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CANCER CARE

THE ROLE OF REPURPOSED DRUGS AND METABOLIC INTERVENTIONS IN TREATING CANCER

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Disclaimer

This is a review of the published literature showing options for repurposed drugs that can be used in cancer treatment. It is not intended as a stand-alone guide to treating cancer. Nothing in this document should be taken as a basis to initiate treatment without guidance or avoid any treatment prescribed by your treating physician. This information is offered as a basis to assist mutual decision-making. Cancer care should always be supervised by a healthcare provider. Patients with cancer should ALWAYS consult with their regular oncologist as well as an integrative provider/oncologist, in addition to their primary care provider.

The treatment interventions outlined in this monograph should be used as ***adjunctive therapy*** in addition to the treatment provided by an oncologist. The goal is to reduce the toxicity of standard chemotherapy/radiotherapy (and lower the dose of chemotherapy when possible) to prevent severe immunosuppression, organ toxicities, and death from standard chemotherapy. Note that this document mentions some potential interactions, such as between antioxidants and chemotherapeutic agents, that must be considered.

Standard chemotherapy targets the rapidly dividing population of cancer cells; these agents commonly adversely affect the tumor microenvironment and may promote the proliferation of cancer stem cells, increasing the potential for metastases. Almost all the interventions listed in this document limit the negative effects on the tumor microenvironment. In addition, many of the agents described herein also target cancer stem cells. This data suggests that these interventions should be used simultaneously with conventional chemotherapy to achieve the best outcomes for our patients.

Please note that this is the first iteration of this document which, as a “living” document, will be continuously updated and refined. Please ensure you are reviewing the most recent version.

Target Audience

This information should be of particular interest to patients with cancer, to help guide them through the complicated issue of using repurposed drugs for cancer treatment. However, as noted above, it should not be used by patients to self-treat and should be supervised by a qualified healthcare provider. Primary care providers and integrative providers of patients with cancer will find essential information within this document. Furthermore, this will be of interest to people who would like to reduce their risk of getting cancer. Patients with existing cancers should attempt to discuss the topics of dietary caloric restriction and adjuvant (concurrent) repurposed drugs with their regular oncologist; however, for obvious reasons (vested interests) many oncologists may be unwilling to broach these topics.

Caution to Patients

This document is based on the highest level of scientific evidence. Patients should review this information, independently validate the reliability of the data, and discuss the treatment

options with their family/healthcare advocates. Patients should formulate a treatment plan with their healthcare provider that is compatible with their values and goals. Patients should, however, vigorously avoid unproven and unscientific interventions that only benefit unscrupulous practitioners.

A repurposed drug is one that is used “off-label,” a common basis for prescribing but which means that it has not been reviewed and approved by the U.S. Food and Drug Administration for that particular indication. Some recommendations may be subject to controversy and differences of opinion among medical authorities. While we believe this monograph offers an accurate view of the current state of the science as it is based on solid evidence and pathophysiological principles, public health agencies and regulatory bodies may have taken contrary positions.

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Additionally, I would like to acknowledge the authors of several books on metabolic oncology that were very useful in guiding my thinking. These include Thomas Seyfried (Cancer as a Metabolic Disease), Otto Warburg (The Metabolism of Tumors), Jane McLelland (How to Starve Cancer), and Travis Christofferson (Tripping over the Truth). I am also grateful for groups like Care Oncology and the Anticancer Fund, who provide a foundation for this work.

Glossary of common abbreviations

AKT: Protein kinase B (PKB or *Akt*)
ALA: alpha-linolenic acid
AMPK: adenosine monophosphate-activated kinase
ARG-1: arginase 1
BRACA1: Breast cancer gene 1
BAX/BAK: members of the Bcl-2 family of apoptotic proteins
CCR6: Chemokine receptor 6
CSC: Cancer stem cells
CI: confidence interval
CGM: continuous glucose monitor
COX: cyclooxygenase
DC: dendritic cell
FOXO1: Forkhead Box O1
EGFR: epidermal growth factor
EGCG: epigallocatechin gallate
ERKs: extracellular-signal-regulated kinases
FGF: fibroblast growth factor
GI: glycemic index
GTCs: Green tea catechins
GDH: glutamate dehydrogenase
HDL: High density lipoprotein
HIF: hypoxia inducible factor
HR: hazard ratio
HK2- Hexokinase-2
HSP: heat shock protein
Hh: Hedgehog pathway
HER2: human epidermal growth factor receptor 2
IGF-1: Insulin-like growth factor 1
IκBα: inhibitor of nuclear factor kappa B
INF: interferon
in vitro: performed in a test tube or culture dish
in vivo: performed in a living organism
GH: growth hormone
IL: interleukin
JAK2: Janus kinase 2
JNK: c-Jun N-terminal kinase
MAPK: mitogen-activated protein kinase
MAMs: metastasis-associated macrophages
MDSC: Myeloid-derived stem cells
MMPs: matrix metalloproteinases
mTOR: mammalian target of rapamycin
NAD: nicotinamide adenine dinucleotide

NF-KB: nuclear factor Kappa beta
NOS: nitric oxide synthase
NK cells: natural killer cells
NSAID: non-steroidal anti-inflammatory drug
Nrf2: nuclear factor E2–related factor 2
OR: odds ratio
PDE5 inhibitor: phosphodiesterase 5 inhibitors
PD-1/PD-1L: Programmed cell death protein 1/ligand
PI3K: phosphoinositide 3-kinase signaling pathway
PGE2: prostaglandin E2
RCT: randomized controlled trial
REM: rapid eye movement
ROS: reactive oxygen species
ReDO: Repurposing Drugs in Oncology
RFS: recurrence-free survival
RR: relative risk
STAT3: signal transducer and activator of transcription 3
TAM: Tumor-associated macrophages
TGF: transforming growth factor
TG: triglyceride
TME: tumor microenvironment
TCR: T cell receptor
TLR: Toll like-receptor
TCGA: The Cancer Genome Atlas Program
TNF: tumor necrosis factor
TRAIL: tumor necrosis factor-related apoptosis-inducing ligand
Tregs: T-regulatory cells
USPSTF: U.S. Preventive Services Taskforce
UV: ultraviolet
VDAC: voltage-dependent anion channel
VCAM1*:* vascular cell adhesion molecule *1*
VEGF: vascular endothelial growth factor
WNT: WNT signaling pathway

FOREWORD

by Dr. Justus Hope

As a physician and board-certified specialist, I have spent over 30 years caring for patients, mainly those suffering from intractable pain. In January 2020, when my friend contracted Glioblastoma, I began researching to figure out how to help him. What I found annoyed me: my friend could do far better if his doctors would add repurposed drug cocktails to his chemotherapy, radiation, and surgery.

A Harvard professor first stumbled upon repurposed drugs for cancer in the 1990s when he used them to cure his own Glioblastoma. That man is still alive today.

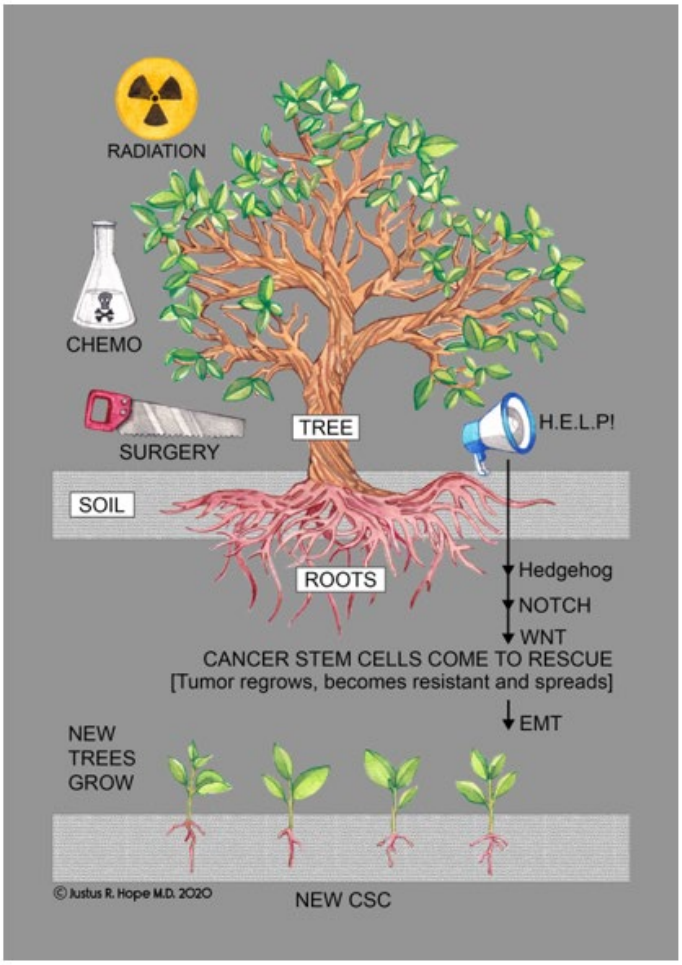

Figure 1: Cancer stem cells are the root of cancer (Source: Dr. Justus Hope)

The most significant problem I see repeatedly is that cancer recurs with resistant metastases. At that point, even with repurposed drugs, it is often a losing battle. This tragedy occurs because the standard treatments of surgery, radiation, and chemotherapy stimulate the growth of cancer stem cells (see Figure 1). Proactively adding repurposed drugs as early as possible can help prevent cancer stem cells from regrowing the tumor into a more resistant and sometimes indestructible form. If we could get all patients and their oncologists to read this document and add a repurposed drug cocktail, along with lifestyle changes, at the onset of a cancer diagnosis (and do this in concert with their treatment plan — whether it be surgery, chemotherapy, and radiation treatment) we would likely see a lot more of these patients not only survive but live better, longer lives.

Justus Hope is a pen name. The author practices medicine under his given name. He has written several books, including *Surviving Cancer, COVID-19, and Disease: The Repurposed Drug Revolution*.

