REVIEW ARTICLE

Red Meats and Processed Meat as the Carcinogenic Foods and Phytochemical-chemoprevention

Anna Meiliana[1,2,*], Nurrani Mustika Dewi[2], Andi Wijaya[1,2]

[1]Postgraduate Program in Clinical Pharmacy, Padjadjaran University, Jl. Eijkman No.38, Bandung, Indonesia
[2]Prodia Clinical Laboratory, Jl. Cisangkuy No.2, Bandung, Indonesia

*Corresponding author. E-mail: anna.meiliana@prodia.co.id

Received date: Aug 13, 2019; Revised date: Oct 31, 2019; Accepted date: Nov 1, 2019

Abstract

BACKGROUND: Along with its increased prevalence, in the past decade, cancer had joined the list of chronic debilitating diseases. Nutrition become substantial aspects, due to its time-dependent effect to modulate inflammation thus trigger carcinogenic effects by altering the immune check point. Thus, nutrition contributes to the progression and therapeutic response of cancer, both in human or animal models.

CONTENT: Meat is well favored food with appreciable appealing. Due to its high nutritional values it plays a central role in human development. Meat or meat derivate are important sources of proteins, minerals and vitamins. Their nutritional importance is worth compare to their economic impact but recent publication of WHO has set the social alarm about the relationship between red and/or processed meat consumption and cancer. On the other side, some natural or biologic agents may inhibit or reverse tumor growth. Some phytochemical agents including curcumin, resveratrol, lycopene, folates and tea polyphenols clinically proved to tune the signaling pathways regulating cell proliferation and apoptosis in transformed cells, enhance the host immune system and sensitize malignant cells to cytotoxic agents.

SUMMARY: Recent studies on chemopreventive agents involves a wide range of molecules, natural (plants, fruits and vegetables) or synthetic will provide better insights for cancer early pathogenesis, important end-point biomarker, and finally potential for reducing the burden of cancer.

KEYWORDS: blocking agents, suppressing agents, red meat, processed meat, chemoprevention, phytochemicals

Indones Biomed J. 2019; 11(3): 225-39

Introduction

Cancer is a set of diseases in which normal cells undergo neoplastic transformation through a series of incremental steps that occur under selective pressure. Any change can be critical to tipping the scales toward the progression to malignancy.(1,2) Cancer is a complex disease with genetic, environmental, clinical, and lifestyle factors, all of which contribute to tumor initiation until malignant progression.(3) In this review, we highlight that somehow cancer could be termed as an inflammatory disease, and how the nutrition by the time will impact as the pro and contra on carcinogenesis process, especially the red meat and processed meat versus some beneficial phytochemical on the contrary.

Recent data appears to confirm that oxidative stress may have a big role in malignant transformation in primary tumors to augment their metastatic potential. A paper published in 2015 suggested the importance of increased production of reactive oxygen species (ROS) to enable and sustain a highly metastatic phenotype, although many opinions still debate for the controversial role of ROS and antioxidants in cancer.(4,5) Previously, cancer thought to be originated from cell autonomous defects (1), but now it become clear that a complex microenvironment engaged the cancer cell in stimulatory or inhibitory interactions

with stromal components. Chronic inflammation could consequence in arising cancer, when malignant cells escape from or suppress immunosurveillance mechanisms.(6) In other words, inflammation and immune process can either stimulate or restrain carcinogenesis and tumor progression, respectively.(7-10)

Red meat contains high biological-value proteins and important micronutrients such as omega-3-polyunsaturated fatty acids, B vitamins, iron (both free iron and heme iron), and zinc. The fat content of red meat varies depending on animal species, age, sex, breed, and feed, and the cut of the meat. Meat processing, such as curing and smoking, can result in formation of carcinogenic chemicals, including N-nitroso-compounds (NOC) and polycyclic aromatic hydrocarbons (PAH). Cooking improves the digestibility and palatability of meat, but can also produce known or suspected carcinogens, including heterocyclic aromatic amines (HAA) and PAH. High-temperature cooking by pan-frying, grilling, or barbecuing generally produces the highest amounts of these chemicals.(11,12) The International Agency for Research on Cancer (IARC) assessed more than 800 epidemiological studies that found the association of cancer with consumption of red meat or processed meat in many countries, from several continents, with diverse ethnicities and diets.(13)

Chemoprevention can be simply defined as using agents or compounds either natural or synthetic to inhibit tumorigenesis or tumor progression. The agents included here might perform their roles either by blocking cancer causing agents so that the DNA mutation will not be allowed, increasing the DNA repairing system or acting on cells with modified DNA, decreasing the cell cycle speed or interfere with events necessary for tumor spreading through metastasis. The classic mechanisms may involve free radical scavenging enzymes activation, chronic inflammation control, and specific signaling pathways downregulation. More recent understanding involving epigenetic aspects suggested several chemo preventive agents such as sulforaphane, green tea derived compounds, resveratrol, isoflavones, etc. Chemoprevention can give benefits on people with cancer or those without cancer but have a higher risk of developing it.(14-18)

Oxidative Stress, Inflammation and Cancer

Almost every mechanism in carcinogenesis involving chronic inflammation, from cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis (19,20), exemplified by many cases such as reflux esophagitis, gastritis, inflammatory bowel disease, silicosis-associated lung cancer, asbestosis-induced mesothelioma and various types of hepatitis induced by viruses, alcohol consumption or a Western-style diet (21). The carcinogenic effects of inflammation may be dependent on chronic stimulation of cellular turnover, which affect in increased stem-cell divisions, thus local mutagenic effects. The agent that cause inflammation itself can promote mutagenesis, enhanced by ROS production either as a side product of locally enhanced metabolism or are generated specifically by macrophages.(22) Nutrition now known to influence inflammation and immune response, promote the development of the dietary inflammatory index and immunonutrition as the term in epidemiological and clinical studies.(23-25) Figure 1 showed how qualitative and quantitative imbalances in food intake chronically predispose organisms, modulating a state of chronic inflammation in a manner dependent on or independent of the immune system, thus affecting to a time-dependent deterioration in function that culminates in the development and progression of cancer.

