CAN FOODS COMBAT CANCER?

Arresting malignancies with diet

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Top-line summary

Epidemiologic studies have consistently linked abundant consumption of plant-based foods to a significant reduction in the risk of developing several cancers. This chemopreventive effect is related to the high content in these foods of a variety of phytochemicals that interfere with several cellular processes involved in the progression of cancer, by mechanisms similar to those of molecularly targeted synthetic drugs. Including foods containing the greatest amounts of these anticancer phytochemicals in the daily diet thus represents a promising approach to preventing the development of cancer as well as for reducing disease recurrence and increasing survival in cancer patients.

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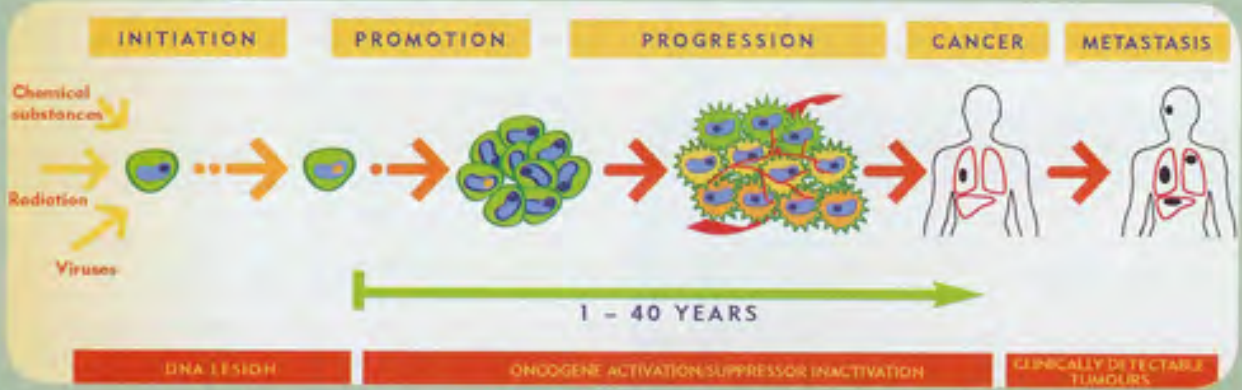
Dietary factors may account for roughly 30% of cancer deaths, similar to the impact of smoking.[1] Large variations in rates of specific cancers among countries, as well as the spectacular changes observed in the cancer incidence rates in migrating populations, imply a close relationship between diet and cancer.[1,2]

Over 200 ecological, case-control and cohort epidemiological studies have consistently associated increased consumption of foods from plant origin, such as fruits, vegetables, whole grains, legumes, nuts, seeds and tea, with a decreased risk for a wide variety of cancers, particularly those of epithelial origin.[3] For example, several studies have shown that up to 70% of gastrointestinal tract cancers could be prevented by increasing the amount of plant-based foods in the diet.[4] Such observations suggest that these foods represent an essential source of molecules with chemopreventive properties — a hypothesis strengthened by a large quantity of experimental data from cellular and animal models in which molecules isolated from various food sources have been found to induce tumour cell death as well as to reverse the development of several cancers.[5,6]

FIGURE 1. The long latency of tumour development



For many years, even decades, cancerous cells remain very vulnerable: only a few of them will succeed in reaching the malignant stage. This vulnerability makes it possible to intervene and interfere at several stages of tumour development, thus preventing the onset of the disease.
Source: Adapted from Béliveau, R. and Gingras, D. *Foods That Fight Cancer: Preventing Cancer Through Diet.* Toronto: McClelland & Stewart Ltd, 2006.

