CANCER CHEMOPREVENTION

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Summary

Despite the intensive study of carcinogenesis that has been ongoing for over 50 years, the rates of cancer incidence and mortality are on the rise worldwide. Every human being is at some risk of developing cancer during their lifetime. Definitive steps can be taken to reduce the risk of cancer initiation through primary cancer chemoprevention. Recurrence or progression of established cancers can be reduced through secondary cancer chemoprevention. Effective chemopreventive agents have been identified in high throughput screens of synthetic compounds and natural materials. In particular, chemopreventive agents derived from natural products have been found to be inherently bioactive and highly effective at preventing or reversing the carcinogenic process in a pleiotropic manner.

Although several chemopreventive agents have shown efficacy in clinical trials, there is

a limited acceptance of prophylactic cancer drugs as an integral component of standard medical practice. An educational effort is necessary so people realize the increasing global burden of late-stage cancer treatment and care can be dramatically lessened by making cancer prevention a top priority. Such an effort should initiate with widespread personalized cancer risk profiling early in life that analyzes genetic and environmental risk factors in order to identify individuals at the highest risk for developing cancer. Based on risk level and cancer type, individual recommendations should then be made to reduce cancer risk, including lifestyle changes, adoption of a chemopreventive diet, and personalized combinations of prescribed chemopreventive agents.

1. Introduction

There were an estimated 8.1 million new cancer patients diagnosed worldwide in 1990 according to the International Agency for Research on Cancer (IARC). By 2005, the estimates approached 11 million per year. It is estimated that the number of new cancer cases could approach 19 million per year by 2010, which far exceeds the rate of projected world population growth. The eradication of certain infectious diseases has increased life expectancies around the world. As a result, the elderly population is larger than ever before. As cancer is a disease that is predominately diagnosed in older adults, the increasing number of people suffering from cancer may soon confront the world with one of the greatest public health problems of the twenty-first century.

The eight most common cancers (lung, stomach, breast, colorectal, mouth, liver, cervix, and esophagus) account for approximately 60% of cancer mortality worldwide. Males are more likely to develop cancers of the lung, colon, rectum, and prostate. The growing incidence of prostate cancer closely correlates with increasing life expectancy. Females are more likely to develop cancers of the breast, colon, and lung. Breast cancer alone kills almost 400,000 women per year globally. There are believed to be one million new cases annually with breast cancer incidence on the rise in most parts of the world. Cervical cancer is the leading cancer among females in the developing world, which is largely attributable to herpes papilloma virus (HPV) infection.

Lung cancer has the highest incidence (13% of total cases) and highest mortality rates. However, it is among the easiest to prevent through lifestyle changes and educational campaigns. As tobacco use is increasing in many developing countries, the lung cancer epidemic is intensifying. The incidence rates for women are rising rapidly in countries where female smoking is established. Smoking is becoming more common among girls in developing countries. Since secondhand smoke was declared a carcinogen in 2002 by IARC, many countries, including the United Kingdom and Sweden, have banned smoking in all workplaces, restaurants, and enclosed public spaces. In the United States, however, only 40% of states have passed laws that entitle an individual to a smoke-free workplace.

Stomach cancer is the second most common cancer worldwide (9.9%). Around two-thirds of all cases are observed in developing areas of the world. The risk is declining in industrialized countries, which is attributed to screening, dietary change, and decreases in infection by *Helicobacter pylori*. Colorectal cancer accounts for 9.7% of all cancers and incidence rates have been increasing. Most cancers of the liver, mouth, and

esophagus occur in developing countries and are closely associated either with viral infection or with certain unhealthy lifestyles.

In 2005, cancer killed approximately 600,000 Americans, making it the second most common cause of death in the US. If these current trends continue, 1 out of every 4 males will die of cancer, as will 1 out of every 5 females. Despite decades of intense research efforts, no drugs have been discovered with the ability to cure cancer. The disease has proven to be complex and it is not realistic to believe that it can be eradicated in the near future. However, enough is already known about cancer development and progression to recommend reasonable and effective measures to prevent exposure to identified risk factors, limit the onset of the disease, delay or reverse its development, and reduce relapse. If the general public embraced the available strategies to prevent cancer initiation, the public burden of the cost of treatment of cancer patients would be greatly reduced. Great strides towards this goal are being made in the field of cancer chemoprevention. Chemoprevention involves the use of specific agents to block or delay the process of carcinogenesis, thereby preventing the development of invasive cancer. Chemopreventive measures are especially appropriate for individuals that are at a high risk of developing cancer and for those predisposed to particularly aggressive or untreatable cancer types.