Caspase-1 activation complexes (inflammasomes), as their name imply, play a critical role in autoinflammatory syndromes, refer to conditions featuring recurrent episodes of systemic inflammation without (known) pathogens, autoantibodies or antigen-specific T cells.(7-9) Inflammasomes can contribute to tissue homeostasis, inflammation and immune responses to affect the formation,

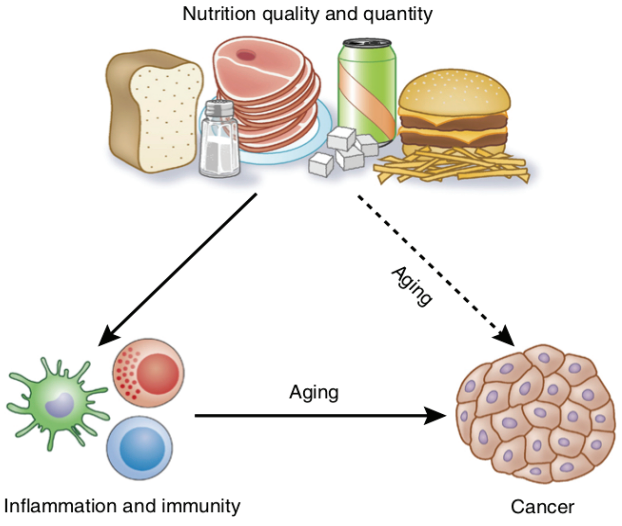

Figure 1. Relationships among nutrition, inflammation and immunity, and cancer.(25) (Adapted with permission from Springer Nature).

progression and therapeutic response of cancer.(10) The contrasting roles of inflammasomes in the complex interplay between malignant cells and their niches operate at the cell-autonomous level. In inflammatory cells, caspase-1 activation can eliminate malignant precursors through programmed cell death and sterile inflammation and carcinogenesis, but contrarily in antigen-presenting cells stimulate anticancer immune responses and the production of trophic factors for cancer cells and their stroma. The inhibition of inflammasomes or their products neutralization, mainly interleukin (IL)-1β and IL-18, showed profound effects on carcinogenesis and tumor progression.(10)

Cancers derived from epithelial cells known as carcinomas while adenocarcinomas derived from epithelium in glandular tissues. They are heterogenous, consist not only cancer cells but also cancer-associated fibroblasts, different tumor-infiltrating immune cells, adipocytes, endothelial cells, pericytes and others. These cells secrete chemokines and cytokines (26,27), affect cancer cells directly or promote cancer-associated inflammation by inducing immune cell infiltration thus lead to tumor initiation, progression, metastasis, but also have a role in cancer treatment. One of the most frequent immune cells involved are myeloid cells, including immature myeloid cells, neutrophils and macrophages, utilized as a cellular source for inflammasomes activation and secreting IL-1β and IL-18.(28) The etiological link between tumorigenesis and the chronic inflammation have been well documented in gastrointestinal (GI) tract cancers, where *Helicobacter pylori* infection associated with chronic gastritis, and colorectal cancer frequently associated with inflammatory bowel disease.(10,26,29). As inflammatory mediators, inflammasomes and their products also proved to be associated with GI cancers.

Oxidative stress mediated mechanisms in carcinogenesis in three stages: initiation, promotion, and progression. Oxidative stress leads to mutations in oncogenes and tumor-suppressor genes in the initiation stages.(30,31) The 8-Hydroxy-20-deoxyguanosine (8-OHdG) elevation usually measured to observe oxidative stress-associated DNA-adduct in precancerous and cancerous tissues or cancer cell lines compare to normal tissue.(32-36) The 8-OHdG could induce GC to TA missense mutations, which will produce a transformed cell if they were escaping repair prior to DNA replication.(36) The formation of 8-OHdG DNA-adducts often related to tumor suppressor (TP53) and oncogene (KRAS) mutation observed in tobacco smoke-induced oxidative stress lungs.(37-39) Many clinical trials studying ROS and antioxidants in cancer showed controversial results, suggest that excessive ROS accumulation promotes severe cellular damage and triggers apoptosis including cancer cells, therefore cancer cells depend on an increased antioxidant capacity, which keeps ROS levels higher than in normal cells, but below a critical threshold able to maintain their viability. ROS limit distant metastasis: only cells with increased antioxidant capacity, or cells with adaptation to build up a powerful antioxidant response are able to succeed in their purpose to metastasize.(4,5,40) Indeed, cancer initiation and progression has been linked to oxidative stress by increasing DNA mutations or inducing DNA damage, genome instability, and cell proliferation.(31)

The transcription factor nuclear factor erythroid 2 (NF-E2)-related factor 2 (Nrf2) belongs to the Cap 'N' Collar (CNC) family that contains a conserved basic leucine zipper (bZIP) structure. Nrf2 mainly function to activate the cellular antioxidant response to combat the harmful effects of extrinsic and intrinsic threats, such as xenobiotics and oxidative stress, make it traditionally regarded as the cell's main defense mechanism for survival, as seen in Figure 2. The dissociated Keap1 is ubiquitinated for proteasomal degradation, inducing Nrf2 translocates to the nucleus and binds to Maf to initiate transcription of antioxidant/detoxification genes such as superoxide dismutase (SOD), heme oxygenase-1 (HMOX-1), nicotinamide adenine dinucleotide phosphate (NADPH): quinone oxidoreductase 1 (NQO1), and glutathione-s-transferases (GSTs) and combat the oxidative stress. Nrf2 defense response activation has been shown to protect against neurodegenerative diseases, aging, diabetes, photo-oxidative stress, cardiovascular disease, inflammation, pulmonary fibrosis, acute pulmonary injury, cancer, also against chemical carcinogen-induced tumor formation in the stomach, bladder and skin.(41-46) Contrarily, mice with single-nucleotide polymorphism (SNP) that reduced expression of Nrf2 are more susceptible to hyperoxia-induced lung damage, supporting the idea of protective role of Nrf2 against ROS and DNA damage in cells.(47-49)