PREFACE

By Dr. Paul Marik

"It is more important to know what kind of person has a disease than to know what kind of disease a person has."
Hippocrates (460-370 BC)

"When we have the power to help, we have the duty of doing so."
Mirko Beljanski (1923-1998)

Years ago, when I had more hair and COVID-19 wasn't even a twinkle in anyone's eye, I became known for developing a treatment for one of the most common causes of death in hospitals — medical sepsis, which takes the lives of around 1,000 people each day in this country alone. My 'cocktail' consisted of three safe, inexpensive, easily accessible drugs that could be repurposed for sepsis. Time after time when I gave patients vitamin C, hydrocortisone, and thiamine, their condition turned around within hours.

Repurposing drugs is nothing new. Around 30 percent of all prescriptions in the United States are written for off-label uses. Bringing new drugs to market can take decades and cost billions of dollars while existing licensed drugs can be repositioned to offer safe, affordable, and effective treatments in a short period of time.

The Front Line COVID-19 Critical Care Alliance (FLCCC) has had great success in using repurposed drugs, as well as vitamins, supplements, and lifestyle changes, to treat COVID, long COVID, and COVID vaccine complications over the past few years. While researching and developing protocols for the above conditions, I began reading huge volumes of information and saw an interesting pattern emerging that led me to investigate the potential role repurposed drugs could play in the treatment of cancer, along with some amazing non-pharmaceutical interventions like intermittent fasting. In doing so, I learned that much of what I once understood about what causes cancer and how it should be treated was wrong or at least misguided.

In putting this document together, I have invested thousands of hours, read more than 700 peer-reviewed papers, and consulted with dozens of doctors and experts. I want to be clear that I am not suggesting I have found a cure for cancer, nor am I the first to propose using repurposed drugs for cancer. What I hope to provide is a well-researched clearinghouse of information that picks up where traditional cancer therapies leave off. I aim to inspire providers caring for cancer patients to broaden their horizons and think creatively about readily available interventions, with science to back up their efficacy, that could improve their patients' outcomes.

While I no longer see patients directly, I will forever be bound by my Hippocratic Oath to 'first do no harm'. I offer this compendium of information as my latest contribution toward that end.

CHAPTER 1: INTRODUCTION

THE SOCIETAL IMPACT OF CANCER

Cancer is a global threat that seriously affects human life, with a prevalence higher than 10 million deaths yearly. Nearly 2 million Americans are expected to be diagnosed with cancer in 2023, with approximately 609,820 deaths (see Table 1). (1) Cancer is the second most common cause of death in the United States, exceeded only by heart disease. At least 42% of newly diagnosed cancers in the U.S. are potentially avoidable, including 19% of cancers caused by smoking and at least 18% caused by a combination of excess body weight, alcohol consumption, poor nutrition, and physical inactivity. (1)

Types of Cancer (MALES)	# of cases	% of cases	Types of Cancer (FEMALES)	# of cases	% of cases
Lung & bronchus	61,170	21	Lung & bronchus	59,910	21
Prostate	34,700	11	Breast	43,170	15
Colon & rectum	28,470	9	Colon & rectum	24,080	8
Pancreas	26,620	8	Pancreas	23,930	8
Liver	19,000	6	Ovary	13,270	5
Leukemia	13,900	4	Uterus	13,030	5
ALL SITES	**322,080**		**ALL SITES**	**287,740**	

Table 1: Leading sites of cancer deaths - 2023 estimates (Source: American Cancer Society)

The doctor who goes by the pen name 'Justus Hope' and who wrote a book on cancer and repurposed drugs, says almost everyone who gets cancer shares at least one common risk factor. These include cigarette smoking (40%), insulin resistance (40%), viruses (10%), and hereditary cancers such as familial adenomatous polyposis, BRACA mutations, etc. (10%). (2)

Curiously, it is not being overweight or obese that is most related to cancer; it is the presence of insulin resistance. (2) Furthermore, patients who have an elevated TG/HDL ratio (a measure of cholesterol levels) are at an increased risk of not only heart disease and Alzheimer's disease but also cancer. (2, 3)

Current treatments for cancer are highly complex and based on multiple modalities (see Figure 2), many of which are extremely expensive and have limited benefit (in terms of quality of life and 5-year survival rate), and many of which are also highly toxic. The National Cancer Institute estimated that, in 2020, cancer-related medical costs in the U.S. were $208.9 billion, which is likely a gross underestimate due to the increasing costs of individual medications. (1)

In 2000, only two oncology drugs garnered more than $1 billion in sales. Just ten years later, the top 10 oncology drugs each exceeded $1 billion in revenue. By 2010, there were three oncology drug sales representatives for every 10 oncologists in the United States. Cancer, you see, is big business. (4) Patients and their families frequently face extreme financial burden and distress as a result of cancer treatment, this is known as “financial toxicity”. (5)

Despite the vast spending on treating common cancers like lung, breast, colorectal, prostate, and pancreas, age-adjusted death rates have remained remarkably stable or have even increased since 1930. (1) Compared to the improvements in preventing and treating heart disease, cancer mortality has remained relatively unchanged over the past 30 years. (6)

Based on data collected between 1992 and 1997 for the 22 most common malignancies, Morgan et al estimated the overall contribution of curative and adjuvant cytotoxic chemotherapy to 5-year survival in adults was estimated to be 2.3% in Australia and 2.1 % in the U.S. (7) More recent data from the U.S. indicate that the 5-year cancer survival rate has only increased from 63% to 68% over the last 25 years (1995 to 2018). This data suggests that despite the billions of dollars spent on cancer therapy, the “traditional” approach has largely failed; alternative, less expensive, less toxic, and more effective therapies are urgently required.

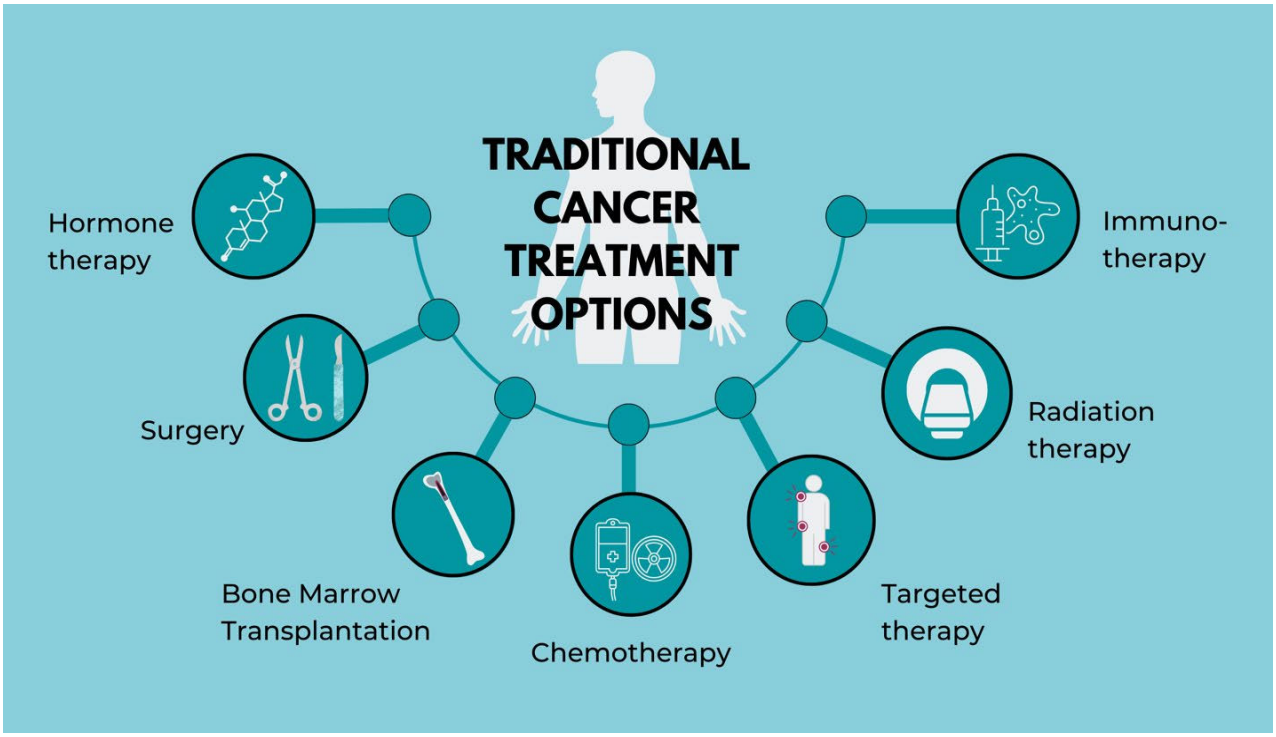

Figure 2: "Modern" cancer treatments are expensive and have limited benefit (Source: FLCCC)

CHAPTER 2: WHAT IS CANCER: UNDERSTANDING ITS PATHOGENETIC CAUSES

A basic tenet in medicine is that to treat a disease, one needs to understand the disease. Cancers are, simply, a disease of uncontrolled cell growth and division, wherein the various natural processes for containing them have partially or completely failed.

The conventional theory is that cancer is caused by genetic mutations and/or genomic instability, which drives a population of cells with the following six "classic" biological properties: (8)

1. Sustaining proliferative signaling
2. Evading growth suppressors
3. Resisting cell death (apoptosis)
4. Enabling replicative immortality
5. Inducing angiogenesis
6. Activating invasion and metastasis

Hanahan and Weinberg, who elucidated these "hallmarks of cancer," excluded the most important and universal finding in all cancer cells, (9) namely the metabolic reprogramming of cancer cells, with aerobic glycolysis — the so-called "Warburg effect" that we will explore below. (10, 11)

Conventional thinking suggests cancer arises from a single cell due to specific mutations in that cell, which are then characteristic of the patient's "cancer genome." The loss of genomic "caretakers" or "guardians," involved in sensing and repairing DNA damage, has been proposed to explain the increased mutability of tumor cells. The loss of these caretaker systems allows genomic instability, thus enabling pre-malignant cells to reach the six essential hallmarks of cancer.

