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Perspective

Clinical Cancer Research

Cancer Prevention and Interception: A New Era for Chemopreventive Approaches

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Abstract

At several recent, internationally attended scientific meetings, including the *American Association for Cancer Research* (AACR)'s "Shaping the Future of Cancer Prevention: A Roadmap for Integrative Cancer Science and Public Health" summit in Leesburg (VA) and the AACR Annual Meeting in New Orleans, the focus on cancer prevention to reduce cancer-related deaths was extensively discussed with renewed attention and emphasis. Cancer prevention should be actively proposed even to healthy individuals, and not just to individuals with high cancer risk. We discuss evaluation of a high cancer risk versus the relatively low risk for side effects of chemopreventive agents. The concept of cancer interception, which is halting transformed cells from becoming malignant cancers, should be adopted for cancer prevention. Potential prevention/interception actions include adopting healthy life style and avoiding carcinogens, repressing inflammation and pathologic angiogenesis, controlling metabolism, correcting insulin resistance and other metabolic alterations. Current drugs with limited toxicity can be repurposed to reduce cancer incidence. Aspirin is now being recommended for the prevention of colorectal cancer and it prevents other neoplasms as well. Metformin and β-blockers could be valuable for reducing pancreatic and breast cancer onset. On the basis of the evaluation of cancer risk, we here call for personalized approaches for cancer prevention and preventive interception and we envisage a list of measures and potential guidelines for preventive and interceptive strategies to reduce cancer burden. Investment into translational research to bring these approaches into public health policies and in the clinic is urgently needed. *Clin Cancer Res; 22(17); 4322–7. ©2016 AACR.*

Introduction

Chronic noncommunicable diseases, in particular cancer, are becoming increasingly significant causes of death and long-term disability in both developed and developing countries. Extended life expectancy over 80 years is not accompanied by healthy ageing; wellbeing often deteriorates after the age of 70 years. The misleading value of addition of years to life without considering health is known as the "Tithonus mistake." In this Greek legend, Eos (Aurora), the goddess of the dawn, felt in love with Tithonus, a mortal who was destined to die. She therefore asked Zeus to grant him immortal life; however, she forgot to ask for eternal youth. Tithonus, although immortal, aged and became increasingly debilitated and suffered. We are now facing the risk of the emergence of a Tithonus generation, with many "added" years, but of low quality of life, burdened by chronic illnesses. Cancer, cardio/cerebrovascular, neurodegenerative diseases, diabetes, and metabolic syndromes have several common causes. It is, therefore, strategic for a call to action in prevention: we have to "prevent the preventable," including cancer and the other chronic degenerative diseases.

Chemoprevention is the use of natural, synthetic (laboratory-made), or biologic (living source) agents, able to delay, reverse, or inhibit tumor progression [as originally defined by Sporn and Newton (1)]. Chemoprevention represents a crucial tool for avoiding cancer insurgence or cancer progression. An ideal chemopreventive agent is a compound that can be administrated for extended periods of time to phenotypically healthy subjects without the occurrence of significant side effects. More intense chemoprevention strategies, although with a more risk for side effects, are suitable for people with higher risk of developing cancer: those with inherited cancer syndromes or family history of cancer, individuals with extensive carcinogen exposure, and patients with a previous cancer (2, 3). A more recent emerging concept is "cancer interception": this means to actively interrupt a cancer development process at early stages before the tumor presents with clinical relevance (Fig. 1; refs. 4 and 5). Like the prevention approaches applied to other complex disorders such as heart disease, development of cancer can be "intercepted" with pharmacologic agents, slowing the growth of a tumor mass from initially transformed foci.

Implementing prevention of tumors should be a primary approach in oncology leading to a call to action in several recent conferences (6, 7). The *American Association for Cancer Research* (AACR)'s Cancer Prevention Summit, "Shaping the Future of Cancer Prevention: A Roadmap for Integrative Cancer Science and Public Health" held in Leesburg, VA, February 3 to 5, 2016, co-chaired by Ernest T. Hawk and Scott M. Lippman, the ESO World Oncology Forum (WOF) "Stop cancer now: prevent the preventable" and the AACR Annual Meeting in New Orleans have tackled several cancer prevention aspects to identify priorities in research, public policy, and services (6). Besides avoiding carcinogens (of chemical, physical, and biologic origin), adopting an appropriate diet and a correct life style (smoke free, low alcohol consumption, and exercise) could offer a "natural" preventive approach to improve individual health status. A healthy life style not only can prevent several cancers, but also cardiovascular and