Nrf2 activation has been noticed to protect against a variety of toxicants and diseases, yet its prolonged activation affecting on several types of cancer progression such as lung, breast, head and neck, ovarian, and endometrial carcinomas with clinically poor prognosis (50-52), partly due to Nrf2's ability to enhance cancer cell proliferation and promote chemoresistance and radioresistance, explaining why Nrf2 expression is induced during the course of drug resistance.(46) Oxidative stress can activate transcription factors such as nuclear factor-kappaB (NF-κB), activator protein 1 (AP-1), p53, hypoxia-inducible factors (HIF)-1α, peroxisome

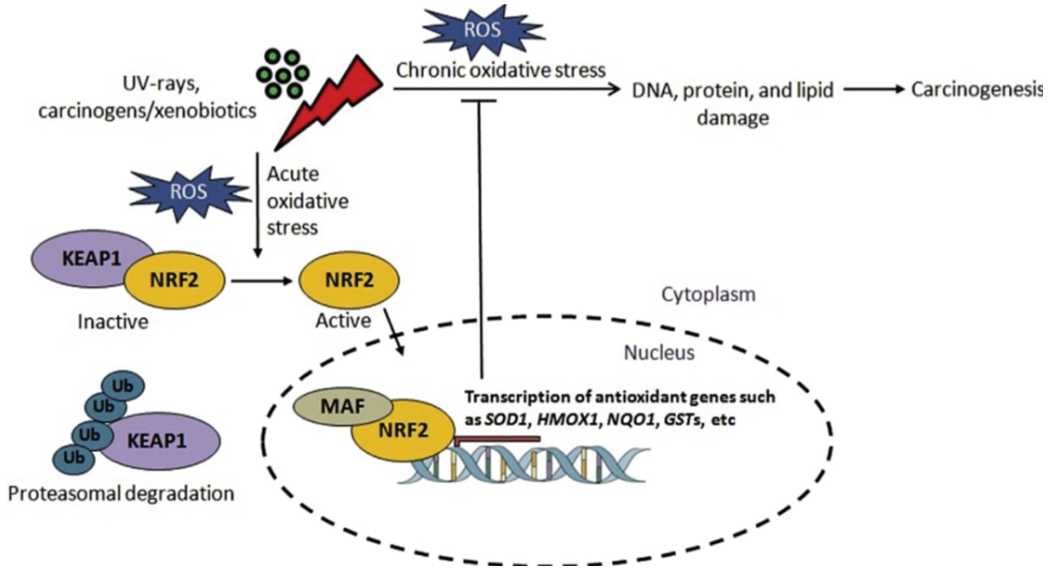

Figure 2. Activation of Nrf2 in response to mild oxidative stress.(39) (Adapted with permission from Elsevier).

proliferator-activated receptors (PPAR)-γ, β-catenin/Wnt, and Nrf2, which lead to the expression of more than 500 genes including those for growth factors, inflammatory cytokines, chemokines, cell cycle regulatory molecules, and anti-inflammatory molecules. Overall, we could suggest that oxidative stress via chronic inflammation are closely link to transform normal cell to tumor cell, tumor cell survival, proliferation, chemoresistance, radioresistance, invasion, angiogenesis and stem cell survival.(31)

Obesity is a risk factor for cancer development and is associated with poor prognosis in multiple tumor types. The positive energy balance linked with obesity induces a variety of systemic changes including altered levels of insulin, insulin-like growth factor (IGF)-1, leptin, adiponectin, steroid hormones, and cytokines. Each of these factors alters the nutritional milieu and has the potential to create an environment that favors tumor initiation and progression.(2)

Consumption of Red and Processed Meat, and Cancer

Red meat is defined as flesh from mammals (pork, beef, lamb, veal, etc.), red when it is raw, due to a higher percentage of red muscle fiber than white.(53) Processed meat regards as preserved and flavored meat using methods such as salting, smoking, fermentation and curing.(13) Previous epidemiological and experimental studies associate red or processed meat consumption to colorectal carcinoma, and increased incidence of many other carcinomas such as oesophageal, gastric, breast, pancreas and lung.(54-56) The International IARC confirmed a sufficient evidence for an association between colorectal carcinoma and consumption of processed meat.(13) The 2007 panel also concluded that cancers of the esophagus, lung, pancreas, prostate, stomach, and endometrium may be linked to red and processed meat consumption; however, the evidence at the time was limited and inconsistent.(53)

GI cancers has a sporadic pattern, and arise in individual by cause of environmental rather than hereditary risk factors, with diet as the strongest contributor.(57) A high-fat diet increases bile acid secretion that is transformed by colonic microbiota into secondary bile acid with genotoxic properties of DNA damage due to ROS and nitric oxide synthase (NOS).(58,59) Protein-rich diets produce inflammatory and toxic nitrogenous metabolites such as phenols, indoles, ammonia, and amines as results of microbial fermentation of undigested protein residues. (60) The nitrogenous metabolites which are well-known potential carcinogens and a prominent risk factor of GI cancer are nitrosamine and nitrosamide, formed by the reaction of nitrosating agents, such as nitrite and secondary amines and amides. They are potent alkylating agents that induce GC to AT transitions at the second base of codon 12 or 13 of the KRAS gene in the epithelial cells, then cause cancer development in the GI tract.(61,62)