The Cancer Genome Atlas Program (TCGA), modeled after the human genome project, was an attempt to determine the characteristic mutations of common cancers. (12) The TCGA assessed mutational signatures using 84,729,690 somatic mutations from 4,645 whole-genome and 19,184 exome sequences that encompassed most types of cancer. (13, 14) The finding of this massive project raises serious doubts concerning the mutation theory of cancer.

The TCGA identified 49 single-base-substitution, 11 double-base-substitution, 4 clustered-base-substitution, and 17 small insertion-and-deletion signatures. However, no specific mutation was characteristic of any particular cancer (except CML and the Philadelphia chromosome). In many tumors no mutation was found, and there was marked heterogeneity of mutations between tumors of the same cell type (intertumoral heterogeneity) and within the same tumor (intratumoral heterogeneity). (15)

In pediatric tumors such as medulloblastoma, the number of driver genes was low (zero to two). In common adult tumors, such as pancreatic, colorectal, breast, and brain cancers, the number of mutated driver genes was frequently between three to six, but several tumors had only one or two driver mutations. The notion that cancer is caused solely by mutations to key genes is becoming harder to maintain. (15) The inconsistencies are too numerous and pronounced.

AN ALTERNATE THEORY: CANCER IS A METABOLIC DISEASE

Travis Christofferson, in his book entitled "Tripping over the Truth", articulated the following:

> "*No researcher can point to any single mutation or combination of mutations and say with confidence that it is alone the cause of cancer. Nor can researchers point to a series of cellular systems rendered dysfunctional by mutations and make the same claims with confidence*." (15)

In a 2009 op-ed for The New York Times, James Watson, a Nobel Prize winner known as the "father of DNA," suggested that "*we may have to turn our main research focus away from decoding the genetic instructions behind cancer and toward understanding the chemical reactions within cancer cells*." (16)

Although very specific processes underlie malignant transformation, many non-specific influences can initiate diseases — including radiation, chemicals, viruses, inflammation, etc. Indeed, it appears that prolonged exposure to almost any provocative agent in the environment can potentially cause cancer. (17) That a very specific process could be initiated in very unspecific ways was considered "the oncogenic paradox" by Szent-Gyorgyi. (17) This paradox remains largely unresolved. (18)

Still, the concept of genetic mutations and genetic instability underpins most conventional cancer treatments. Big Pharma and the medical establishment have propagated this concept to promote the use of very expensive and toxic chemotherapeutic drugs; as mentioned above, cancer is profitable for the pharmaceutical industry. Curing cancer is not the goal.

There is considerable evidence that the genetic mutation theory may not be entirely correct. Dr. Thomas Seyfried provides a compelling argument that cancer is primarily a metabolic rather than a genetic disease. (18, 19) His underlying hypothesis is that cancer is a mitochondrial disorder with impaired oxidative phosphorylation and energy production; the genomic abnormalities are likely secondary to disordered energy production and cellular metabolism. Dr. Seyfried has clearly demonstrated that disordered mitochondrial function and energy production are common to all cancers. (18, 19) The view of cancer as primarily a metabolic disease will dramatically impact the approach to cancer management and prevention.

The idea that cancer is a metabolic disease was first noted by Otto Warburg in 1927, who was awarded the Nobel Prize in Medicine and Physiology in 1931 for his discoveries. (10, 11) Dr.

Warburg, reported that cancer cells are dependent on aerobic glycolysis (breakdown of glucose to lactate) with impaired oxidative phosphorylation (pyruvate does not enter the Krebs cycle in the mitochondria). (10, 11) In simple terms, this means cancer feeds on glucose.

In contrast to normal differentiated cells, which rely primarily on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes, most cancer cells instead rely on aerobic glycolysis, a phenomenon termed “the Warburg effect.” (20) Dr. Warburg proposed that irreversible damage to respiration was the prime cause of cancer. Aerobic glycolysis in cancer cells involves elevated glucose uptake with lactic acid production in the presence of oxygen. (18)

Following his extensive research on tumor metabolism, Dr. Warburg stated: “Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in the normal body cell by fermentation of sugar.” (10, 11)

This metabolic phenotype is the basis for tumor imaging using labeled glucose analogs and has become an important diagnostic tool for cancer detection and management. Genes for glycolysis are overexpressed in the majority of cancers examined. (18) Numerous studies show that tumor mitochondria are structurally and functionally abnormal and incapable of generating normal levels of energy. (21-26) In addition, there is compelling evidence that mitochondrial dysfunction, operating largely through the RTG response (mitochondrial stress signaling), underlies the mutator phenotype of tumor cells. (27-31) Impaired mitochondrial function can induce abnormalities in tumor suppressor genes and oncogenes.

It is well documented that tumorigenicity can be suppressed when cytoplasm from enucleated normal cells is fused with tumor cells to form cybrids, suggesting that normal mitochondria can suppress the tumorigenic phenotype. (32, 33) Singh and co-workers provided additional evidence for the role of mitochondria in the suppression of tumorigenicity by showing that exogenous transfer of wild-type mitochondria to cells with depleted mitochondria (rho0 cells) could reverse the altered expression of the APE1 multifunctional protein and the tumorigenic phenotype. (34) It is also well documented that nuclei from cancer cells can be reprogrammed to form normal tissues when transplanted into normal cytoplasm, despite the continued presence of the tumor-associated genomic defects in the cells of the derived tissues. (35, 36)

Viruses have long been recognized as the cause of some cancers. It is interesting that several cancer-associated viruses localize to, or accumulate in, the mitochondria. Viral alteration of mitochondrial function could potentially disrupt energy metabolism, thus altering expression of tumor suppressor genes and oncogenes over time. Viruses that can affect mitochondrial function include the Epstein-Barr virus (EBV), Kaposi’s sarcoma-associated herpes virus (KSHV), human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human T-cell leukemia virus type 1 (HTLV-1) as well as SARS-CoV-2. (37-39)

A cell's first line of defense against becoming cancerous is apoptosis. The apoptotic pathway is kept in check by anti-apoptotic factors; these two systems function in balance, and when one or the other becomes dominant, the cell either apoptoses, or it resists apoptotic signals. *The metabolic approach to cancer treatment promotes apoptotic pathways.*

COVID-19, SPIKE PROTEIN, AND "TURBO CANCERS"

Exposure to the spike protein, particularly following mRNA vaccination for COVID-19, has been reported in social media and non-traditional news outlets to be associated with "turbo cancers". These include new cancers which are highly malignant, often in young patients and rare cell types/locations, as well as tumor recurrences in patients after remission. It has been proposed that long COVID-19 can predispose recovered patients to develop cancer and accelerate cancer progression. (40) The U.S. Department of Defense Medical Epidemiology Database (DMED) (41) reported a 664% increase in malignant neoplasms following the deployment of COVID-19 mRNA vaccination in the military (until this data was erroneously removed).

It has been suggested that SARS-CoV-2 converts normal cells into cancer cells by modulating central metabolic pathways or hampering genomic integrity mechanisms, consequently inhibiting the apoptotic machinery and/or enhancing cell proliferation. (40, 42) The specific pathogenic mechanisms by which SARS-CoV-2 and/or the spike protein leads to increased tumorigenesis have not been well studied, however, several possible mechanisms exist. The spike protein damages mitochondria and alters mitochondrial function; this may play a central role in cancer cell development and propagation. (43-46) SARS-CoV-2 results in dysregulated innate and adaptive immunity. Depletion of CD8+ and natural killer cells reduces immune surveillance and alters the tumor microenvironment to promote tumor proliferation and metastases. (47) The retinoblastoma protein (pRB) is a tumor suppressor protein that prevents excessive cell growth by inhibiting cell cycle until a cell is ready to divide. The non-structural protein 15 (Nsp15) of coronaviruses induces the nuclear export and ubiquitination of pRB leading to its degradation via proteasomes. (48) A second potential oncogenic mechanism has been hypothesized for SARS-CoV-2 consisting of the degradation of the tumor suppressor protein p53 mediated by NSP 2 and Nsp3. (49) The open reading frame 8 (ORF8) protein of SARS-CoV-2 interacts with p62, the main autophagic cargo receptor, thereby inhibiting autophagy. (50) Spike protein impairs type I IFN signaling increasing the risk of cancer as type I IFN signaling suppresses proliferation of cancer cells by arresting the cell cycle, in part through upregulation of p53 and various cyclin-dependent kinase inhibitors. (51, 52) Metabolic reprogramming is a distinctive feature of SARS-CoV-2, and this may play a role in tumorigenesis. Metabolic reprogramming includes amino acid and lipid metabolism, carbohydrate and energy metabolism, and immune-related pathways. (40)

In a patient with cancer, it may be difficult to establish a causal role with SARS-CoV-2/spike protein. However, the tumor can be stained for spike protein, establishing this causal association. As these "turbo" cancers are frequently highly malignant and aggressive treatment is suggested.

CANCER SIGNAL PATHWAYS

Signaling pathways are a core system in which cells regulate various physiological processes and respond to external stimuli. Normally, cells have a complete set of regulatory mechanisms for initiating and/or inhibiting signal reception, cascade transmission, and ultimately gene expression, but in cancer cells, the signaling pathway is usually overactivated, and the balance is broken. Almost all the nutraceutical and repurposed drugs listed in this document have anticarcinogenic effects by promoting and/or inhibiting signal transmission through the targeted regulation of multiple links in important signal pathways. The most relevant pathways include the following:

Hexokinase-2 (HK2) pathway. In 1977, Pete Pedersen isolated the metabolic defect responsible for the Warburg effect: the hijacking of normal hexokinase by hexokinase II (HK2), followed by its massive overproduction. (15, 53) Hexokinase is the first step in glycolysis in the cytoplasm. Cancer cells have switched to an embryonic form of hexokinase (HK2), which then translocates from the cytoplasm to the outer mitochondrial membrane, where it is attached to the voltage-dependent anion channel (VDAC). (54-56) The VDAC is a pore-like opening in the outer membrane involved in shuttling nutrients and signaling molecules in and out of the mitochondria. HK2 is the major bound hexokinase isoform expressed in cancer cells that exhibit the Warburg effect. By stationing itself on the outer mitochondrial membrane, HK2 helps immortalize cancer cells, escapes product inhibition, and gains preferential access to newly synthesized ATP for phosphorylating glucose. (57) The attachment of HK2 to the VDAC on the outer mitochondrial membrane creates a state of apoptosis resistance and shunts ATP out of the mitochondria to the cytoplasm to support glycolysis. When bound to HK2, the VDAC gate is “locked”, preventing the release of cytochrome c, thereby preventing apoptosis, and effectively immortalizing the cell. Several drugs target HK2, separating the enzyme from the outer mitochondrial membrane; these include 3-bromopyruvate, resveratrol, and its derivative pterostilbene, quercetin, and curcumin.