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Translational Relevance

Cancer interception, defined as an active way to fight cancer and carcinogenesis at early stages, has recently emerged as a new concept in oncology. Agents with known chemopreventive/angiopreventive activities might be able to "intercept" carcinogenesis before malignant conversion, invasion, and dissemination. Investigation of molecules allowing cancer interception, through modulation of specific molecular pathways in cancer cells or in tumor supporting host components, is urgently needed. Cancer prevention should be actively and broadly applied, with personalized prevention and precision interception approaches based on the evaluation of cancer risk versus the risk for side effects of chemopreventive or interceptive agents. We suggest a summary of actions that can be envisaged both at prevention or "interception" level, which may reduce the increasing burden of cancer due to extended lifespan.

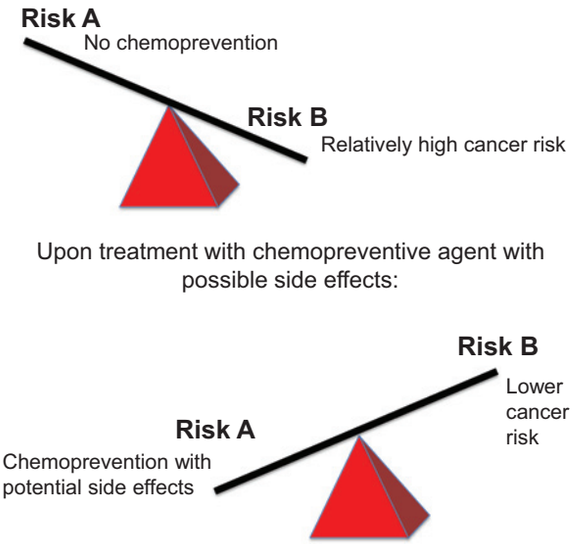

Figure 2.
Risk versus risk evaluation. All individuals are at risk for developing cancer; thus, chemoprevention approaches are needed even in low-risk populations. As risk level increases, there is greater tolerance of collateral effects to obtain greater benefit in cancer prevention.

cerebrovascular disease, metabolic syndrome, and type II diabetes. Drug repurposing has also been debated as an effective option. Existing drugs such as aspirin, and other NSAIDs, metformin, and tamoxifen have shown to reduce cancer risk in observational studies or clinical trials with relatively low-risk profiles (8–15). Very recently, the U.S. preventive service task force found adequate evidence that aspirin reduces the incidence of colorectal cancer in adults after 10 years of use, recommending taking low-dose aspirin for the primary prevention of cardiovascular disease and colorectal cancer in adults ages 50 to 59 years who have a 10% or greater 10-year cardiovascular disease risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years (16). Preclinical and clinical evidence indicate that β-blockers are promising approaches to prevent cancer (17, 18). We can also envisage development of other efficient cancer-preventive drugs with minimal toxicity. Discovering more effective and affordable derivatives from natural and dietary sources with little or no side effects could represent a complementary strategy in cancer prevention. Several natural phytochemicals have been chemically modified to improve pharmacokinetics and customer acceptance, an example of this is aspirin itself. The appeal of using drugs with well-described mechanisms of action and safety profiles has led to renewed interest in repurposing such agents for cancer prevention (14).

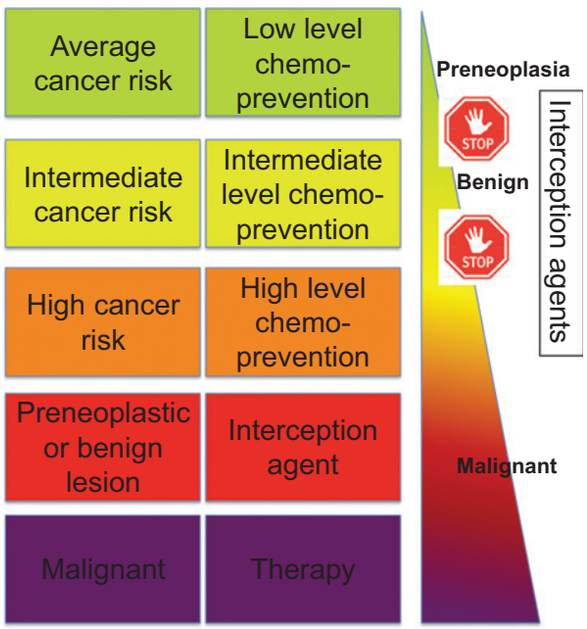

Figure 1.
Cancer prevention in the general population at "lowest" risk of developing cancer must be with low toxicity interventions. As cancer risk level increases, more efficacious drugs with higher side effects are warranted. Interception approaches can be used with preneoplastic and even benign lesions.