Figure 3 explain some probable mechanisms on the association between red/processed meat and colorectal carcinomabring out heme, NOCs, heterocyclic amines (HCAs), N-glycolylneuraminic acid (Neu5Gc) and PAHs which were contained in the red and processed meat to be

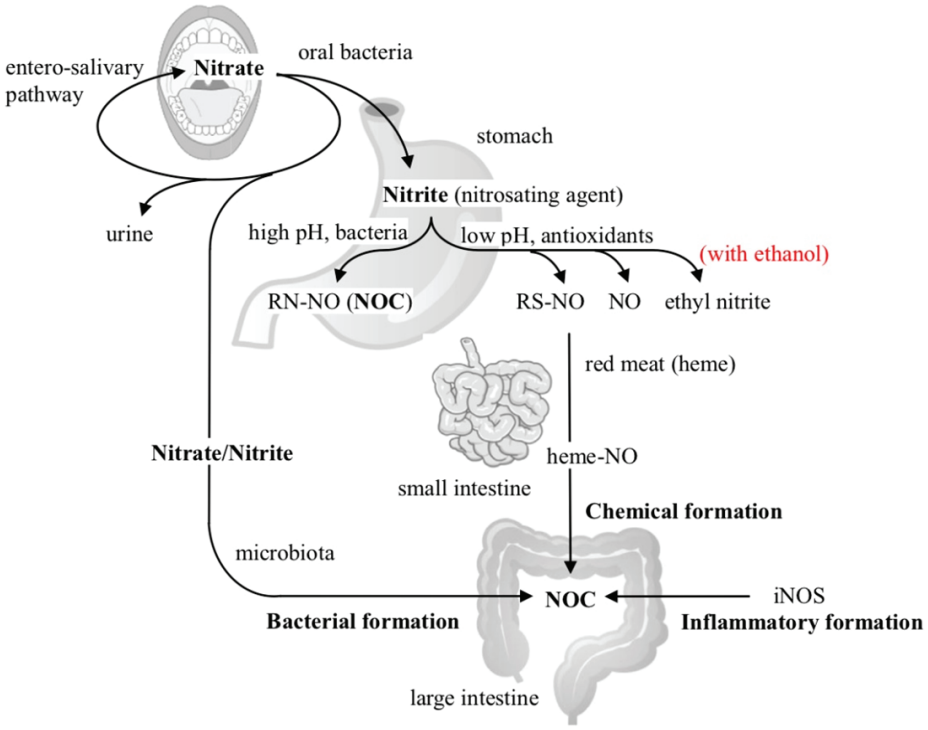

Figure 3. Proposed schema showing the metabolism of dietary nitrate/nitrite and NOC formation in the gastrointestinal tract.(55) (Adapted with permission from Elsevier).

the carcinogenic mediators especially heme, although the exact mechanisms is still vague and controversial. Unless washed out by the gastric acid and antioxidant, red meat consumption can reach the lower intestine as precursors of nitrosating agents, together with bacterial formation from gut will modulate inflammation in the large intestine and by the time increased the cancer risk.(63) Multiple homeostatic signals especially Wnt signaling pathway regulate the homeostasis for normal colon epithelial architecture, the surface epithelial cells were controlled and well-balanced as well as new cells replacements from the crypts.(64,65) The key genes involved were known upregulated high heme ingestion.(66) Another evidence showed that heme iron induce G>A transition in adenomatous polyposis coli (APC) gene, rising 80% incident of the colon cancers considering APC is a tumor suppressor gene.(67,68) After the mutations, β-catenin accumulates within colonic epithelial cells and gets translocated to the nucleus, forming a complex with DNA binding factor T-cell factor. Further, this will lead to transcription factors activation promoting uncontrolled cell proliferation of the colonic epithelial crypts.(68) TP53 and KRAS were also known to be mutated with the presence of high heme. Moreover, heme leads to free radical formation and generation of DNA adducts in colorectal epithelial cells via lipid peroxidation. Intestinalk dysbiosis will promote heme carcinogenic properties. Anyhow, a balanced diet containing green vegetables, olive oil and calcium may reduce the heme's carcinogenic effects.(69)

Chemoprevention: An Essential Approach to Controlling Cancer

Cancer can be defined as the dysregulated of cells proliferation. Many factors could induce cancers including environmental exposures (*e.g.*, asbestos, ultraviolet radiation), lifestyle choices (tobacco, obesity, physical inactivity), infectious agents (*e.g.*, human papillomavirus (HPV), human immunodeficiency virus (HIV), hepatitis B virus, *Helicobacter pylori*), and inherited conditions and mutations (*e.g.*, familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer, and the breast cancer (BRCA)1 and BRCA2). Chemoprevention termed as the use of drugs or other compounds to inhibit or reverse of the carcinogenic process.(70) Clinically, chemoprevention agents divided into three categories: primary chemoprevention (suited for they who may be at increased risk for disease), secondary chemoprevention (for patients with premalignant lesions that may progress to an invasive disease), and tertiary chemoprevention (to prevent recurrence or second primary cancers disease in those individuals who have already endured potentially curative therapy, such as treatment with aromatase inhibitors).(71) Current primary chemoprevention agents including nonsteroidal antiinflammatory drugs (NSAIDs) (*e.g.*, aspirin, sulindac, celecoxib), vitamins and their derivatives (*e.g.*, retinoids, selenium, vitamin E), minerals

(*e.g.*, calcium), and plant extracts (*e.g.*, wheat bran fiber, tea catechins, flavonoids, berry extracts, curcumin).(15)