1.1. Cancer

Cancer is a progressive disease that develops in distinct stages (initiation, promotion, and progression) that are separated by long periods of latency. Figure 1A shows a hypothetical timeline of the development of untreated breast cancer. The first stage, initiation, may occur decades before an individual is clinically diagnosed with cancer. During initiation, mutations occur that predispose a cell to become tumorigenic. Some of these mutation events are preventable, some may be caused by inherited genomic instability, and others are due to free radical damage caused by metabolic by-products. Likely sites of primary mutations are within genes that activate oncogenes or silence tumor suppressor genes. Over time, subsequent mutations in multiple genes cause repetitive cycles of proliferation, selection, and clonal expansion that ultimately lead to the second stage, promotion.

During promotion, sustained angiogenesis occurs at the site of an early-stage tumor composed of cells that have acquired the ability to evade apoptosis. Additional mutation events may shorten the amount of time spend in this stage. The third stage, progression, occurs when the tumor becomes malignant and metastasizes to new regions of the body. Many cancers are not diagnosed until this final stage, at which point it becomes a very difficult and expensive disease to treat, often requiring surgery in combination with toxic doses of expensive chemotherapeutic drugs and radiotherapy. Without treatment, the spread of secondary tumors throughout the body may ultimately cause death due to organ failure.

The sequential accumulation of genetic and molecular alterations over a period of many years prior to the onset of invasive cancer provides a large window of opportunity for cancer chemoprevention. The transition from one cancer stage to the next can be stimulated or prevented by certain factors. Each individual has a unique cancer risk

profile that is determined by genetic and epigenetic factors that cause genomic instability. Once a cancer risk profile is evaluated for an individual, personalized recommendations can then be made for appropriate preventive measures that are available to prevent or reverse the carcinogenic process.

Figure 1B shows how a person predisposed to breast cancer may prevent disease onset by actively practicing chemoprevention. In this example, genetic profiling at birth identifies a *BRCA1* mutation, indicating a predisposition for breast cancer development. Armed with this knowledge, this person adopts a healthy lifestyle and actively avoids carcinogen exposure. Doctors preemptively screen this individual for early signs of breast cancer starting at 20 years old and prescribe chemopreventive drugs. When such precautions are taken, it is possible for breast cancer to be avoided entirely or, in the worst case, detected as such an early stage that prompt therapy would practically ensure complete remission.

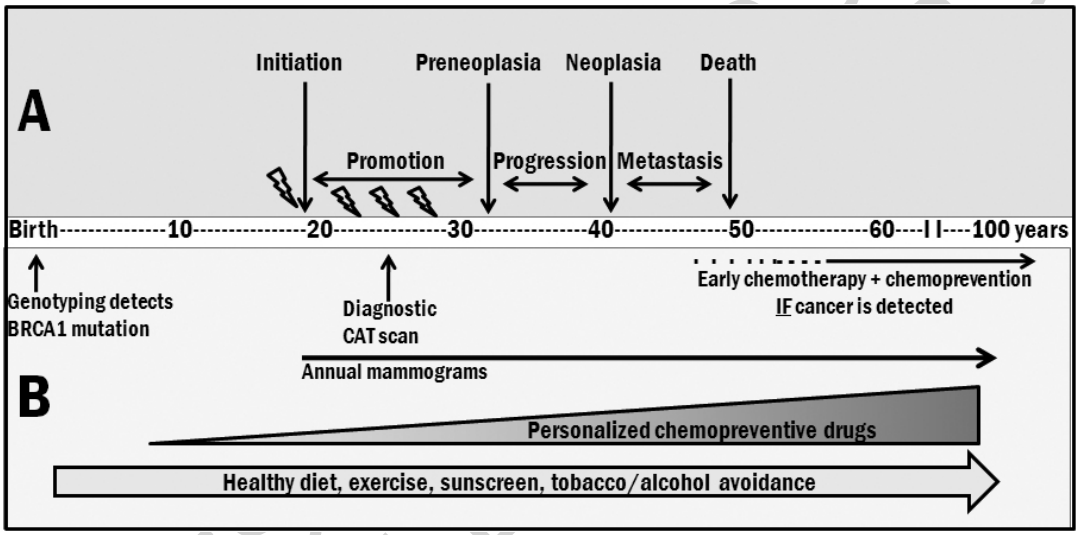

Figure 1. Hypothetical timeline of breast cancer progression in the absence (A) or presence (B) of active chemoprevention. Lightning bolts indicate oncogenic mutation events.

1.2. Cancer Risk Factors

Every human being is at risk of developing cancer at some point during their lives. It was first realized over a century ago that certain occupational hazards put people at an increased risk. In 1907, it was documented that sailors had a higher rate of skin cancer, which was linked to sunlight exposure. In 1930, benzo(*a*)pyrene was isolated from coal tar and determined to cause lung cancer in chimney sweeps. Over time, an increasing number of environmental hazards have been linked to mutational events that trigger cancer initiation. Table 1 provides a classification of some carcinogenic compounds. Many of these compounds exist in nature, such as aflatoxins. Aflatoxins, some of the most carcinogenic substances known, are naturally produced by many species of fungi. Others carcinogens are concentrated in products such as cigarettes (benzene, polycyclic aromatic hydrocarbons, formaldehyde, arsenic, and cadmium).