An important question to ask is: "Who is really "healthy"? Approximately 1 in 3 women, and 1 in 2 males, will have a cancer diagnosed in their lifetime (4, 19). Approximately 1 in 4 will die from a cancer. Preneoplastic lesions and malignant cancer can be present in phenotypically normal people with no symptoms. Healthy life style and caloric balance accompanied by exercise should be the general policy to apply from childhood on, but a certain degree of cancer chemoprevention can and must be applied in phenotypically normal people. This is based on the low risk for side effects connected to use of selected cancer chemoprevention drugs, versus the higher risk to become affected by a serious and deadly disease (3). Here we suggest a "risk versus risk" model (2), where we weigh the risks of undesired effects associated with a specific chemopreventive molecule versus its potential preventive effect in decreasing the risk of getting cancer (Fig. 2). As the individual cancer risk increases (due to genetic, metabolic, carcinogenic behaviors, or exposure, as listed in Table 1), a person may undertake cancer

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Table 1. A potential "to do" list in cancer prevention and preventive interception

	Prevention	Interception
1	Do not smoke.	-Quit smoking (often requires a multitask, structured intervention). Take low-dose aspirin or other chemoprevention measures.
2	Avoid chemical carcinogens in the environment and at work place. Make your environment smoke free.	-Fight for your rights: receive attention if you have been exposed to asbestos, PAH, and other carcinogens in the work place or environment.
3	Avoid physical carcinogens, example: overexposure to sunlight and other sources of UV.	-Do periodic screening for premalignant skin lesions.
4	Avoid biologic carcinogens. Vaccines for virally induced cancer (example: HPV).	-Antibiotics for bacterial-associated cancer (example: *Helicobacter pylori*). Do periodic screening for premalignant lesions in the uterine cervix
5	Avoid overweight and obesity, eat properly	-Lose weight, change dietary habits
6	Avoid foods that might be potentially carcinogenic	-Limit salt, red and processed meat; avoid soft drinks
7	Limit alcohol. Do not overcome 1 glass per day in women and 2 glasses in men	-Cut back or quit drinking
8	Keep your gut flora and your microbiota "healthy"	-Restore your intestinal flora with a healthy life style and diet. Near future: dietary supplements containing "healthy" microbiome components
9	Avoid a sedentary lifestyle, be physically active	-Get on an exercise program
10	Control risk factors: inflammation, metabolic syndrome	-With low level risk conditions, take some chemopreventive strategies with few side effects: aspirin, metformin, flavonoids, curcumin
11	Prefer breast feeding your children rather than using formula	-Monitor changes in your body (e.g., breast lumps).
12	If there are familial cases of cancer, get genetic counseling and do relevant chemoprevention for the cancers at risk.	-Do periodic screening for premalignant lesions for breast, colon and prostate. With high risk consider a chemoprevention trial. Near future: precision prevention.

Abbreviations: PAH, polycyclic aromatic hydrocarbons; UV, ultraviolet light.

prevention approaches associated with higher risk for side effects. Combinations of chemoprevention drugs should also be considered (3, 20). We are moving toward an era of personalized prevention and interception where several opportunities for stratified risk assessment can lead to effective risk reduction at individual level (21).

To reduce mortality, we must reduce incidence. The most recent statement of Michael Sporn presented in a keynote lecture during the ESO World Oncology Forum (WOF) "Stop cancer now: prevent the preventable" (7) is that of "incidence drives mortality." More cancers means more deaths due to cancer, and this concept separates early diagnosis, which can be life-saving in younger individuals but can lead to "overdiagnosis" in particular in the elderly, from cancer prevention, that is avoiding or delaying a tumor insurgence.