The failure to control cancer deaths from common epithelial malignancies, such as those that occur in the lung, breast, prostate, colon, pancreas and ovary, provides the ultimate rationale for an approach based on prevention. The logical approach to controlling cancer is to prevent it before the complex series of genetic and epigenetic events that result in invasive and metastatic malignancy have occurred. (16) We need to refine our insights into early disease pathogenesis, together with enhanced screening for success risk assessment and any new risk models based on cellular and molecular insights.(15)

Cancer chemoprevention refers to the use of agents for the inhibition, delay, or reversal of carcinogenesis before invasion. At the molecular level, cancer chemoprevention intended for disruption or at least delay the multiple pathways and processes among the three stages of carcinogenesis: initiation, promotion, and progression. (72,73) Chemopreventive agents are referred as blocking agents since they block mutagenic interactions with DNA, either permanently evading damaged DNA by inactivating or metabolizing carcinogens directly, acting as free-radical scavengers, or physiologically inducing anti-oxidative enzyme activity and triggering mechanisms of DNA repair. (73,74) Blocking agents can also modify the epigenomic landscape.(75) In the present review, agents examined in the context of cancer chemoprevention are classified in four major categories, which are hormonal, medications, diet-related agents, and vaccines.(14) Because chemoprevention refers to the wide-spread and long-term use of compounds by the general healthy population, safety is an issue of paramount importance that needs to be addressed in studies with long follow-up in large segments of the population in order to be able to identify even rare side effects.(14) Chemoprevention will have to be taken for years, so ideally it should has little or no toxicity, with high efficacy in multiple sites, can be taken orally, low cost, and the mechanism of action is known.(18)

On the contrary, suppressing agents refer to compounds that affect later stages of carcinogenesis (promotion and progression) by decreasing the proliferative capacity of initiated cells.(73) They hinder the proliferation of cancer cell by down-regulating signal transduction pathways such as NF-κB, mammalian target of rapamycin (mTOR), signal transducer and activator of transcription 3 (STAT-3), and many others (76-79), also by restraining enzymes that modulate signal transduction to hormone responsive elements such as cytochrome P450 (80). Suppressing agents are also likely to promote apoptosis pathways while inhibiting the angiogenesis, epithelial mesenchymal transition, invasion, and dissemination pathways thus reduce or delay the cells metastatic evolving ability, therefore decreasing the cancer mortality.(74,79-81)

Based on epidemiological studies that people have lower incidence of cancer when they consume diet richer in fruits and vegetables, several chemoprevention molecules derived from spices, teas, fruits and vegetables including lemon, saffron, garlic, broccoli, pomegranate, berries, and others, suggested this happening due to all possible vitamins and other micronutrients, especially the antioxidant ones, such as vitamin A, C, and E, omega-3 fatty acids, and folate as in mediteranian diet.(39) Curcumin and green tea derived molecules showed their ability to stabilize IκB, the cytoplasmic inhibitor of NF-κB, so it cannot be translocated to the nucleus to act as a pro-inflammatory molecule, as we know that chronic inflammation associated with tumor progression as its role in ROS formation, lead to DNA alteration, promote several genes involved in cell proliferation for example via NF-κB.(82,83)

Oxidative stress is not the only one to promote transcription factors which express the enzymes for free radical scavenging but also some phytochemicals including sulphoraphane and resveratrol, derived from cruciferous vegetables such as broccoli and grapes in order. Nrf2, one transcription factor that acts as cell's most important regulator of antioxidant defenses, binds to cis-enhancer sequences called antioxidant responsive elements that are 5′-flanking of the promoter regions for genes encoding detoxifying and antioxidant enzymes, such as GST and NADPH:NQO1.(46,84,85)

Some phytochemical such as resveratrol, apigenin, curcumin, fisetin, quercetin, 6-gingerol, and piperlonguminine can either induce apoptosis or cell death through autophagy by different mechanisms.(86) Other studies exploit some phytochemicals to inhibit metastasis generation of tumor cells via epithelial mesenchymal transition. It was also found that silibinin, curcumin, green tea derived compounds, 6-gingerol, and resveratrol could inhibit matrix metalloproteinases (MMPs) expression, especially MMP-9, and in other side increasing E-cadherin molecule, that maintain the cells to keep attached each other, make it more challenging for them to migrate in adjacent tissue invasion.(87-89) Some phytochemicals supplement such as Protandim (*Bacopa monniera*, *Camellia sinensis*, *Curcuma longa*, *Silybum marianum*, and *Withania somnifera*) showed to be a potent activator of Nrf2 in both cell culture and animal models (74,90,91),

while many are also known to inhibit the conversion of procarcinogens to their electrophilic (DNA damaging) species (17).

Current studies showed that epigenetic was importantly involved in the progression of cancer as found in Table 1. Several epigenetic mechanisms relating to nucleosome organization including DNA methylation, histone post-translational modifications, such as methylation, acetylation, phosphorylation and nucleosomes occupancy dynamics have been described to be altered during cancer development.(92-94) They are potentially reversible count on environmental fluctuation such as nutrition, oxidative stress, pollution, inflammation, and life style. (93,95) Therefore, epigenetic give a potential approach for cancer therapy. Currently, FDA approved the DNA methyltransferase (DNMT) inhibitors 5-azacytidine (5-

Table 1. Mechanism of action of the different bioactive compounds on epigenetic alterations.(18) (Adapted with permission from Frontiers Media).