Alkylating Agents	Hydrazines
α-Halo ethers	Hydrazine and hydrazine salts
Bis(chloromethyl) ether	1,2-Diethyl hydrazine
Methyl chloromethyl ether	1,1-Dimethyl hydrazine
Sulfonates	
1,4-Butanediol dimethylsulfonate (myleran)	*N*-Nitroso Coumpounds
Diethyl sulfate	*N*-Nitrosodimethylamine
Dimethyl sulfate	*N*-Nitroso-*N*-alkyureas
Ethyl methanesulfonate	
Methyl trifluoromethanesulfonate	Aromatic Amines
Epoxides	4-Aminobiphenyl
Ethylene oxide	Benzidine (4,4'-diaminobiphenyl)
Epichlorohydrin	α-Napthylamine
Propylene oxide	β-Napthylamine
Azridines	Aniline
Ethylenimine	2,4-Diaminotoluene
2-methylaziridine	*o*-Toluidine
Diazo, azo, and azoxy compounds	
4-methylaminoazobenzene	Aromatic Hydrocarbons
Electrophylic alkenes and alkynes	Benzene
Acrylonitrile	Benz[a]anthracene
Acrolein	Benzo[a]pyrene
Ethyl acrylate	
	Natural Products (including antitumor drugs)
Acylating Agents	Adiramycin
β-Propiolactone	Aflatoxins
β-Butyrolactone	Progesterone
Dimethylcarbamyl chloride	
	Miscellaneous Organic Compounds
Organohalogen Compounds	Formaldehyde gas
Carbon tetrachloride	Acetaldehyde
Chloroform	1,4-Dioxane
1,2-Dibromoethane	Urethane (ethyl carbamate)
1,4-Dichlorobenzene	Hexamethylphosphoramide
1,2-Dichloroethane	Styrene
Hexachlorobenzene	
Methyl iodide	Heavy Metals
Mustard gas (bis(2-chloroethyl)sulfide)	Arsenic and certain As compounds
Tetrachloroethylene	Beryllium and certain Be compounds
Trichloroethylene	Cadmium and certain Cd compounds
2,4,6-Trichlorophenol	Chromium and certain Cr compounds
Vinyl chloride	Lead and certain Pb compounds
	Nickel and certain Ni compounds
	Selenium sulfide

Table 1. Classes of carcinogenic compounds (modified from the Prudent Practices in the Laboratory: Handling and Disposal of Chemicals; National Academy Press, Washington, D.C., 1995).

Many of the risk factors associated with cancer can be eliminated by simple lifestyle changes. The adoption of a healthy lifestyle that incorporates exercise and a diet rich in fruits and vegetables is advised for the prevention of many diseases, including cancer. Evidence suggests that one third of the cancer deaths that occur in the US each year can be attributed to diet and physical activity habits, with another third attributable to cigarette smoking. With regular exercise and medical care, the elimination of obesity and tobacco use, and limited red meat and increased fruit and vegetable consumption, it is predicted that 70% of cancers are preventable. Another preventable cause of certain

cancers are infectious agents, such as hepatitis B and C in liver cancer, Epstein-Barr virus in nasopharyngeal cancer and specific lymphomas, HPV in cervical cancer, and *Helicobacter pylori* in gastric cancer. Additional preventable risk factors that exist in developing countries include a lack of healthcare, limited access to a healthy diet and clean water, and unclean and stressful living and working conditions.

It is estimated that 10% of all cancers are caused by inherited mutations. Mutations in the adenomatous polyposis coli (*APC)* gene, common in the inherited syndrome of familial adenomatous polyposis (FAP), are found in 80% of all colorectal adenomas and carcinomas. Other inherited mutations include the *BRCA1* and *BRCA2* genes in breast cancer and the *hMSH2* gene in colorectal cancer. There is evidence that specific polymorphic forms of DNA repair enzymes, growth factor receptors, protein kinases, or transcription factors predispose individuals to cancer susceptibility. Although these genetic risk factors are not preventable, many of them can be identified by genetic profiling.