The p53 pathway (the tumor suppressor pathway). (58) The p53 pathway is activated by sensor kinases which monitor the cell’s DNA for damage or errors. Upon detection of damage, they phosphorylate the nuclear localization factor of the p53 tumor suppressor protein, allowing it to translocate to the cell nucleus and begin expressing p21, p16, p15, and p19; this activates the cell cycle arrest pathway, initiating DNA repair, and preventing cell division. If the repair is deemed to have failed, BAX, BAK, and/or PUMA are expressed, among others, initiating the mitochondrial caspase cascade, which initiates apoptosis.

The TGF-β pathway. The TGF-β pathway plays a crucial role in regulating cell growth, differentiation, and apoptosis. (59) Upon binding to its cell surface receptors, TGF-β activates SMAD transcription factors, leading to the repression of anti-apoptotic genes and the activation of pro-apoptotic genes. This pathway acts as a tumor suppressor by promoting apoptosis in abnormal cells and inhibiting the growth of precancerous cells. Defects in this pathway can lead to uncontrolled cell growth and the development of cancer.

The Wnt signaling pathway. The Wnt signaling pathway plays a crucial role in the regulation of cell proliferation and differentiation. (60) In normal conditions, Wnt signaling maintains the balance between cell proliferation and apoptosis to ensure healthy tissue growth. However, when the pathway is activated excessively or inappropriately, it can lead to the development of cancer.

The Notch signaling pathway. The Notch signaling pathway is a signaling mechanism that plays a role in cell differentiation, proliferation, and apoptosis. (61) Disruptions in the Notch pathway, such as mutations in Notch receptors or ligands, can lead to the dysregulation of cell proliferation and differentiation, contributing to the development of cancer.

The PI3K/AKT signaling pathway. The phosphoinositide 3-kinase (PI3K) signaling pathway is linked to both growth control and glucose metabolism. The activation of the PI3K/AKT signaling pathway occurs when growth factor receptors on the cell surface bind to their ligands, triggering the activation of PI3K. (62) Once activated, AKT phosphorylates and inhibits the activity of pro-apoptotic proteins, such as BAD and FOXO. AKT also activates mTORC1, which regulates cellular metabolism and promotes cell survival by stimulating the expression of anti-apoptotic genes Bcl-2 and Bcl-xL.

The Hedgehog Pathway. Hedgehog (Hh) is one of the few signaling pathways that is frequently used during development for intercellular communication. (63) Hh is important for the organogenesis of almost all organs in mammals, as well as in regeneration and homeostasis. Further, Hh signaling is disrupted in diverse types of cancer. Mebendazole decreases the activity of the Hedgehog pathway, which is common in gliomas, melanomas, lung cancers, ovarian cancers, and colorectal cancer. (64)

The insulin growth factor-1 (IGF-1) pathway. Insulin-like growth factor 1 (IGF-1) is produced primarily by the liver as an endocrine hormone, as well as in target tissues in a paracrine/autocrine manner. IGF-1 signaling is mainly mediated by binding to its specific receptor, the insulin-like growth factor 1 receptor (IGF-1R) leading to the activation of the AKT signaling pathway resulting in cell growth, proliferation, and inhibition of programmed cell death. An elevated level of circulating IGF-1 is an established risk factor for many cancer types, whereas a decrease in IGF-1 levels is associated with lower cancer incidence.

CANCER IMMUNITY

Inflammation is an essential pillar of immune defense. However, chronic inflammation is considered a hallmark of cancer initiation and progression. Chronic inflammation demonstrates a potential to induce complex changes at molecular, cellular, and organ level and thereby alter the tumor microenvironment (TME). Cancer cells frequently secrete several growth factors that stimulate myelopoiesis and recruit myeloid cells to TME (see Figure 3). (65, 66) Therefore, the TMEs of various cancers are characterized by the high infiltration of monocytes, macrophages, granulocytes, and dendritic cells. Most myeloid cells within TMEs are present in an immature form; however, cancer-derived growth factors modify these myeloid cells into cells that support carcinogenesis by enhancing proliferation, migration, and metastasis and enabling cancer cell survival and immune evasion. Therefore, in addition to abnormalities in apoptosis, patients with cancer have derangements in immunity with the immune system failing to recognize the cancer cell as foreign. The following cells play a major role in altering the TME and promoting carcinogenesis.

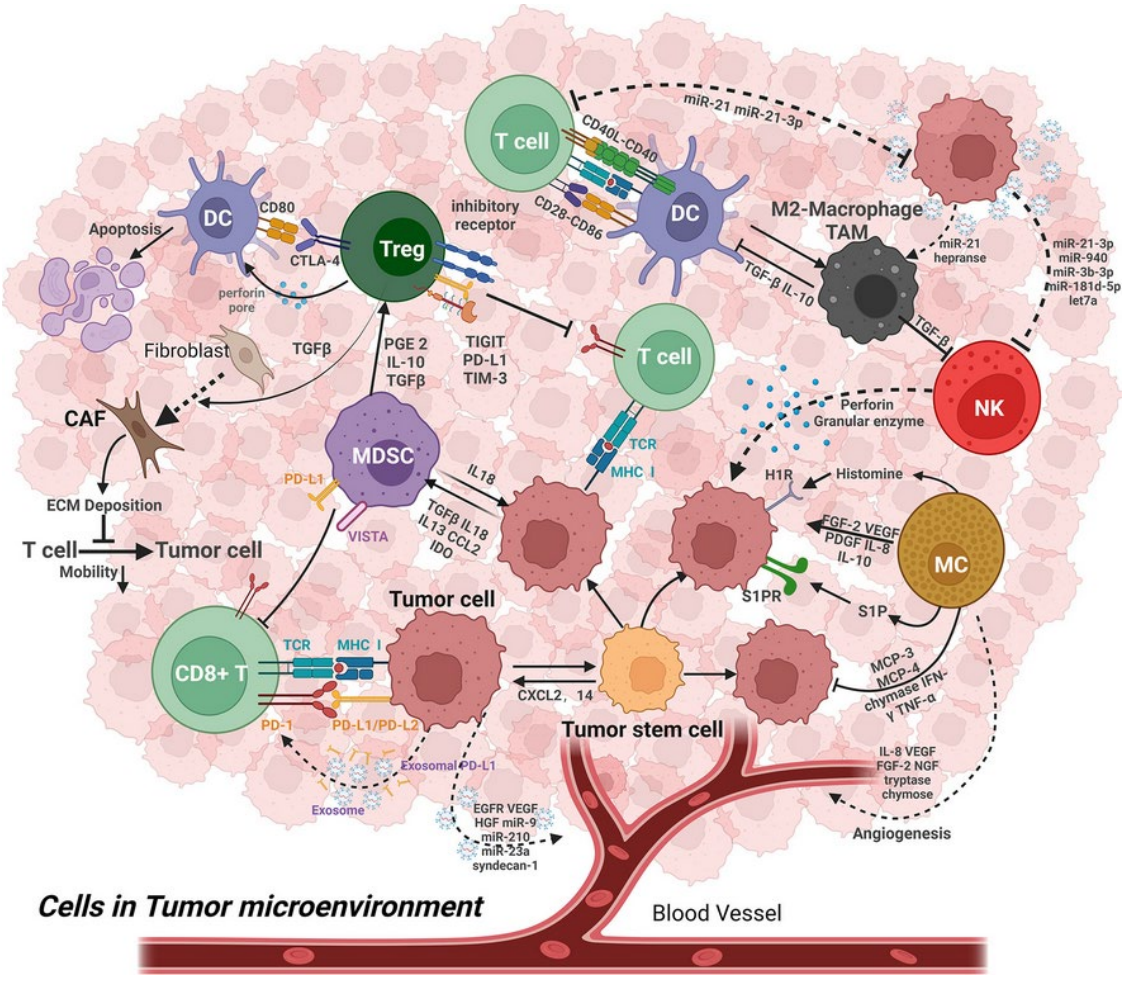

Figure 3. The cellular and structural components in the tumor microenvironment (source: Wang et al. Reproduced under [Creative Commons Attribution International license](#)) (66)

Myeloid-derived stem cells (MDSC). The establishment of primary tumor cells in distant organs, termed metastasis, is the principal cause of cancer mortality. Despite "curative" resection of the primary tumor, many patients have disseminated tumor cells at the time of diagnosis. Tumor cells can be found in the bone marrow of cancer patients at the time of their primary tumor resection. (67) These patients may then develop overt metastases months, years, or even decades later. This latency period, during which cancer cells do not grow and remain in a quiescent or equilibrium state, is known as "cancer dormancy." The timeline of metastatic dormancy is regulated by interactions between the tumor, its microenvironment, angiogenesis, and tumor antigen-specific T-cell responses. One such mediator of dormancy is myeloid-derived suppressor cells (MDSCs), whose number in infiltrating tumors has been associated with cancer stage, grade, patient survival, and metastasis in a broad range of tumor pathologies (see Figure 4). (68, 69)

Extensive studies have revealed a role for MDSCs in tumor escape from adaptive and innate immune responses, facilitating tumor progression and metastasis. (68, 70-74) Host immunity via tumor-specific cytotoxic T-lymphocytes can control disseminated tumor cell growth,