Mechanism of action	Neoplasia	Study type	Target genes
ISOFLAVONES			
Decreased methylation	Breast cancer	*In vitro*	BRCA1, BRCA2, ATM, APC, PTEN; SERPINB5
Increased acetylation	Breast cancer	Preclinical studies: *in vitro* and *in vivo*	ERα
Increased active mark H3K4 and acetylation	Breast cancer	*In vitro* and *in vivo* (xenografts)	$p16^{INK4a}$; $p21^{WAF1}$
Increased repressive mark H3K27	Uterine leiomyomas	Human	$p16^{INK4a}$; $p21^{WAF1}$
Increased acetylation, decreased methylation and increased active mark H3K4	Prostate cancer	*In vitro*	$p16^{INK4a}$; $p21^{WAF1}$, BTG3, AKT, CYLD
EPIGALLOCATECHIN GALLATE			
Decreased methylation	Breast, colorectal and skin cancer	*In vitro*	$p16^{INK4a}$; $p21^{WAF1}$, RARβ, RXRα, MGMT, MLH1
Decreased methylation	Oral squamous carcinoma	*In vitro*	RECK
Increased tumor suppressor miR	Hepatocarcinoma	*In vitro*	BCL-2
Decreased oncomir	NSCLC	*In vivo*	p53
RESVERATROL			
Decreased oncomiRs	Colorectal cancer	*In vitro*	TGFβ1
Incresead methylation	Breast cancer	*In vitro*	AURKA PLK1
Increased tumor suppressor miRs	Colorectal cancer	*In vitro*	E2F3
Hyperacetylation	Breast cancer	*In vivo*	BRCA1
SULFORAPHANE			
Hyperacetylation	Colorectal and prostate cancer	*In vitro* *In vivo*	BAX p21
Hyperacetylation	Breast cancer	*In vitro*	Caspases Cytochrome c
Decreased methylation	Breast and prostate cancer	*In vitro*	PTEN RARβ2
Hyperacetylation Decreased repressive mark	Breast cancer	*In vivo*	hTERT
CURCUMIN			
Decreased methylation	Colorectal cancer	*In vitro*	NF-κB pathway
Decreased methylation	Cervical cancer	*In vitro*	RARβ2
Decreased methylation	Myeloid leukemia	*In vitro* *In vivo*	$p15^{INK4B}$
Increased suppressor miRs Decreased oncomiRs	Colorectal cancer	*In vitro*	Cyclin D1 and E1 CDK4 and 6 cMYC
Increased suppressor miRs Decreased oncomiRs	Melanoma	*In vivo*	BCL-2 PCNA
Increased suppressor miRs	Pancreatic carcinoma	*In vivo*	Notch1 MMp-9

AZA) and 2′-deoxy-5-azacytidine (DAC) for the treatment of myelodysplasia myelodysplastic syndrome (MDS), a preleukemic syndrome and myelomonocytic leukemia, and the results are promising too for solid tumor therapy.(92,96,97) Epigenetics complementing the chemoprevention mechanisms, opening up the possibilities for new molecules findings, particularly to prevent the disease and reach a better quality of life.(16)

Cruciferous Vegetable Intake and Risk of Cancer

Mostly healthy diets against chronic diseases including cancer recommend to increase vegetables and fruits consumption, as many growing evidences support that fruits and vegetables might be beneficial in cancer prevention.(98,99) Cruciferous vegetables specifically, named for their cross-shaped flowers, including cabbage, broccoli, brussel's sprouts, cauliflower and other members of the family, contain many nutrients with cancer-fighting properties.(100) Present meta-analysis studies representing a pooled total of 18,673 cases summarized the inverse associations between cruciferous vegetables consumption with risk of lung, colorectal, stomach, breast, prostate, and other cancers.(101-111) About 200-250 g/day broccoli consumption for 10 days has been showed to decrease tobacco smoke-induced DNA damage in smokers.(112,113)

The protective effect of cruciferous vegetables on breast cancer is biologically conceivable if we look deeper into their key components. Glucosinolates, the precursors of isothiocyanates (ITCs) and indole-3-carbinol believed to have anticancer properties, are especially rich in cruciferous vegetables.(107) Previous study screened the extract of cruciferous vegetables and found that sulphoraphane [1-isothiocyanato-4-(methylsulfinyl) butane].(85) A phytochemical belonging to a large chemical family of isothiocyanates, a potent antioxidant involving Nrf2 signaling and Aryl hydrocarbon receptor (Ahr) pathway.(114) By inhibition of phase I activating enzymes (*e.g.*, cytochrome P450 (CYP)1A1 and CYP1A2), inhibits CYP1B1 in MCF10A cells (115), inhibits CYP3A4 in human hepatocytes (116). Induction of phase II detoxifying enzymes, such as GSTs, ITCs may protect cells against cancer initiation by neutralizing endogenous and exogenous electrophiles in breast tissue.(108,109) While indole-3-carbinol induce 2-hydroxylation of estradiol, resulting in nonestrogenic metabolites (110), binding to the estrogen receptor (ER) thus downregulates the ER signaling and prevent the development of estrogen-related cancers including breast, endometrial and cervical cancers.(102,111) Interestingly, the inverse association seems to be stronger for advanced stages of cancer. Current studies on isothiocyanates, including phenethyl isothiocyanate and sulforaphane, with addition of other chemicals from the same vegetables such as 3,3′-diindolylmethane, have been shown to inhibit prostate cancer cell growth and induction of apoptosis *in vitro* and *in vivo* by repression of androgen receptor and induction of endogenous cyclin-dependent kinase.(117-119)

Cruciferous Vegetable Intake and Risk of Cancer

In modern advances of medical technology worldwide, in fact cancer cases keep growing.(120) Diet and exercises were known to significantly impact this prevalence, renewing interest in dietary phytochemical research, especially those including polyphenols, alkaloids, carotenoids, and nitrogen compounds.(121-124) These groups of phytochemicals showed the ability to affect cell proliferation and cell cycle regulation, involve in multiple signaling pathways that are often disrupted in tumor initiation, proliferation and propagation.(17,124-127)