Ethnicity also plays a role in the likelihood of developing cancer. African-American men have the highest incidence of prostate cancer in the world. They are 60% more likely than white American men to develop the disease and are twice as likely to die from it, whereas Asian-American men are at the lowest risk for prostate cancer in the US. African-American women develop breast cancer at a lower rate than their white counterparts but they have a higher breast cancer mortality rate. They are twice as likely to have triple-negative tumors, which are aggressive cancers that lack receptors for estrogen, progesterone, and human epidermal growth factor receptor-2 (HER2). Without these receptors, drugs such as tamoxifen, aromatase inhibitors, and trastuzumab are ineffective. Basal-like carcinomas have an even worse prognosis in young African-American women. Therefore, African-Americans should be routinely screened for certain types of cancers and actively take measures to prevent them. For example, there is evidence that the risk of developing basal-like carcinomas can be reduced by breastfeeding and a reduction in abdominal obesity.

A study by the American Cancer Society found that obese individuals have a significantly higher risk of death from cancer than a person of average weight. Obese men had a five-fold higher risk for liver cancer while obese women had a six-fold higher risk for uterine cancer. Several factors are believed to contribute. Obese individuals tend to have higher levels of insulin-like growth factor (IGF-1), which exhibits antiapoptotic activity. Adipose tissue releases high levels of inflammatory cytokines that may stimulate the growth of cancer cells. Obese individuals are advised to perform regular and moderate exercise, which controls weight, lowers IGF-1 and cytokine levels, and has been shown to reduce the risk of colon cancer by 30%. Blood estrogen levels are also reduced by regular exercise, which may protect against breast cancer.

Although every individual is at some risk for developing cancer, many risk factors are only serious concerns when present in combination. It is important that cancer risk profiles are developed for each individual in order to recommend personalized cancer prevention strategies. Potential environmental carcinogens that could have dramatic effects on cancer incidence should be especially avoided by high risk individuals. For

example, a high intake of dairy products has been suggested to increase the risk of prostate cancer. Diets rich in red meat and animal fat are associated with an increased risk of colorectal cancer. Cooking red meat at high temperatures generates mutagenic heterocyclic amines (HCA). Bisphenol A, a xenoestrogen found in many plastics used for food storage, has been linked to a higher risk of breast and prostate cancers. Individuals that have been treated for cancer are at risk of recurrence. Clearly, individuals with the highest risk for cancer would benefit the most from chemopreventive measures. In addition, individuals at high risk would be more likely to accept limited side-effects that could result from chemopreventive treatment strategies.

1.3. Cancer Prevention

Cancer prevention strategies can be separated into primary and secondary prevention. Primary cancer prevention involves making lifestyle changes to prevent cancer from initiating. Secondary cancer prevention involves preventing or reversing the progression of an established cancer. Chemoprevention can be used with either strategy. Chemoprevention focuses on the development of pharmacological, biological, and nutritional interventions to prevent, reverse, or delay carcinogenesis. The field of cancer chemoprevention began in 1966 when Lee Wattenberg demonstrated that compounds associated with fruits and vegetables (indoles and isothiocyanates) could prevent cancer development in an animal model. He classified chemopreventive agents into three categories based on their underlying mechanisms of action: inhibitors of carcinogen formation, blocking (antiinitiation) agents, and suppressing (antiproliferation/antiprogression) agents. Ten years later, the term “chemoprevention” was first coined by Michael Sporn.

The cornerstone of primary cancer prevention is to implement lifestyle changes. The following recommendations should be followed by all individuals to limit the risk of cancer development:

- Consume a low fat (less than 30% of total calories/day) and high fiber (20-30 g/day) diet.
- Eat 5-9 servings of fruits and vegetables/day.
- Control caloric intake to achieve ideal body weight.
- Do not use tobacco products.
- Avoid excessive sun exposure. Use protective clothing and sunscreen.
- Avoid alcohol (no more than 1 drink/day for females and 2 drinks/day for males).
- Avoid exposure to carcinogens. Monitor living areas for asbestos and radon.
- Practice safe sex.

The most important aspect of secondary cancer prevention is early detection. Testing that is available to detect prostate cancer includes a rectal exam and monitoring levels of prostate specific antigen (PSA). For colon cancer detection, a rectal exam, stool blood test, and sigmoidoscopy or colonoscopy are recommended followed by immediate removal of any detected adenomas. Skin and oral cancers can be detected through routine screening exams. Females should be regularly monitored for breast cancer through self-breast exams as well as mammograms. Cervical cancer can be detected through a pelvic exam or a Pap smear. Many of these screening tests are routinely

practiced in health clinics. Some are only performed in populations over the age of 50 or those with a family history of cancer. If an individual is genetically predisposed to a specific type of cancer, screening and chemoprevention for that cancer type can begin early in life. The costs for some screening techniques are prohibitive, such as magnetic resonance imaging (MRI), which can cost over US$1,000. It is not reasonable to screen the general population using such a technique. Newer technologies, such as genetic and molecular profiling of a blood sample, are rapid and inexpensive. Once optimized, such testing should be performed on all individuals at a young age in order to accurately assess risk profiles based on genetic factors.

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Biographical Sketches

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