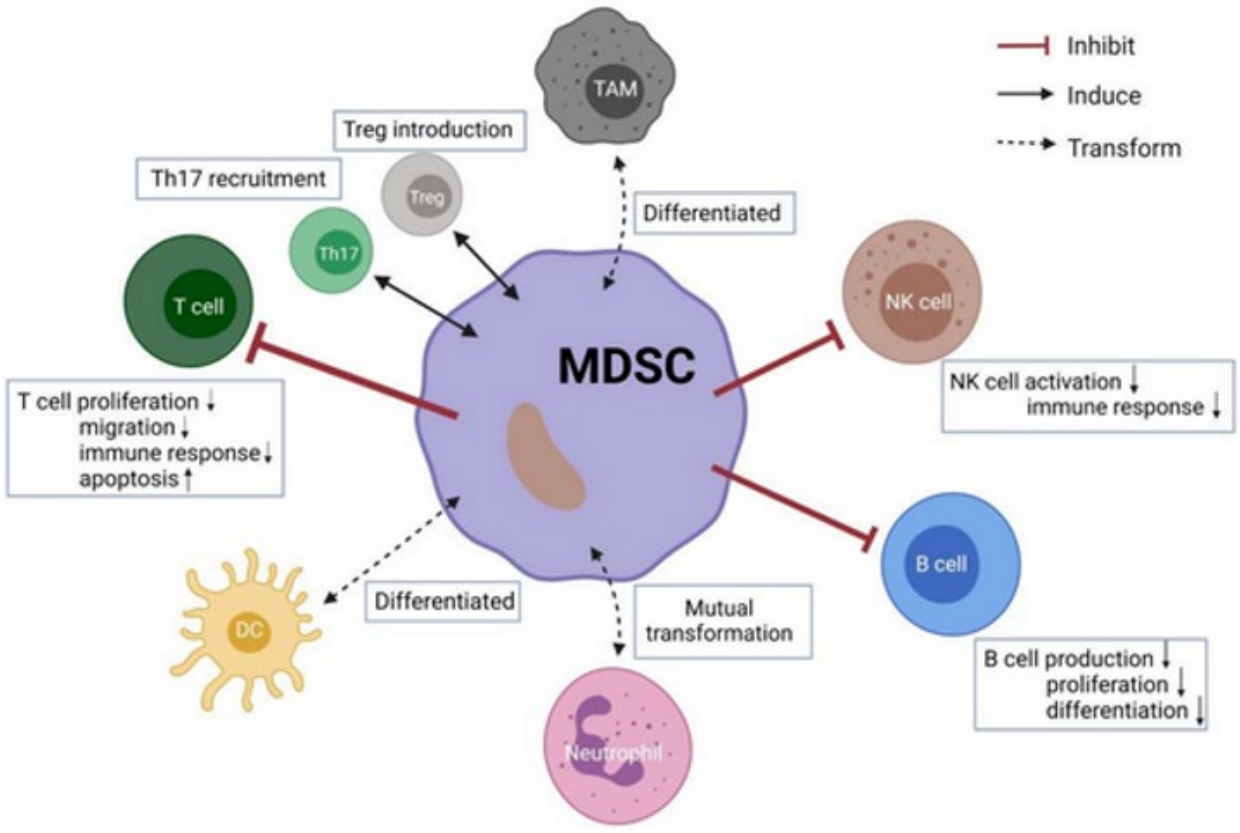

Figure 4. Crosstalk between MDSCs and other immune cells. Up arrows mean increased, and down arrows mean decreased. (Source Ma et al. Reproduced under Creative Commons Attribution International License) (69)

resulting in a dormant lesion that can be held in stasis for years or decades until released from dormancy in association with an increase in MDSCs reversing host T-cell responses. MDSCs contribute to immune evasion by inducing T-cell dysfunction through the production of reactive oxygen species, arginase-1 (ARG1), and nitric oxide synthase (NOS). ARG1 hydrolyzes extracellular L-arginine into urea and ornithine. L-arginine is required for T-cell proliferation, cytokine production, and expression of the T-cell receptor. (75)

MDSCs can not only inhibit clonal expansion of activated effector T cells, but also induce tumor-specific Treg lymphocytes to further establish and maintain T-cell tolerance in the tumor-bearing host. (73, 76, 77) In addition, by downregulating interferon, overexpressing inflammatory cytokines, and creating leaky vasculature by overexpressing matrix metalloproteinase 9 and other remodeling factors which compromise the integrity of the extracellular matrix and the basal membrane, MDSCs promote cancer cell invasion. (72)

T-regulatory cells (Tregs). Tregs universally labeled by CD4+CD25+Foxp3+CD127low/− are differentiated from traditional T lymphocytes. (78-81) To maintain immune homeostasis, Treg cells inhibit abnormal or excessive immune reactions to self- and non-self-antigens. By stifling the anti-tumor immune response of effector T cells, NK cells, and dendritic cells, Treg cells contribute to the growth and spread of tumors in the TME. (79, 81, 82) An unfavorable prognosis is associated with high Treg cell infiltration in the TME in patients with diverse cancer types. (82-88) Treg cells cause immune suppression by the production of immunosuppressive cytokines, the consumption of interleukin-2 and IL 2 receptors, modulation of CD80 and CD86 expression by dendritic cells, and direct killing of effector T cells. (82) Tregs also contribute significantly to angiogenesis via the VEGF/VEGFR pathway.

Natural Killer Cells (NK cells). Natural killer (NK) cells are the most relevant cancer-fighting cells of the innate immune system. NK cells play a vital role in recognizing and responding to abnormal cells, including cancerous and infected cells, in the immune system. T-cells possess T-cell receptors (TCRs) that allow them to bind MHC-I-peptide complexes on the cell surface, which determines whether an immune response will be initiated. Failures occur in the expression of the transporter associated with antigen processing (TAP) complex, and β2-microglobulin; these cause a loss of MHC-I self-antigen transport and surface presentation capacity, which causes the failure of the NK cell to destroy the cancerous cell.

Tumor-associated macrophages. Macrophages recruited from circulating monocytes to tumors and influenced by the presence of cancer to promote tumor malignancy and progression are often referred to as tumor-associated macrophages (TAMs) (see Figure 5). (89-91) Macrophages are divided into the M1 and M2 subgroups based on morphological, phenotypic, and functional variability. M2 macrophages have been shown to have protumor characteristics and to promote tumor development and metastasis, whereas M1 macrophages play a critical role in antitumor immunity and largely mediate proinflammatory activities in the tumor microenvironment (TME). (91-93) In metastatic tumors, macrophages have different phenotypes and functions from primary tumors and are often called metastasis-associated macrophages (MAMs).

TAMs mostly arise from bone-marrow-derived monocytes with the chemokine CCL2 produced by tumor cells being the major recruitment factor. Bone-marrow-derived monocytes include both classical monocytes and monocytic MDSCs (M-MDSCs), (94) and are crucial for the negative regulation of immune responses. (95, 96)

The immune system is skewed toward a tumor-promoting response because of the release of IL-10 by MDSCs, which inhibits the secretion of IL-12 by macrophages. Macrophages also cause MDSCs to produce more IL-10, which raises levels of IL-6 and TNF- in macrophages. (95) MDSC IL-6 was reported to be elevated by tumor cells, and vice versa. (95) The ratio of tumor cells to MDSC and macrophages controls inflammation within solid tumors, and interactions between these cells have the potential to drastically change the inflammatory environment within the tumor microenvironment. (92, 95) A high infiltration of macrophages in human solid tumors is associated with poor clinical outcomes. (91-93, 95-104) Similarly, the expression of macrophage growth factors or their chemoattractants, such as CSF1 and CCL2, in tumors or in the circulation is often associated with poor prognosis. (89)

TAMs are the crucial and dominant immune cells in the TME and significantly contribute to tumor progression by promoting angiogenesis, mediating tumor immunosuppression by inhibiting T cell function, they secrete chemokines which contribute to the recruitment of T regulatory cells in the tumor microenvironment and promote tumor cell intravasation via VEGF expression (see Figure 5). TAMs are activated by mediators secreted from tumor-infiltrating lymphocytes such as Th2, Treg cells, IL-10, TGF-β. (105) By reducing antitumor immunity, Foxp3+ regulatory T (Treg) cells and tumor-associated macrophages (TAMs) both aid in the growth of tumors. Researchers identified TAMs and Tregs as responsible for direct tumor immune evasion. (106) TAMs and Tregs combine to form a cellular network that is partially redundant and contributes to the robustness of tumor immunosuppression as well as resistance to immunotherapy. (92, 106)

TAMs play a major role in tumor metastases. (107) Cancer-associated fibroblast are produced because of the mesenchymal transition of endothelial cells during the growth of tumors, and they secrete Heat shock protein-90 alpha (*Hsp90α)*, which promotes M2 polarization and maintains an immunosuppressive milieu. (108) By secreting different mediators that alter the tumor promoting TME, TAMs can accelerate the growth of tumors. Proangiogenic growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor- (TGF-), NF-kB-mediated factors that prevent apoptosis, and proangiogenic growth factors (99) that promote cancer cell migration and metastasis. (92) TAMs can also increase the tumor stemness, which upregulates the release of immunosuppressive cytokines such as IL-1ra. (92, 109) By releasing growth factors like the epidermal growth factor receptor (EGFR), which encourages the proliferation of cancer cells, TAMs may directly drive the proliferation of cancer cells. (110) In hepatocellular carcinoma, active Wnt/-catenin signaling induced by a greater number of invading macrophages can promote the proliferation of tumor progenitor cells, and targeted macrophage reduction can diminish Wnt and slow tumor growth. (111)

By controlling the PI3k/Akt pathways in cancer cells, TAMs may block proapoptotic cytokines such tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). (112) By introducing miRNAs into cancer cells, such as colorectal cancer and pancreatic ductal adenocarcinoma cells, exosomes produced by M2 macrophages spread malignancy. (113) Metastatic cells use the Cysteine-cysteine motif chemokine ligand 20 (CCL20), also known as macrophage inflammatory protein-3α, MIP*3α*) - Chemokine receptor 6 (CCR6) axis/pathway to attract monocytes and differentiate them into metastasis-associated macrophages (MAMs) that support tumor cell survival and metastasis by suppressing T cells. (92, 98) Additionally, TAMs release several enzymes, such as matrix metalloproteinases (MMPs) and cyclooxygenase type-2 (COX-2), which all work to promote angiogenesis by destroying the matrix and enabling endothelial cells to invade. (114) Despite TAMs having pro-tumorigenic characteristics, they can ingest tumor cells, and cause tumor apoptosis by releasing NO, ROS, and IL-12, which encourage anti-tumor responses and limit tumor growth in specific situations. (115) This suggests that immunosuppressive and immunostimulatory TAM can coexist in the same tumor. (92, 95, 116)