Carcinogenesis is a multistep process transforming a cell in its molecular level to undergo uncontrolled cellular division.(128) For the last fifty years, many research found innumerable critical molecular players and targeted pathways, which activate proto-oncogenes and inactivation of tumor suppressor genes, therefore cells represented tumor initiation, promotion and progression.(129,130) At initiation, after exposure to a carcinogenic agent, tumor cells start in a rapid and irreversible process, followed by its distribution and transportation to tissues causing non-lethal mutations in cellular DNA. The accumulation of this selective clonal initiated cells will add irreversible genetic changes which persist with each new cycle of proliferation.(130)

Tumor promotion, in contrast, is a relatively lengthy and reversible process where actively proliferating pre-neoplastic cells begin to divide and multiply as seen in Figure 4.(131) Tumor progression, as the final stage, occurs after the mutations has reached an invasive cellular phenotype with metastatic potential.(130,132) Either dietary- and non-dietary-derived phytochemicals (molecules found in plants) cancer chemoprevention focusing on finding natural agents that specifically impact the earliest prevention of

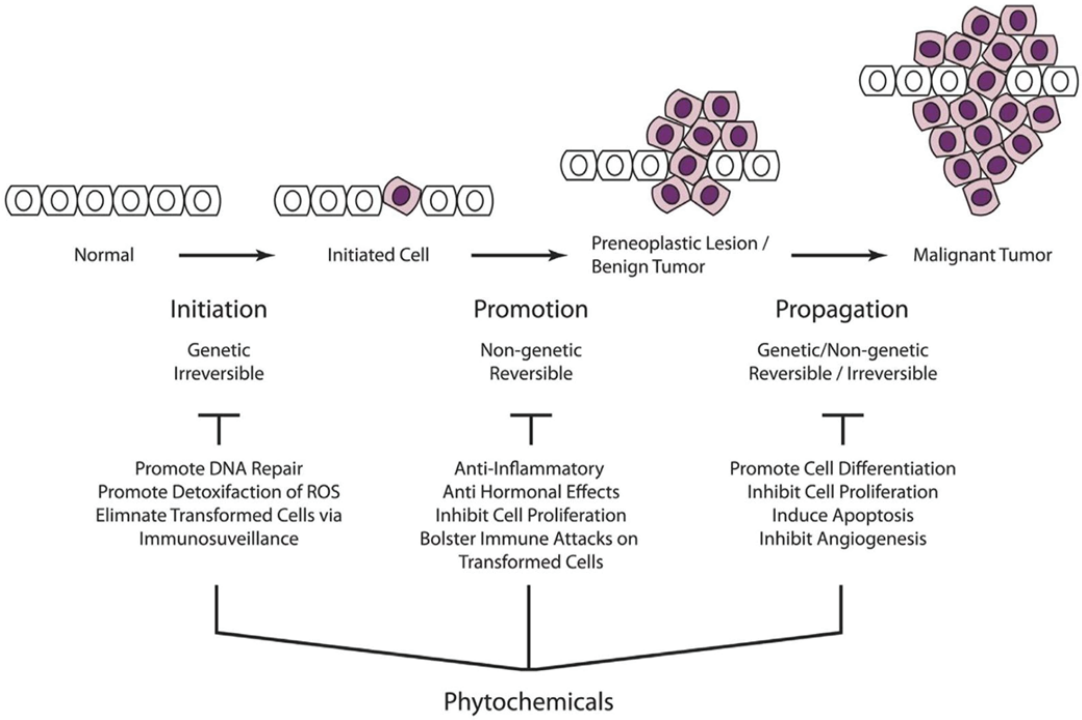

Figure 4. Carcinogenesis is a multistep process that ultimately reprogram a normal cell into a cancer cell.(131) Adapted with permission from Impact Journals).

cellular transformation (protecting DNA from mutation) by modulation of cytoprotective enzyme activation. (74,79,133-137) For example, phytochemicals agent that prevent carcinogens to reach its targeted sites, and at once support detoxification of highly reactive molecules. (134) Phytochemicals also enhance innate immune surveillance to eliminate transformed cells.(135) Finally, phytochemicals improve DNA repair mechanisms, tumor suppressors and inhibit cellular proliferation pathways.(133-137) As a primary chemoprevention, some phytochemicals appear to alter the epigenome and reverse abnormal gene expression through modulation of DNMTs, methyl binding proteins (MBDs), histone deacetylases (HDACs), micro RNAs (miRNAs), and several other epigenetic mechanisms. Thus, phytochemicals promote genomic integrity and cellular homeostasis in both *in vitro* and *in vivo* models.(75)

Natural agents have emerged as novel therapeutic agents of drug-repositioning to influence autophagic activity.(138) Table 2 describes some natural agents and their mechanisms in cancer. Several natural agents modulate autophagy. For example, tanshinone IIA (139), ursolic acid (140), quercetin (141), fisetin (142), resveratrol (143), and honokiol (144) act as inhibitors of the AKT/ mTOR pathway. Tanshinone IIA modulates the initiation of phagophore formation. Ginsensoside (145) and ursolic acid (146) affect the formation of autophagosomes. Ginsenoside RO inhibits autophagosome-lysosome fusion.(147) Curcumin, or turmeric (bis-α, β-unsaturated β-diketone), is a gold-colored spice widely used in Indian cooking, textile dyes, and in traditional Ayurvedic medicine I, contain polyphenol derived from the roots of the perennial *Curcuma longa* plant. Curcumin inhibits the growth of a variety of cell lines *in vitro*, by affecting the cell cycle arrest and apoptosis, specifically by modulating NF-κB, cyclooxygenase-2 (COX-2), tumor necrosis factor alpha (TNF-α), STAT-3 and cyclin D1.(148-151)

Resveratrol is a phytoalexin found in many fruits and plants including red wine, grapes, berries and peanuts. (152) Highest levels of resveratrol found in the roots of the *Polygonum cuspidatum*, or Japanese knotweed, which is traditionally used as Chinese medicinal treatments for dermatitis, bacterial infections and inflammation. Previous studies identified the anti-cancer properties of resveratrol against several different tumor types in multiple stages. At higher dose, resveratrol could induce apoptosis and studies in rats showed resveratrol mediates a down-regulation of androgen receptor expression and suppression of androgen responsive glandular kallikrein, an orthologue of the human prostate specific antigen.(153-158) Another effects of resveratrol may be achieved through promoting innate immune system immunosurveillance and therefore enhancing elimination of spontaneous tumor cells prior to proliferation.(131)

Table 2. Some natural agents' chemo-preventive mechanism.

