopreventive agents. Natural products like tea may be effective in combined chemo- prevention strategies.

Advances in chemoprevention of head and neck cancer

Head and neck squamous cell carcinoma (HNSCC) is a devastating disease with a poor outcome in advanced stages, accounting for approximately 3% of all malignancies, with an estimated 37,200 new cases and 11,000 deaths annually in the U.S. Tobacco and alcohol are widely recognized risk factors.

The most well-studied agents in head and neck cancer chemoprevention include vitamin A, other retinoids, beta-carotene, vitamin E, selenium, and COX-2 inhibitors. In addition, the investigation of biomarkers has led to the development of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and farnesyl transferase inhibitors (FTIs) that target EGFR and H-*ras* and are new promising agents for chemoprevention.

Chemoprevention of oral cancer

Oral cancer causes considerable morbidity and is associated with a 5-year survival rate of less than 50%. It is a major problem in populations in which alcohol and tobacco use are prevalent such as in lower socioeconomic communities. Oral cancer, like cancers in many other sites, is often preceded by the development of premalignant lesions of the oral mucosa, also termed intraepithelial neoplasia. Premalignant lesions and malignant lesions of the upper aerodigestive tract have been shown to express genotypic and phenotypic abnormalities including increased DNA index, specific chromosomal abnormalities, and an inactivating mutation of the *p53* tumor suppressor gene. The dysregulation of p53 in the mucosal epithelium correlates with increased proliferative activity. Moreover, p53 status has been shown to be a predictor of progression of premalignant oral dysplasias to invasive cancers. These molecular alterations have stimulated rational chemopreventive agent selection that targets specific abnormalities detected in the cells of the oral mucosa.

Several classes of agents have shown promise as

chemopreventive agents including the nonsteroidal anti-inflammatory drugs (NSAIDs), which possess a valid scientific basis for the chemoprevention of multiple cancers. For those cancers in which they have demonstrated chemopreventive potential, evidence of efficacy is derived from epidemiological, animal studies in relevant model systems, and from tissue cell culture studies.

Chemoprevention of urological cancer

Cancer is a major cause of mortality and morbidity throughout the world, and ranks as the second leading cause of death in the United States. Most cancers have a latent period of 10 to 20 years, which provides ample time for preventive measures. Transitional cell carcinoma of the bladder and adenocarcinoma of the prostate have protracted courses and may be ideal for chemopreventive strategies. Epidemiological reports provide the strongest evidence of a protective role for dietary agents in cancer of the bladder, prostate and kidney. Observational and recent experimental trials support these findings in cases of adenocarcinoma of the prostate and transitional cell carcinoma of the bladder. There is strong evidence for a protective effect of vitamin A in bladder cancer. Superior protection has been reported with a combination of high doses of vitamins A, B6, C and E plus zinc. For prostate cancer strong evidence exists for a preventive effect of reduced fat intake, vitamin E, selenium and soy proteins. A lesser benefit is also suggested with intake of vitamins D and C. Evidence of chemoprevention against renal cell cancer is supported mainly by epidemiological studies, and animal studies indicate possible benefit of vitamin D supplementation.

Chemoprevention of ovarian cancer

Epidemiologic and experimental studies suggest that oral contraceptives (OCP) and a synthetic form of vitamin A called N-(4-hydroxyphenyl) retinamide (4-HPR) may reduce the risk of ovarian cancer, but mechanisms of action of these agents remain unknown.

Several studies have correlated the risk of ovarian cancer with frequency of ovulation. OCPs suppress ovulation, but the decrease in risk of developing ovarian cancer is not directly proportional to the number of menstrual cycles suppressed. This suggests that other mechanisms might also contribute to chemopreventive effects.

A recent study in primates indicates that treatment with oral contraceptives or with progestins can increase apoptosis (cell death) in ovarian surface epithelial cells. Apoptosis is considered a defense mechanism of the organism against cancerous cells. Our group has found that transforming growth factor-beta (TGFß) induces apoptosis in abnormal ovarian cells.

Chemoprevention of bone cancer

A bone tumor is an abnormal growth of cells within the bone that may be benign or malignant (cancerous). The cause of bone tumors is unknown. They often arise in areas of rapid growth. Possible causes include inherited mutations, trauma, and radiation, but in most cases no specific cause is found. Bone tumors may be benign or malignant. Osteochondromas are the most common benign bone tumors, and occur most often in people between the ages of 10 and 20. Some benign bone tumors go away on their own and do not require treatment [12]. These benign tumors are monitored periodically by x-ray. Malignant bone tumors occur as a primary bone tumor or as metastasis (cancer spread from another area of the body). Primary bone tumors are rare (less than 1% of all malignant tumors) and are most common in young men. Malignant bone tumors include osteosarcomas, Ewing's sarcoma, fibrosarcoma, and chondrosarcoma.