Those opposing the adoption of therapeutic cancer prevention, mostly impute their choice to the scarcity of mortality data, failing to appreciate two key issues: (i) the current lack of power of most prevention trials to show survival benefit at current lengths of follow-up (see the remarkable chemopreventive effect of aspirin after 5–10 years; ref. 22) and (ii) the substantial impact of just reducing cancer incidence, which is difficult to "measure." Preventing cancer incidence not only has potential individual benefits, such as circumventing negative effects on quality of life and avoiding treatments with substantial morbidity, but will also have a positive impact on healthcare systems in terms of improved allocation of resources. Actions leading to a prevention or delay of cancer onset will have a greater influence on mortality than early diagnosis. Leslie Ford quoted Thomas Adams (1618) in the WOF forum (7): "He is a better physician that keeps diseases off us, than he that cures them being on us; prevention is so much better than healing because it saves the labor of being sick."

A provocative article in early 2015 implied that the majority of cancers are due to chance, rather than predictable causes (23). The conclusions of this article were highly criticized by many in the scientific community (24–30). There are a number of "risk factors," many of which are unchangeable, including age, gender, inherited genes, personal, and family history of disease. Other risk factors are actionable and we must avoid or treat them (for an update, see ref. 29).

Although there is a stochastic factor in cell transformation and uncontrolled neoplastic proliferation, a substantial number of tumors could be halted. On the basis of the increasing attention and scientific developments in the prevention field in the precision medicine era (11, 20, 31), in Table 1 we summarize in a list potential "to do" items to stop cancer before it starts or, in second instance, before it becomes fatal, in a prevention or interception setting.

Key points represented in the table are discussed below:

- Tobacco kills around 6 million people each year; of these more than 600,000 are the result of nonsmokers being exposed to second-hand smoke (32). Lung cancer is the most common neoplasm worldwide contributing 13% of the total number of new cases diagnosed. Cancers caused by tobacco use could almost be totally prevented; however, this is easier said than done. Chemoprevention among tobacco users could be applied (33); for example, long-term use of aspirin has been found to substantially reduce deaths due to adenocarcinomas of the lung, esophagus, and colorectum (22), all enhanced in smokers. We feel that primary care physicians should ask smokers and former smokers who are not at increased risk for bleeding to take low-dose aspirin.
- Neoplasms associated to infectious agents, such as cervical and certain head and neck cancers (human papillomavirus virus, HPV), hepatocarcinoma (hepatitis B or hepatitis C virus), and gastric cancer (Helicobacter pylori) can be restrained though immunoprevention (20). The strategies to be used can be: avoiding infection through behavioral changes and protection, preventive vaccinations where possible, or antibiotic or antiviral treatment of the infectious agents. Over the next decade we will see the effect on cancer incidence of the HPV vaccines and new therapies for hepatitis C infection.
- Basal cell carcinoma has a high incidence (although rarely fatal), whereas melanoma is highly curable when detected and

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removed early, it can be fatal when it progresses. Limiting exposure to ultraviolet light could reduce the number of melanomas and other skin cancer cases. This should be accompanied by dietary sources or vitamin D supplementation, which has been recently associated with a better prognosis in several tumors (34–36).