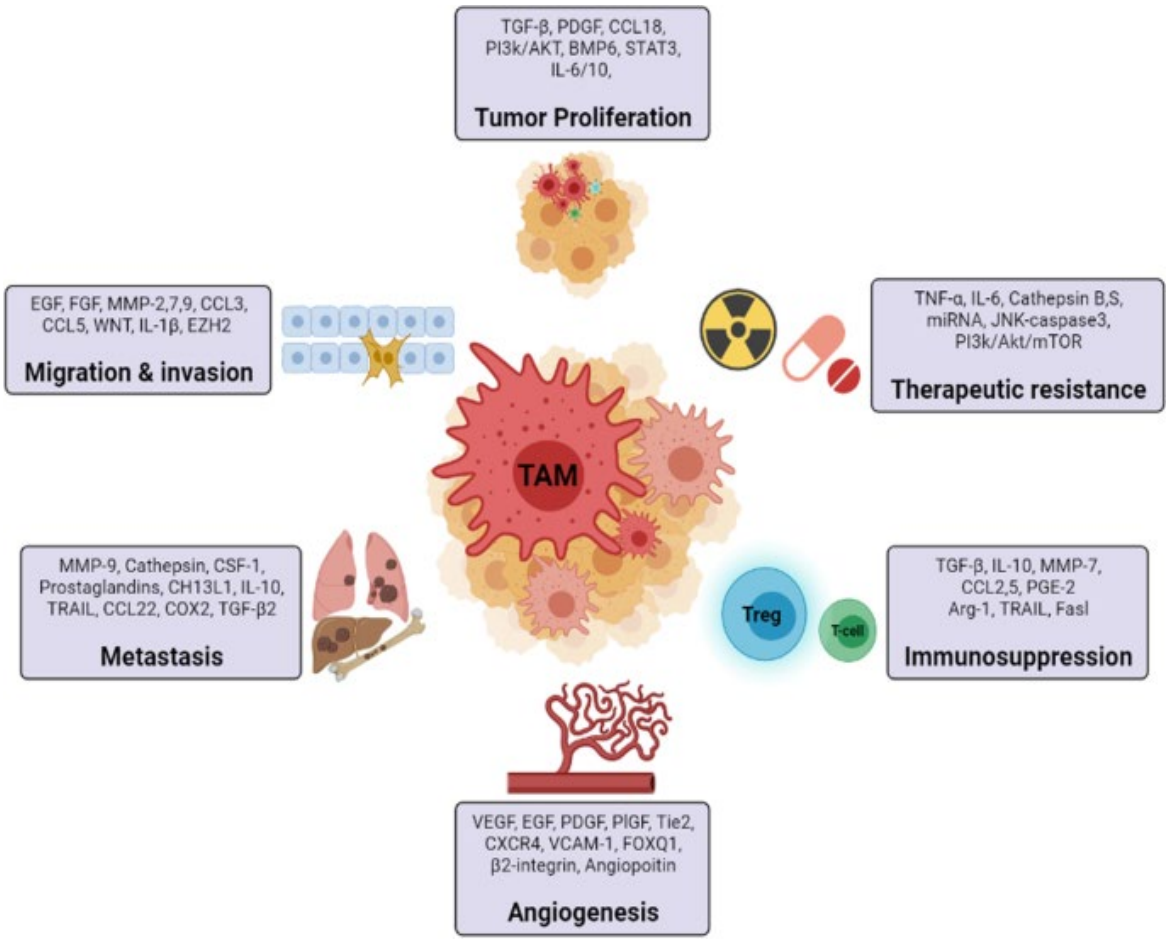

Figure 5. The role of tumor associated macrophages in cancer. (Source: Reproduced from Kumari et al under Creative Commons Attribution 4.0 International License). (91)

PLATELETS AND CANCER

Platelets have been implicated in enabling successful metastasis and worsening the prognosis of patients with cancer by guarding tumor cells from immune elimination and promoting arrest and extravasation of tumor cells. (117-119) Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Platelet-derived TGFβ and direct platelet-tumor cell contacts synergistically activate the TGFβ/Smad and NF-κB pathways in cancer cells, resulting in their transition to an invasive mesenchymal-like phenotype and enhanced metastasis in vivo. (117) In a symbiotic manner, tumor-derived bioactive molecules have been shown to prompt an increase in platelet activation and production. (120, 121)

ANGIOGENESIS AND METASTASIS

Angiogenesis involves neovascularization or the formation of new capillaries from existing blood vessels and is associated with the processes of tissue inflammation, wound healing, and tumorigenesis. Angiogenesis is required for most tumors to grow beyond an approximate size of 0.2-2.0 mm. In addition to its role in up-regulating glycolysis in response to hypoxia, HIF-1α is the main transcription factor for vascular endothelial growth factor (VEGF), which stimulates angiogenesis.

Metastasis is the general term used to describe the spread of cancer cells from the primary tumor to surrounding tissues and to distant organs and is a primary cause of cancer morbidity and mortality. To complete the metastatic cascade, cancer cells must detach from the primary tumor, intravasate into the circulatory and lymphatic systems, evade immune attack, extravasate at distant capillary beds, and invade and proliferate in distant organs. The macrophage hypothesis of metastasis suggests that metastatic cells arise following fusions of macrophages or bone marrow-derived hematopoietic cells with committed tumor cells. (107)

CANCER STEM CELLS (CSC)

Despite arising initially from a single cell, almost all tumors become very heterogeneous, expressing different markers, and containing proliferative and more differentiated cells. Tumor heterogeneity may be responsible for tumor progression, metastasis, resistance to therapy, and relapse. (122) Fast-growing cancer cells make up the bulk of a tumor with a smaller population of cancer stem cells (CSC). CSCs are a cell population similar to stem cells with characteristics of self-renewal and differentiation potential in tumor tissue. (123) Although CSCs are similar to stem cells in terms of function, because of the lack of a negative feedback regulation mechanism for stem cell self-renewal, their powerful proliferation and multidirectional differentiation abilities are unrestricted, which allows CSCs to maintain certain activities during chemotherapy and radiotherapy. When the external environment is suitable, CSCs will rapidly proliferate to reactivate the formation and growth of tumors.

CSCs are defined by their functional properties and can self-renew and propagate the tumor over an extended period and recapitulate the different cell lineages found in the primary tumors. CSCs reside in particular tumor microenvironment niches that play an important role in regulating their proliferation, renewal, differentiation, and stemness. (122) Inflammation and hypoxia promote the acquisition of a CSC phenotype and its maintenance. (122) Chemotherapy induces changes in the tumor microenvironment that support CSC survival and tumor relapse.

The CSC colony is slow-growing and resembles normal cells in many respects. Chemotherapy and radiation all attempt to kill the fast-dividing cancer cells; however, they also kill fast-dividing normal cells, including the hair, lining of the gastrointestinal tract, and bone marrow.(2) However, like normal cells, chemotherapy spares CSC. Furthermore, both chemotherapy and radiation treatment have a stimulating effect on the CSC population, causing them to grow resistant new tumor cells and replace the bulk of what was removed (See Figure 1). (2, 122, 124) Dr. Hope considers this like the effect of "pruning a tree thereby stimulating new growth" (see Foreword). The tumors of patients with breast cancer brain metastasis were reported to be highly cancer stem-like cell-enriched, suggesting that brain metastases probably arise by the seeding of cancer cells with stem features. (125) In bladder cancer, the resistance of tumor cells to chemotherapy was caused by slow-cycling CSCs that were stimulated to proliferate in between cycles of chemotherapy. (126) The proliferative response of CSCs was promoted by prostaglandin E2 (PGE2) release by cancer cells that were killed by the chemotherapy. Targeting PGE2 by monoclonal blocking antibody or by the administration of cyclooxygenase-2 inhibitor attenuated chemoresistance and suggested that targeting this pathway in between cycles of chemotherapy may enhance the therapeutic response in bladder cancer.

The successful elimination of a cancer requires an anticancer therapy that will affect both differentiated cancer cells and CSC. At present, conventional therapy that includes radio-, chemo-, and immunotherapy kills rapidly proliferating and differentiated cells. These treatments may cause the tumor to shrink but will not prevent it from recurring. Thus, a combination of treatments that target both rapidly-proliferating cancer cells and the quiescent or slow-proliferating cancer stem cells is required. (57)

Adding repurposed drugs to attack CSC should be a priority and should be done at the time of initiation of chemotherapy and radiation therapy. (2) Common repurposed drugs that can attack CSC include green tea extract, melatonin, vitamin D3, metformin, curcumin, statins (atorvastatin), berberine, mebendazole, doxycycline, ivermectin, resveratrol, aspirin, diclofenac phosphodiesterase 5-inhibitors, and omega-3 fatty acids. (2, 127-130)

HOW CHEMOTHERAPY ACTIVATES CANCER AGGRESSIVITY

Another problem with chemotherapy is that the drugs make cancer more aggressive by activating massive inflammation in the body. Chemotherapy activates the inflammatory master controller, NF-KB, which produces the inflammatory cytokine IL-6. (131) This massive, chemotherapy-induced increase in inflammation has the following consequences: (57)

- Stimulates more rapid cancer growth (proliferation).
- More resistance to apoptosis (programmed cell death).
- More invasive and metastatic behavior of the cancer.
- Stimulates angiogenesis.
- Creates a chemo-resistant cancer cell population.

These findings suggest that patients should receive anti-inflammatory therapies concomitant with chemotherapeutic agents. In addition, almost all the repurposed anticancer drugs listed in this monograph potentiate the effects of standard chemotherapy agents allowing a dose reduction of these agents.