The most common cancers that spread to the bone are cancer of the breast, lung, prostate, kidney, and thyroid. These forms of cancer usually affect older people. The incidence of bone cancer is also increased in families with familial cancer

syndromes. The incidence of bone cancer in children is approximately 5 cases per million children each year. Benign bone tumors may not require treatment, but may be looked at regularly, to check if they grow or shrink. Surgical removal of the tumor may be necessary. Treatment for malignant tumors that have spread to the bone depends on the primary tissue or organ involved. Radiation therapy with chemotherapy or hormone therapy is often used. Primary malignant tumors of the bone (tumors that start in the bone) are rare and require treatment at centers with experience treating these cancers. After biopsy, a combination of chemotherapy and surgery is usually necessary. Radiation therapy may be needed before or after surgery.

Chemoprevention of cervical cancer

The greatest potential for the chemoprevention of cervical cancer is in women with human papillomavirus (HPV) infection, an abnormal screening test or a non-invasive neoplastic lesion. Potential chemopreventive agents include micronutrients, antiviral agents and immune modifiers[8]. Randomised controlled clinical trials have generally been small and the results have not been encouraging. Beneficial effects on neoplasia have been shown for a couple of agents that have since been abandoned due to adverse side-effects. Indoles were used successfully in a very small clinical trial of women with high-grade cervical intraepithelial neoplasia and a larger trial using diindolylmethane in women with mildly abnormal cervical smears is underway. Although definitive trials need to use a robust clinical endpoint (such as histology), all future trials should include biomarkers to study the subclinical effect of the study agent.

Chemoprevention of testicular cancer

The role of caspase-3 (CPP32) protease in the molecular pathways of genistein-induced cell death in TM4 cells was investigated. Fluorescence microscopy with Hoechst-33258-PI nuclear stain was used to distinguish between apoptosis and necrosis pathways of cell death. The viability of the test cells was assessed with both the trypan blue exclusion and MTT tetrazolium (3-[4, 5-dimethyl-thiazol-2-yl]-2,5-diphenyltetralzolium bromide, 2.5 mg/mL) assays. Caspase-3 enzymatic activity was determined using CasPASE Apoptosis Assay Kit. The overall results from all the data demonstrated that: i) genistein exerts dose- and time-dependent effects on TM4 testis cells; ii) apoptosis is induced by lower concentrations of genistein and necrosis induced by higher concentrations of genistein; iii) genistein induced activation caspase-3 enzymatic activity; iv) genistein-induction of apoptosis and necrosis was significantly inhibited by the caspase-3 inhibitor, z-DEV-FMK; v) sodium azide induced necrosis without activation of CPP32 enzymatic activity, and induction of apoptosis; and vi) genistein-induced apoptosis was associated with activation of CPP32 enzymatic activity in the cells. The overall results indicate a strong evidence of caspase-3 (CPP332) mediation in the molecular pathways of genistein-induced apoptosis in testicular cells. Apoptosis is the physiologically programmed cell death in which intrinsic mechanisms participate in the death of the cell, in contrast to necrosis, which induces inflammatory response in the affected cell. The fact that the chemopreventive role of several cancer drugs is due to induction of apoptosis augments the biotherapeutic potential of genistein for the treatment of malignant diseases including prostate and testicular cancers [6]. It is therefore inevitable that identification of the apoptotic pathways and the points at which regulation occurs could be instrumental in the design of genistein biotherapy for such diseases.

Chemoprevention of brain cancer

Chlorogenic acid (CHL), the most potent functional inhibitor of the microsomal glucose-6-phosphate translocase (G6PT), is thought to possess cancer chemopreventive properties. It is not known, however, whether any G6PT functions are involved in tumorigenesis. We investigated the effects of CHL and the potential role of G6PT in regulating the

invasive phenotype of brain tumor-derived glioma cells.

Conclusion

The suppressing agents are compounds that inhibit carcinogenesis when administered subsequent to a course of carcinogen administration that would result in the occurrence of cancer. The number of classes of compounds that act as suppressing agent is smaller than that of blocking agents. The most extensively studied suppressing agents are the retinoids [12]. Chemopreventive approaches using enzyme modulation with both type A and type B blocking agents may also present potential risks and may result in unanticipated problems. Any attempt to modulate metabolizing enzymes of either phase I or phase II by dietary components or inducing drugs to reduce cancer risk should be carefully investigated. However, the sheer complexity involved in the prospective prevention of cancer does not constitute a sufficient excuse for ignoring the approach [13].

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