- More than 33% of all cancer-related deaths worldwide (more than 7 million) can be prevented with a correct diet, exercise, and life style changes (37). One-third of cancers in developed countries are related to obesity or overweight, unhealthy, or poor nutrition. The increase of economic development has been reported to correlate with the incidence of some types of cancer, including lung, colon, breast, and prostate cancer. Breast cancer is the second most common cancer, and the first in women, with nearly 1.7 million new cases. Colorectal cancer is the third most common cancer with nearly 1.4 million new cases in 2012. Changes in the world food economy are reflected in shifting dietary patterns; for example, there is an increased consumption of energy-dense diets rich in fat, mainly saturated fat, high in animal proteins, and low in unrefined carbohydrates and vitamins. These high-energy dietary patterns are often associated with reduced energy consumption and a sedentary lifestyle. More attention is now devoted to researching the benefits of exercise not only for general health, but also for prevention of noncommunicable diseases, including cancer (38, 39).
- Experts who have attended the latest WOF "Prevent the Preventable" (7) as well as the AACR Prevention Summit (6) and AACR annual meeting, discussed on the role of microbiota and immune system. Increasing evidence suggests that our microbiota and the associated immune response are linked to increased or decreased risk for cancer (40). It is clear that the gut microbiota is also associated with our diet. In addition to health benefits associated with the microbiome, a balanced diet is a strongly recommended not only for prevention but also in the presence of overt oncologic disease: an increasing number of studies correlate the diet regimen to a greater response to chemotherapy: in the Clinical Trials web site of NIH several hundred clinical studies are reported that correlate diet with chemotherapy efficacy.
- In the context of chemoprevention, the concept of targeting host factors and the tumor microenvironment (2) before the potential cancer cell becomes transformed has only recently been highlighted. Angioprevention (13), defined as the potential to block tumor growth by inhibiting changes in the microenvironment, inflammation, and the neoangiogenic process, is suitable to maintain transformed cells as small, indolent hyperplastic foci. We would now propose the concept of "angiogenesis interception" as a means for keeping precancerous lesions indolent for as long as possible. Repression of inflammation (41) is also a key point, as demonstrated by several epidemiologic studies showing, as stated above, that a bland anti-inflammatory agent, aspirin, can reduce incidence of many types of carcinomas (42). Because cancer is a disease of the body, and not just the transformed cell, epidemiology reveals important issues of gender and socioeconomic health disparities. Ethnic issues as well as social, educational, and economical have a strong impact, and this was one focus of the AACR prevention Summit (6) and AACR annual meeting.
- Molecular tools can change perspectives in cancer research. U.S. insurance companies are proposing to offer coverage for a whole genome and proteome molecular diagnostic platform to diagnose molecular alterations in cancer and identify personalized therapeutic regimens. The advantage of application of precision medicine in the oncology setting has emerged from research and represents a significant milestone in the war against cancer. We should be able to think of personal precision prevention and interception as well. We believe that insurance companies as well as public health care would be interested in investment in precision prevention and interception, given the substantially lower cost and lower impact on the individual's life. Future directions in personalized prevention include genetic, epigenetic, proteomics, metabolomics, microbiomics, immunologic, and other biomarker assays to identify pathways that are associated with cancer initiation and development.

Cancer mortality accounts for nearly 25% of all deaths in the WHO European Region, is the second leading cause of mortality overall with 14.1 million new cancer cases worldwide in 2012, and is now the foremost cause of death in the United States in the 40–80 age range (19). Cancer will soon be the number one killer in the world, if we do not act now. This number of deaths due to cancer is predicted to increase to 24 million by 2035 (43), almost doubling the cancer burden. With the growing costs of new cancer drug treatments, this is unsustainable even for the most well-developed countries (44).

Faced with this potential health and economic catastrophe, we must invest more in cancer prevention research. In January 2016, President Barack Obama and Vice President Joe Biden pleaded for a unified endeavor to cure cancer and announced the creation of a "national cancer moonshot"; the speech of Biden closing the AACR Annual Meeting in Orlando indicated a clear commitment to support a collective fight to end cancer. In our opinion, a "moonshot" going toward cancer prevention, as suggested by the AACR Summit (6), is highly desirable and absolutely necessary. In spite of all the evidence that cancer can be prevented or intercepted early on, the research investment for cancer prevention represents less than 3% of all cancer funding. Given the fact that cancer is, for a considerable extent, a preventable disease, the International Agency for Research on Cancer (IARC), and the World Health Organization (WHO), have launched in 2014 a new European Code Against Cancer with the participation of the European Commission. The Code provides 12 ways to help people adopt healthier lifestyles and to boost cancer prevention across Europe (45). Avoiding risk factors, having a healthy life style, and taking compounds inhibiting cancer insurgence and to intercept progression after initiation, cancer risk can be substantially decreased. However, we can do much more with the clinical application of chemoprevention, angioprevention, and cancer interception. Public and private structures should devote their attention and funding toward cancer prevention and interception, avoiding the predicted significant rise in cancer morbidity and death if we do not act soon.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: A. Albini, A. DeCensi, F. Cavalli, A. Costa
Development of methodology: A. Albini, A. Costa

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Albini
Writing, review, and/or revision of the manuscript: A. Albini, A. DeCensi, F. Cavalli, A. Costa
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): F. Cavalli
Study supervision: A. Albini, A. DeCensi

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