CHAPTER 3: PREVENTING CANCER

As previously mentioned, at least 42% of newly diagnosed cancers in the United States could potentially be avoided. (1) The most important interventions to reduce the risk of cancer include: quitting smoking, limiting (or stopping) alcohol consumption, improving nutrition, adopting time-restricted eating (see FLCCC guide to fasting and healthy eating), treating metabolic syndrome/insulin resistance (see FLCCC insulin resistance protocol), engaging in moderate physical exercise, and supplementing with vitamin D3. (1) Smoked and processed meats should be avoided as they are indisputably related to a number of cancers, most notably gastric cancer. (132, 133)

The DO-HEALTH trial was a three-year, multicenter, 2 × 2 × 2 factorial design double-blind, randomized controlled trial to test the individual and combined benefit of supplemental vitamin D3 (2000 IU/day), and/or 1 g per day of marine Omega-3s, and/or a simple home strength exercise program. These were compared to placebo and control exercise. (134, 135) While each intervention individually reduced the risk of cancer, the combination was synergistically highly effective in reducing the risk of cancer (the adjusted hazard ratio of adjusted HR was 0.39). Although reported as a negative study, the Vitamin D and Omega-3 Trial (VITAL) funded by the NIH further corroborated the protective effect of vitamin D on cancer mortality, reporting lower rates of death caused by cancer among participants randomized to vitamin D3 vs placebo (HR, 0.72 [95% CI, 0.52-1.00]). (136) In addition, many other nutraceuticals appear to be highly effective in preventing cancer. Published peer-reviewed studies strongly support the use of green tea catechins in reducing the risk of numerous cancers. (137, 138) In addition, melatonin has numerous health benefits including increasing health span and decreasing the risk of neurodegenerative diseases; this natural hormone may also likely be effective in preventing cancer.

Metformin suppresses tumor initiation, growth, and spread and is recognized as an effective anticancer drug even for non-diabetics. Diabetics taking metformin had a lower all-cause mortality than normal non-diabetics not taking it. (139) Metformin has been demonstrated to reduce the risk of prostate cancer in men with type 2 diabetes. (140) Meta-analyses have examined the role of metformin in the primary prevention of cancer, where it was found to significantly reduce overall cancer incidence. (141, 142)

Based on this data we suggest the following interventions for all individuals to reduce their risk of cancer:

- Quit smoking.
- Reduce or limit the use of alcohol.
- Lose weight: adopt a healthy diet, manage insulin resistance, and follow a time-restricted eating plan.
- Avoid processed food and processed vegetable oils. (143)
- Avoid sugary beverages and pure fruit juices. (144, 145)

- Vitamin D3: 5000 u/day and adjusted according to vitamin D3 level (see Table 3).
- Omega 3 fatty acids: 2-4 g/day.
- Green tea catechins: 500-1000 mg/day. (137, 146) Green tea extract should be taken during/after a meal, rather than on an empty stomach. (147) See precautions in the section labeled 'Green Tea'.
- Melatonin: 0.75–5 mg (extended/slow release) at night. (127, 148)
- Metformin: Metformin should be considered in anyone at high risk of cancer, whether their risk extends from diabetes, prediabetes, insulin resistance, chronic viral infection, smoking, or genetics. Requires doctor's evaluation, approval, and prescription. (Suggested dose ranges from 250-2000 mg daily.) (2)
- Regular aerobic exercise and resistance training 30 minutes/day (walking, home strength training, etc.).
- Stress reduction (meditation, yoga, mindfulness exercises, etc).(149-151)
- At least 8 hours of high-quality sleep (ensure adequate sleep hygiene). (151-154)

Familial adenomatous polyposis (FAP) is a hereditary condition that causes colon cancer at a young age. Many patients choose to have a total colectomy before the age of 20 rather than risk fatal cancer development. In a mouse model of FAP, the combination of mebendazole and sulindac (an NSAID) reduced the number of polyps by 90%. (155) These preclinical findings support the consideration of clinical trials for patients with FAP as well as other high-risk cancer patients. The use of phosphodiesterase-5 inhibitors (e.g., sildenafil) is associated with a lower risk of colorectal cancer in men with benign colorectal neoplasms. (156)

CHAPTER 4: THE METABOLIC APPROACH TO TREATING CANCER

Although mitochondrial replacement therapy could, in principle, restore a more normal energy metabolism and differentiated state to tumor cells, it is unlikely that this therapeutic approach would be available in the foreseeable future. (18, 19) However, if cancer is primarily a disease of energy metabolism, then rational approaches to cancer management can be found in therapies that specifically target energy metabolism.

The goal of metabolic adjunctive treatments is to "starve the cancer cell" by modulating energy pathways that are important to the survival of cancer cells and thereby reduce cancer growth and cancer metastases (the cause of death in over 90% of cancer patients). An approach to cancer treatment is emerging with research showing impressive results from the use of metabolically targeted drug cocktails alongside conventional chemotherapy. The metabolic protocol is designed to work primarily by restricting the overall ability of cancer cells to take up and use (i.e., 'metabolize') energy. By starving cancer cells of energy substrates, metabolic interventions may reduce the capacity of cancer cells to defend themselves against chemotherapy and radiation. The metabolic protocol may also act on the many dysregulated signaling pathways within cancer cells helping to enable apoptosis, or "programmed cell death," allowing chemotherapy and radiation to kill cancer cells more effectively.

The most important and central approach to the metabolic treatment of cancers is dietary calorie (glucose) restriction. This is supplemented with pharmacologic and nutraceutical compounds that target specific cancer pathways and interventions that restore "normal" anticancer immunity.

It is important to emphasize that there is no single "magic bullet" and that multiple interventions act synergistically and simultaneously to promote cancer cell death. This approach is similar to that of the Care Oncology Clinic, which uses the patented *Metabolic Oncology COC Protocol™* consisting of a combination of conventional pharmaceuticals (metformin, atorvastatin, mebendazole, doxycycline, and an NSAID) that hypothetically work together to restrict the overall ability of cancer cells to take up and use energy. (157) However, similar to the work of Jane McLelland, (158) we suggest a more extensive and targeted list of pharmacologic and nutraceutical compounds.

The metabolic approach to cancer should be considered as adjunctive to more "traditional" approaches to cancer treatment. The metabolic treatments will likely act synergistically with the more traditional approaches, thereby increasing tumor response rate, limiting the toxicities of standard chemotherapy, limiting the risk of metastasis, and leading to an improvement in overall quality of life. This combined approach will allow for reduced dosages of standard chemotherapeutic agents, drastically reducing their toxicity.

DIETARY CALORIC RESTRICTION, THE KETOGENIC DIET, AND "REAL" FOOD

Numerous studies show that dietary energy restriction is a general metabolic therapy that naturally lowers circulating glucose levels and significantly reduces the growth and progression of numerous tumor types, including cancers of the breast, brain, colon, pancreas, lung, and prostate. (159-165) An impressive body of evidence indicates that dietary energy restriction can retard the growth rate of many tumors regardless of the specific genetic defects expressed within the tumor. (159-165)

As demonstrated by Dr. Otto Warburg, almost all cancer cells are dependent on glucose as a metabolic fuel via aerobic glycolysis, (10, 11) with hyperglycemia being a potent promotor of tumor cell proliferation and associated with poor survival. (166) Although the mechanisms responsible for the caloric-restriction-mediated reduction in tumorigenesis have not been unequivocally identified, they may involve caloric-restriction-induced epigenetic changes as well as changes in growth signals and in the sirtuin pathway. (167)

Dietary energy restriction specifically targets the IGF-1/PI3K/Akt/HIF-1α signaling pathway, which underlies several cancer hallmarks including cell proliferation, evasion of apoptosis, and angiogenesis. IGF-1 production is stimulated by growth hormone (GH) and can be inhibited by calorie restriction, suggesting it could play a central role in the protective effect of calorie restriction. In this regard, humans with mutations in the GH receptor (known as Laron syndrome) have low serum IGF-1 levels, and have a remarkably low risk of developing cancer. (167) Glucose reduction not only reduces insulin but also reduces circulating levels of IGF-1, which is necessary for driving tumor cell metabolism and growth.

Dietary energy restriction targets inflammation and the signaling pathways involved with driving tumor angiogenesis. Indeed, calorie restriction is considered a simple and effective therapy for targeting tumor angiogenesis and inflammation.

Calorie restriction results in the downregulation of multiple genes and metabolic pathways regulating glycolysis. Besides lowering circulating glucose levels, dietary energy restriction elevates circulating levels of fatty acids and ketone bodies (β-hydroxybutyrate and acetoacetate). Fats, and especially ketones, can replace glucose as a primary metabolic fuel under calorie restriction. This is a conserved physiological adaptation that evolved to spare protein during periods of starvation. Many tumors, however, have abnormalities in the genes and enzymes needed to metabolize ketone bodies for energy. Elevation in ketone bodies is well known to be able to suppress blood glucose levels and glycolysis, which are major drivers of tumor growth. A transition from carbohydrates to ketones for energy is a simple way to target energy metabolism in glycolysis-dependent tumor cells while enhancing the metabolic efficiency of normal cells. Metabolism of ketone bodies and fatty acids for energy requires inner mitochondrial membrane integrity and efficient respiration, which tumor cells largely lack. Under fasting conditions, ketone bodies are produced in the liver from fatty acids as the main source of brain energy. Ketone bodies bypass the glycolytic pathway in the cytoplasm and are metabolized directly to acetyl CoA in the mitochondria.

Ketone bodies have been shown to inhibit histone deacetylases and may decrease tumor growth. In addition, the ketone body β -hydroxybutyrate acts as an endogenous histone deacetylase inhibitor, resulting in downstream signaling that protects against oxidative stress. (168-171) Calorie restriction, which lowers blood glucose and elevates blood beta-hydroxybutyrate, reduces nuclear expression of phosphorylated NF-kB (p65), cytosolic expression of phosphorylated IkB, total IkB, and DNA promoter binding activity of activated NF-kB. (172) NF-kB is a major driver of inflammation in the tumor microenvironment.