INTERFERENCE WITH GROWTH OF EXISTING MICROTUMOURS

Carcinogenesis is a rather slow process: over a long period of time precancerous cells mutate key genes involved in growth control, acquire resistance to apoptosis and trigger angiogenesis in order to grow and invade the host tissues. During this process, which may take place over several years or even several decades (**Figure 1**, page 31), tumour cells are vulnerable — they are more susceptible to anticancer agents than are mature tumours. Several characteristics contribute to the vulnerability of these microtumours:

- low genetic diversity reduces their resistance to anticancer molecules
- lack of an appropriate blood vessel supply restricts their growth and dissemination as metastases
- their relatively small number of malignant cells increases the chance of eradicating the tumour foci

Preventing cancer by interfering with the development of precancerous cells is extremely important since the formation of tumours is a random event that occurs relatively often over the life of an individual. The tissues of healthy persons contain a significant number of these latent tumours; for example, as shown in **Table 1**, pathological studies performed on individuals deceased from causes not related to cancer have shown that over 30% to 50% of women aged 40–50 years old had premalignant microscopic breast tumours, while 40% of similarly-aged men had precancerous cells in their prostate gland.[8] Even more strikingly, virtually every individual (98%) has small, latent tumours in the thyroid, although these tumours are only very rarely detected clinically.[8] It thus appears that the spontaneous formation of small tumours is a frequent event but that in most cases our natural defense mechanisms tightly control growth, maintaining them in a microscopic and harmless state.[9] The appearance of a clinically detectable tumour and life-threatening cancer thus implies that the small tumours have overwhelmed the defensive barriers and acquired the ability to grow and invade the host tissues. Thus, preventing the development of cancer by continuously attacking latent tumours could represent a very promising approach to reducing the cancer burden in society.

ANTICANCER PROPERTIES OF PHYTOCHEMICALS

Growing evidence indicates that that dietary-derived anticancer molecules interfere with cancer development through their inhibitory effect on the process of carcinogenesis. The chemopreventive properties of plant-based foods arise from their high content of phytochemicals, molecules that are endowed with potent anticancer properties. A daily intake of a mixture of fruits, vegetables and drinks such as green tea and red wine contains about 1 to 2 g of these phytochemicals, and entails ingestion of about 5000 to 10,000 different compounds.[10] Although all plant-based foods contain phytochemicals, the quantity and activity varies greatly from one food to another. This is a very important concept when attempting to explain the anticancer properties of plant-based foods since many of the phytochemicals showing the highest levels of cancer prevention activity are present only in a few specific foods, as shown in **Figure 2**. The isoflavones in soybeans, the resveratrol in grapes, the curcumin in turmeric, the isothiocyanates and indoles in broccoli and the catechins in green tea are all anticancer molecules that each occur naturally in a very select group of foods. Thus, while the intake of foods from plant origin is crucial for the prevention of cancer, the development of effective dietary-derived chemopreventive strategies requires taking into account the phytochemical content of particular foods.

The phytochemicals in plant-based foods target several key events involved in the development of cancer. **Table 2** shows several phytochemicals derived from dietary sources that are known to interfere with tumour promotion and progression. Numerous laboratory, animal and human studies have shown that these molecules restrict cancer cell growth by a number of mechanisms identical to those through which synthetic molecularly targeted chemotherapeutic agents exert their activity.[9,10] This has led to the hypothesis that phytochemicals could serve as alternatives to chemically-designed antineoplastic

TABLE 1. Spontaneous formation of tumours[8]

Organ	percent detected at autopsy	percent detected clinically
breast tumours in women age 40–50 years	33%	1%
prostate tumours in men aged 40–50 years	40%	2%
thyroid tumours in adults aged 50–70 years	98% (estimate)	0.1%

FIGURE 2. Major anticancer phytochemicals derived from the diet

Source: Adapted from Béliveau, R. and Gingras, D. *Foods That Fight Cancer: Preventing Cancer Through Diet*. Toronto: McClelland & Stewart Ltd, 2006.

agents, as constituents of therapeutic drug combinations or as adjuvant treatments.[1] Among the biological activities associated with phytochemicals, intensive research over the last few years has identified a number of key mechanisms by which these molecules interfere with tumour progression.