Natural Agents	Cancer Preventing Mechanisms	References
Tanshinone IIA, ursolic acid, quercerin, fisetin, resveratrol and honokiol	Inhibitors of the AKT/mTOR pathway	(139-144)
Tanshinone IIA	Modulates the initiation of phagophore formation	(139)
Ginsensoside and ursolic acid	Affect the formation of autophagosomes	(145,146)
Ginsenoside Ro	Inhibits autophagosome-lysosome fusion	(147)
Curcumin, or turmeric (bis-α, β-unsaturated β-diketone)	Inhibits the growth of a variety of cell lines *in vitro* , by affecting the cell cycle arrest and apoptosis, specifically by modulating NF-κB, COX-2,TNF-α, STAT-3 and cyclin D1	(148-151)
Resveratrol	Induce apoptosis, promoting innate immune system immunosurveillance	(153-158)
Epigallocatechin-3-gallate (EGCG)	Induce apoptosis and inhibit tumor cell growth, inhibit angiogenesis, modulating the immune system, and activating enzyme systems involved in cellular detoxification through the glutathione S-transferase and quinone reductase pathways	(161,162)
Lycopene, beta carotene, Vitamins A, C, E, selenium	Prevent inflammation, preventing cellular damage induced by free ROS	(163)
Folate, or folacin, pteroylglutamic acid or vitamin B9	Roles as a cofactor in carbon transfer reactions essential in DNA synthesis, repair and methylation	(164)
Apigenin (4′,5,7-trihydroxyflavone)	Promoting cell cycle arrest and enhance apoptosis in cancer cells and xenograft models, downregulate NF-κB activity through the suppression of phosphorylation of p65, and Akt signaling, regulating Bcl-2, cyclin D1, cyclooxygenase-2, MMP-9 and NOS-2 expression in prostate carcinoma.	(175-177,180)

Camellia sinensis, or tea, known as the most ancient and popular beverages consumed around the world. Different species of tea contains some combination of polyphenols, alkaloids, minerals, and other volatile organic compounds. (159) Epigallocatechin-3-gallate (EGCG) and Epicatechin-3-gallate (ECG) found in a very high level in tea, especially higher in green tea.(160) Catechin polyphenols perform a strong antioxidant activity and thought to be able to prevent specific DNA damage by ROS, thereby preventing tumor mutagenesis of normal cells.(161,162) Tea polyphenols in pre-clinical studies showed to induce apoptosis and inhibit tumor cell growth, inhibit angiogenesis, modulating the immune system, and activating enzyme systems involved in cellular detoxification through the GST and quinone reductase pathways.(161,162)

Endogenous antioxidants naturally produced in our body help to neutralize ROS, while external sources of antioxidants obtained from fruits, vegetables and grains.(129) Lycopene, beta carotene, Vitamins A, C, E, selenium and other dietary antioxidants known to prevent inflammation, preventing cellular damage induced by free ROS, thus slow the cancer development.(163)

Folate, or folacin, pteroylglutamic acid or vitamin B9, is a water-solute B-vitamin. Folate roles as a cofactor in carbon transfer reactions essential in DNA synthesis, repair and methylation.(164) Humans can not synthesize folates *de novo*, so we take folic acid supplements. Large prospective studies showed ~25% reduction in colorectal cancer risk in subjects who takes high folate compared to ones with lower intake (165), and a meta analysis study reported a significant reduction in breast cancer risk in women who take higher folate in their diet although no correlation was found between circulating folate level and breast cancer risk (166).

Lycopene is a natural carotenoid found in many fruits and vegetables especially in tomatoes and its derivative products.(167) Recent studies showed that lycopene involved in antioxidant reactions including SOD-1 and GST-omega-1 thus downregulate ROS expression, and ROS generating proteins.(168) Another study pointed lycopene

to inhibit cell proliferation, induce apoptosis, and attenuate the metastatic capacity of prostate cancer cells (169,170), as supported by the data that linked increased consumption of lycopene-rich food with lower prostate cancer risks (170-172).

Apigenin (4′,5,7-trihydroxyflavone), also abundant in fruits and vegetables, is a kind of flavonoid with a broad spectrum of anti-proliferative activities against many cancer cells.(173,174) Several proposed mechanisms of apigenin reported its role in promoting cell cycle arrest and enhance apoptosis in cancer cells and xenograft models (175,176), downregulate NF-κB activity through the suppression of phosphorylation of p65 (177), and Akt signaling (178-179). Apigenin exerted potent chemopreventive activities through regulating B-cell lymphoma 2 (BCL-2), cyclin D1, cyclooxygenase-2, MMP-9 and NOS-2 expression in prostate carcinoma.(180)

Conclusion

Many studies provide the role of red meat and processed meat in colorectal, esophagus, liver, kidney, and prostate cancer, which etiology mechanisms suggested by means of HCAs, polycyclic PAHs, NOCs, and heme iron. On the contrary, several dietary agents clearly shown to have anti-cancer properties and contribute as one variable affecting the cancer prevalence. However, understanding how these dietary agents interact with cancer cells, the immune system and oxidative stress pathways may one day expose a way of safe, pleasant, non-toxic and economical anti-cancer therapeutics.

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