

Table 1. Examples of dietary factors or chemopreventive agents that target specific stages of carcinogenesis

Prevention strategy	Examples
Tumor initiation	
Inhibit carcinogen activation	Epigallocatechin gallate (EGCG), selenium, phenyl-isothiocyanate (PEITC), indole-3-carbinol, coumarins, ellagic acid, resveratrol, genistein
Scavenge electrophiles	Ellagic acid, EGCG
Enhance carcinogen detoxification	Oltipraz, diallyl sulfide, PEITC, EGCG, N-acetylcysteine, resveratrol
Enhance DNA repair	Calorie restriction, EGCG, selenium
Tumor promotion/progression	
Scavenge reactive oxygen species	Antioxidants (carotenoids, α -tocopherol, ascorbic acid, EGCG), selenium, calorie restriction
Alter gene expression	Retinoids (all- <i>trans</i> retinoic acid, fenretinide), calorie restriction, monoterpenes (i.e., <i>d</i> -limonene), dehydroepiandrosterone (DHEA), fluasterone, genistein
Decrease inflammation	Nonsteroidal anti-inflammatory drugs, calorie restriction, DHEA, fluasterone, antihistamines
Suppress proliferation	Calorie restriction, difluoromethylornithine, selenium, tamoxifen, DHEA, fluasterone, genistein, retinoids
Induce differentiation	Retinoids, calcium, sodium butyrate
Encourage apoptosis	DHEA, fluasterone, fenretinide, sodium butyrate

metabolism of xenobiotic compounds, as well as by ultraviolet radiation and gamma radiation—can also cause extensive DNA damage. For instance, proto-oncogenes and tumor suppressor genes are normal cellular genes that can be mutated to cause uncontrolled cell growth or other characteristics that increase the probability of neoplastic transformation (11–13).

Metabolic activation of procarcinogens (i.e., carcinogens requiring enzymatic conversion to DNA-reactive intermediates) is generally catalyzed by cytochrome P450 enzymes through oxidation. More than 100 distinct mammalian P450 enzymes have been identified (14). In addition, there are other enzyme systems involved in carcinogen activation such as peroxidases (including the cyclooxygenases, which will be discussed in more detail below) and certain transferases such as N-acetyltransferase and sulfotransferase (15,16). Each of these enzymes provides a potential target for modulating carcinogen activation.

One common feature of the metabolic activation of all procarcinogens is that their ultimate DNA-reactive carcinogenic species are electrophilic (17). In addition, many direct-acting carcinogens damage DNA through electrophilic intermediates (18). Thus, the electrophilicity of the ultimate carcinogenic species serves as a shared intervention target for most chemical carcinogens. The electrophilic metabolites may themselves be ROS and interact as such with DNA (19). Oxygen-free radicals may also be involved in a step required for activation of a procarcinogen, and thus the reactions involved in metabolic activation of carcinogens may release ROS that can in turn attack DNA (19). Thus, directly scavenging DNA-reactive intermediates with antioxidants or other agents that can scavenge electrophiles constitutes a plausible strategy for modulating this early stage of carcinogenesis.

Carcinogen Detoxification

In addition to the carcinogen-activating enzymes, a series of enzymes (the so-called phase II enzymes) detoxify activated carcinogens, thus preventing their binding to DNA. The induction of the glutathione S-transferases (GSTs) is an important response for the detoxification of xenobiotics (20). This class of enzymes couples a number of diverse substrates to glutathione to excrete them from the body. GSTs are segregated into three classes based on their sequence homology and specificity for substrates (21). Other detoxification enzymes include uridine diphosphate-glucuronosyl transferase, quinone reductase, and the epoxide hydrolases (22,23). The efficiency with which these and other enzymes detoxify carcinogens is a critical factor in determining the carcinogenicity of a particular xenobiotic.

DNA Repair Processes

The generation of DNA-reactive intermediates by most chemical carcinogens leads to the production of DNA adducts or other types of damage. As reviewed by Mitchell et al. (24), normal mammalian cells can efficiently remove DNA damage induced by carcinogens. Cells use different strategies to repair DNA damage, depending on the structure of the damage and its location in the genome. For example, small lesions (such as alkylated DNA bases) can be repaired by a mechanism termed base excision repair (25). This process involves removal of the damaged base followed by a “small cut-and-patch” repair involving removal of a few nucleotides. When methylation occurs at either the O⁶ or O⁴ positions of guanine or thymine, the modified bases can be repaired by the direct transfer of the methyl group to a methyl transferase (26). Bulky carcinogen-induced DNA adducts and ultraviolet light photodimers can be repaired through a “large cut-and-patch” mechanism involving a region of approximately 27–29 nucleotides that includes the damaged bases; this is termed nucleotide excision repair (27). The integrity of the genetic information is threatened not only by various environmental exposures but also by errors produced during normal DNA replication, for example, non-Watson-Crick base-pairing and slippage during DNA replication. To correct the errors resulting from such mis-replication, cells have also developed a mismatch repair mechanism (28).

NUTRITIONAL MODULATION AND CHEMOPREVENTION OF TUMOR INITIATION PROCESSES: EXAMPLES

Inhibiting Carcinogen Activation

Fruits, vegetables, herbs, and other foodstuffs (as well as inedible plants) contain numerous chemical constituents known to affect the metabolic activation of chemical carcinogens. Examples of food sources containing agents that decrease carcinogen activation are the cruciferous vegetables, such as cauliflower, broccoli, and cabbage. The crucifers are sources of isothiocyanates, which are known to interfere with the metabolism of nitrosamines. Studies by Chung et al. (29), Hecht (30), Stoner and Mukhtar (31), and Morse et al. (32,33) have shown conclusively that the metabolism and carcinogenicity of the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone are decreased by the administration of phenylisothiocyanate. Extensive structure-activity studies by these