Defense against DNA-damaging events

A number of factors can induce damage to DNA and initiate cancer. Free radicals, environmental or diet-associated chemicals, UV irradiation and certain viruses all have the capacity to cause significant damage to the cells that may ultimately lead to cancer.[14] Once they enter the body, most if not all environmental carcinogens are metabolized by the so-called Phase I metabolism, a group of biochemical reactions primarily catalyzed by the cytochrome P450 enzymes.[14] These reactions often convert procarcinogens into highly reactive chemical intermediates that can bind and alter the function of key cellular macromolecules such as DNA. A second group, the Phase II enzymes, conjugate these reactive intermediates with a number of endogenous factors, resulting in the production of water-soluble products that can be excreted by the body.[15]

Considerable evidence indicates that several chemopreventive phytochemicals elicit their anticancer effects by modulating these enzymatic systems, either by reducing their carcinogenic potential (through inhibition of the Phase I enzymes) or by increasing the excretion of the carcinogens, through increase of Phase II enzyme activities.[16] The most well-documented example of such a mechanism of action is the remarkable anticarcinogenic activity of isothiocyanates, compounds plentiful in cruciferous vegetables. Isothiocyanates inhibit tumourigenesis induced by a wide variety of chemical carcinogens, an effect related to their reduction of genetic damage by inhibiting Phase I enzymes and activating Phase II enzymes.[16,17]

TABLE 2. Pharmacological targets of dietary-derived phytochemicals[5,6,32]

Target	examples	best food sources
Inhibition		
tumour invasion and metastasis	epigallocatechin gallate	green tea
growth factor receptor-mediated signal transduction	delphinidin ellagic acid	blueberries, raspberries, nuts
inflammatory enzymes (e.g. COX2)	curcumin resveratrol	turmeric grapes
transcription factor activity (e.g. NFκB, AP1)	curcumin resveratrol	turmeric grapes
multidrug resistance	diallyl sulfide	garlic
angiogenesis	epigallocatechin gallate	green tea
estrogenic actions	genistein	soy
metabolic activation of carcinogens via Phase I enzymes	indole-3-carbinol	cabbage
Activation		
tumour cell apoptosis	phenethyl isothiocyanate	cabbage, watercress
immune system function	lentinan	shiitake
detoxification via Phase II enzymes	sulforaphane	broccoli

A number of phytochemicals that modulate the host's defense mechanism against DNA-damaging molecules are also found in several other fruits and vegetables, including garlic and related members of the allium family and citrus fruits.

Cytotoxicity against tumour cells

In vitro experimental systems using cells isolated from various human tumours are being widely used to study the anticancer properties of diet-derived phytochemicals. These studies have identified several molecules that inhibit tumour growth by compromising tumour cell survival, leading to apoptosis. Of particular interest are the strong proapoptotic activity of several isothiocyanates from cruciferous vegetables, such as phenethyl isothiocyanate (PEITC),[18] and the potent cytotoxic effect of curcumin and resveratrol against several tumour cell lines.[19,20] How these cytotoxic properties contribute to the chemopreventive effects of these phytochemicals remains unclear — possibly by preventing the growth of cells that have already acquired an initiated phenotype, i.e. precancerous cells.

Antiangiogenic properties

Tumour angiogenesis — the process by which tumour cells stimulate the formation of a new blood vessel network necessary for their growth and progression — plays an essential role in the development of cancer.[21] Interestingly, many phytochemicals have recently been shown to possess strong antiangiogenic activities.[22] For example, a polyphenol abundant in green tea, epigallocatechin gallate (EGCG), was found to potently inhibit a receptor (VEGFR-2) that plays an essential role in angiogenesis.[23,24] This inhibitory effect occurs at low concentrations of EGCG, and recent observational evidence shows that moderate green tea consumption may be associated with clear clinical benefits in some patients with chronic lymphocytic leukemia (CLL).[25] An antiangiogenic effect is not restricted to green tea catechins since potent VEGFR inhibitory activity was also recently identified for delphinidin, an abundant blueberry anthocyanidin.[26] Similarly, ellagic acid, a phenolic acid plentiful in some fruits including raspberries and strawberries, also interferes with VEGFR-2 and strongly inhibits the activity of another receptor found in perivascular cells, PDGFR.[27] The combined inhibitory effect of these receptor tyrosine kinases that are essential for angiogeneses leads to the inhibition of angiogenesis in both in vitro and in vivo assays.[5] As discussed above, increasing evidence suggests that the antiangiogenic effects of these phytochemicals may play a crucial role in the chemopreventive effect of these molecules by preventing latent tumours from growing and reaching a lethal stage.

Increase in intestinal absorption and inhibition of hepatic metabolism

Another manner by which dietary-derived phytochemicals may influence tumour progression involves an indirect mechanism whereby a given molecule

with little intrinsic anticancer action may greatly influence the bioavailability of another phytochemical with potent anticancer activity. The best known example of this indirect synergistic mechanism is the effect of piperine, a component of black pepper, on the serum concentration of curcumin. In the absence of piperine, curcumin is poorly absorbed and rapidly excreted, but when co-administered with piperine the absorption of curcumin is increased about a thousand-fold,[27] an effect related to the inhibition of glucuronidation of the molecule.[28]

Anti-inflammatory effects

It is becoming increasingly clear that inflammatory stimuli sustain the progression of several cancers, including those of the colorectum, breast and lung. The reduction of inflammation by dietary-derived phytochemicals may thus significantly contribute to their chemopreventive properties. Some phytochemicals inhibit inflammation by interfering with various inflammatory cascades, including those originating from the COX2 enzyme and those involving the activation of the NF B transcription factors.[29] Curcumin from turmeric and resveratrol from grapes are the best examples of such dietary-derived modulators of inflammatory responses: these molecules reduce the transcription and the expression of COX2 leading to a decrease in the production of prostaglandins.[11]

ADVANTAGES OF PHYTOCHEMICALS FROM FOOD

Foods are an extremely attractive source of anticancer phytochemicals to counteract the progression of cancer. In several cases, anticancer molecules from foods show therapeutic properties that are analogous to those of synthetic drugs. In contrast to synthetic molecules, however, whose inherent toxicity limits their usage for purposes of prevention, the anticancer molecules present naturally in foods were presumably selected by cultural evolution as being beneficial for health and thus lack secondary harmful effects. This lack of toxicity implies that it is possible to use these molecules on a daily basis to prevent the development of cancer, a "metronomic" approach (i.e. continuous or frequent application of a low-dose treatment) that is increasingly recognized as an efficient way to restrain tumour progression.[32] Finally, dietary-derived phytochemicals interfere with several crucial aspects of tumour progression, and this pleiotropic mechanism of action increases their efficacy against multifactorial diseases such as cancer. The daily intake of foods rich in anticancer molecules may thus be likened to a preventive, non-toxic version of chemotherapy that is harmless to the physiology of normal tissue and that may stop microtumours from attaining a stage having pathological consequences. The adoption of dietary patterns emphasizing abundant consumption of foods from plant origin — fruits and vegetables, whole grains, legumes, nuts, seeds (**Table 3**) — thus represents a vital component of lifestyles to prevent cancer.

TABLE 3. Foods with chemopreventive properties to include in the daily diet

	Daily intake
Brussels sprouts	1/2 cup
Broccoli, cauliflower, cabbage	1/2 cup
Garlic	2 cloves
Onions, shallots	1/2 cup
Spinach, watercress	1/2 cup
Soy (edamame, dry roasted soybeans)	1/2 cup
Freshly ground flax seeds	1 tablespoon
Tomatoe paste	1 tablespoon
Turmeric	1 teaspoon
Black pepper	1/2 teaspoon
Blueberries, raspberries, blackberries	1/2 cup
Dried cranberries	1/2 cup
Grapes	1/2 cup
Dark chocolate (70% cocoa)	40 grams
Citrus fruit juice	1/2 cup
Green tea	3 times 250 ml
Red wine	1 glass

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