The randomized controlled trial by Chi et al describes how adhering to a caloric-restricted diet for 6 months can have therapeutic benefits in slowing the growth of prostate cancer. (173) The men in the control group were instructed to avoid any dietary changes, whereas the men in the calorie-restricted group were coached by a dietician to restrict dietary carbohydrates to <20 grams/day. The authors found that elevated levels of serum ketone bodies (3- hydroxy-2-methylbutyric acid) at both 3 and 6 months were associated with significantly longer prostate cancer antigen doubling time ($p < 0.0001$), which is a marker of prostate cancer growth rate. These findings support the concept that elevations in ketone bodies are associated with reduced tumor growth.

A ketogenic diet following completed courses of chemotherapy and radiotherapy was further reported to be associated with long-term survival in a patient with metastatic non-small cell lung cancer. (174) “Long-term” survival has been reported in patients with glioblastoma on a ketogenic diet. (174, 175) Furthermore, evidence shows that therapeutic ketosis can act synergistically with conventional chemotherapeutic drugs, irradiation, and surgery to enhance cancer management, thus improving both progression-free and overall survival. (175) In addition, it is highly likely that therapeutic ketosis acts synergistically with the repurposed anticancer drugs reviewed in this document. Therapeutic ketosis requires a blood glucose < 90 mg/dl and a blood ketone > 2 mmol/l, aiming for a Glucose-Ketone Index < 2. (176) See the Glucose-Ketone Index Calculator in the section on caloric restriction. There are no known drugs that can simultaneously target as many tumor-associated signaling pathways as can calorie restriction. Hence, energy restriction can be a cost-effective adjuvant therapy to traditional chemo- or radiation therapies, which are more toxic, costly, and generally less focused in their therapeutic action than dietary energy restriction.

According to Dr. Seyfried: “Most human metastatic cancers have multiple characteristics of macrophages. We found that neoplastic cells with macrophage characteristics are heavily dependent on glutamine for growth. We have not yet found any tumor cell that can survive for very long under prolonged restriction of glucose and glutamine. Furthermore, we have not yet found any fatty acid or ketone body that can replace either glucose or glutamine as a growth metabolite. It, therefore, becomes essential to simultaneously restrict both glucose and glutamine while placing the person in nutritional ketosis for successful cancer management.”

Although dietary energy restriction and anti-glycolytic cancer drugs will have therapeutic efficacy against many tumors that depend largely on glycolysis and glucose for growth, these

therapeutic approaches could be less effective against those tumor cells that depend more heavily on glutamine than on glucose for energy. Glutamine is a major energy metabolite for many tumor cells and especially for cells of hematopoietic or myeloid lineage. Green tea polyphenol (EGCG) targets glutamine metabolism by inhibiting glutamate dehydrogenase activity under low glucose conditions (see section below). (137, 177-181) In addition, resveratrol and curcumin inhibit glutaminolysis. (2) Glioblastoma, breast cancer, pancreatic cancer lung cancer prostate cancer, and lymphoma may depend on glutamine as a source of energy. (2)

REAL FOOD: THE BANTING DIET

Patients are strongly recommended to eat “real food” and not processed food. If it looks like food, it is likely food. If it comes in a box or carton, has a food label, and/or a long list of chemicals and additives with long and complex names it is not food. A high proportion of the population (60-80%) eating a Western diet is addicted to processed food. (182) Processed food addiction is a recognized “substance use disorder” (SUD) and should be treated as such. Animal experiments demonstrate that sugar and fructose are more addictive than cocaine and heroin and that carbohydrate addicts demonstrated many of the behaviors of those with a SUD. (182)

A low carbohydrate-high fat (LCHF) dietary pattern is especially important for patients with cancer. As already discussed, a low carbohydrate ketogenic diet is essential to control blood glucose levels. Furthermore, a real food diet high in both soluble and insoluble fiber and fermented foods is critical to normalize the microbiome. Alterations in the microbiome play an important role in both tumorigenesis and tumor propagation. Altered gut microbiota is associated with resistance to chemotherapeutic drugs while restoration of a normal microbiome improves the response to the anticancer drugs. (183-186) Antibiotics cause severe dysbiosis; this is associated with an increased risk of cancer and reduced response to chemotherapy. (187, 188)

The Banting Diet comes close to meeting the criteria of the ideal real-food diet. (189-191) William Banting (1796-1878), a Victorian undertaker, is regarded as the father of the low-carbohydrate diet. In 1863, Banting wrote a booklet called *Letter on Corpulence, Address to the Public,* which contained the particular plan for the diet he followed. (189, 191) It was written as an open letter in the form of a personal testimonial. Banting accounted for all his unsuccessful fasts, diets, spas, and exercise regimens in his past. His previously unsuccessful attempts had been on the advice of various medical experts. He then described the dietary change that finally had worked for him, following the advice of another medical expert. "My kind and valued medical adviser is not a doctor for obesity, but stands on the pinnacle of fame in the treatment of another malady, which, as he well knows, is frequently induced by [corpulence]." His own diet consisted of meat, greens, fruits, and dry wine. The emphasis was on avoiding sugar,

saccharine matter, starch, beer, milk, and butter. Banting's pamphlet was popular for years to come and would be used as a model for modern diets.

The Banting diet consists mainly of animal protein (including poultry, eggs, and fish), saturated animal fats (including lard, duck fat, and butter), coconut oil, olive oil, and macadamia oil, some cheeses and dairy products, some nuts and seeds, fresh vegetables grown mainly above the ground and a few berries. (190) The Banting diet excludes all processed “food”, pre-packed, boxed, and “food” in wrappers as well as “fast food”. It excludes all foods with sugar, fructose, and maltose as well as grain products (wheat, barley, oats, rye) and soy products. (190) Soy products are genetically modified, toxic non-foods. (190) Replace all seed oils (canola, sunflower, safflower, cottonseed, soy) with healthy saturated fats; extra virgin olive oil and virgin coconut oil are freely encouraged. High-fat dairy products are suggested and not skimmed or fat-free dairy.

MANAGEMENT OF CANCER CACHEXIA

Cancer-associated cachexia is a disorder characterized by loss of body weight with specific losses of skeletal muscle and adipose tissue. (192, 193) It is characterized by a negative protein and energy balance. Cancer cachexia is driven by a variable combination of reduced food intake and metabolic changes, including elevated energy expenditure, excess catabolism, and inflammation. (192) Cancer cachexia is defined as weight loss greater than 5%, or BMI <20 and any degree of weight loss >2%; or skeletal muscle index consistent with sarcopenia (males <7·26 kg/m²; females <5·45 kg/m²). (194) Cancer cachexia is associated with reduced physical function, reduced tolerance to anticancer therapy, and reduced survival. (192, 193) Cancer cachexia is common in patients with advanced cancer.

The therapeutic strategy is to address coexisting treatable factors. The treatment of cancer cachexia should be chosen in a way that can be continued according to the patient’s condition and lifestyle. Patients with advanced cancer who can complete an exercise program show improvements in physical function and quality of life (see exercise [intervention 10] in section on metabolic treatments of cancer). In RCTs in patients with advanced cancer, nutritional therapy alone has not demonstrated consistent efficacy on weight, quality of life, and survival.(195, 196) Nevertheless, we suggest three nutrient-dense meals a day (following the Banting Diet). Intermittent fasting/time-restricted feeding should be avoided (except during chemotherapy); however, patients should avoid snacking between meals and should avoid eating within 3-4 hours before going to sleep (to promote autophagy while sleeping).

Furthermore, we suggest a complete nutritional “shake” containing superfoods such as plant protein, super green, omega-3 fatty acids, vitamins, adaptogenic herbs, probiotics, fiber, mushrooms, and berries (e.g. Ka’Chava ™ https://www.kachava.com/ and 310 Shakes™ https://310nutrition.com/). These “superfood shakes” are preferred over regular protein shakes.

Tube feeding should be avoided as this may negatively impact quality of life. Pharmacological therapies for cachexia have limited efficacy and are difficult to improve the severely reduced muscle mass in patients with cachexia. (193) Anamorelin, a ghrelin receptor agonist, is currently the only drug available for the indication of cancer cachexia in a limited number of countries.(197) However, it has been reported that anamorelin elevates IGF-1 which promotes tumor growth. (198)

INTERMITTENT FASTING, AUTOPHAGY, AND CANCER

[The reader is referred to the FLCCC Guide to Fasting and Healthy Eating for more detailed information.]

Fasting has a profound effect on promoting immune system homeostasis, improving mitochondrial health, and increasing stem cell production. (199-203) Fasting stimulates the clearing of damaged mitochondria (mitophagy), misfolded and foreign proteins, and damaged cells (autophagy). Intermittent fasting/time-restricted eating is the single most effective method to activate autophagy. However, the role of intermittent fasting and autophagy in cancer is complex (see below).

The 2016 Nobel Prize in Physiology or Medicine was awarded to Yoshinori Ohsumi for his initial elucidation of the morphological and molecular mechanisms of autophagy in the 1990s. (204, 205) Macroautophagy (herein referred to as autophagy) is a conserved lysosomal degradation pathway for the intracellular recycling of macromolecules and clearance of damaged organelles and misfolded proteins to ensure cellular homeostasis. (206) Dysfunctional autophagy contributes to many diseases, including cancer. However, autophagy can suppress or promote tumors depending on their developmental stage and type. Modulating autophagy for cancer treatment is a therapeutic approach currently under intense investigation.

During autophagy, cytoplasmic constituents (damaged proteins, misfolded proteins, foreign proteins) are engulfed within double-membrane vesicles called autophagosomes, which subsequently fuse with lysosomes to form autolysosomes, where the cargo is degraded or recycled (see Figure 6). Autophagy occurs at basal levels under physiological conditions and can also be upregulated in response to stressful stimuli such as hypoxia, nutritional deprivation, DNA damage, and cytotoxic agents. (206) The molecular machinery that mediates the autophagic process is evolutionarily conserved in higher eukaryotes and regulated by specific genes (ATG genes), which were initially characterized in yeast.

Intermittent fasting/time-restricted eating is the most effective therapy for the treatment of insulin resistance, metabolic syndrome, and type II diabetes. Intermittent fasting has additional benefits in prolonging health span, alleviating the symptoms/curing many chronic diseases, as well as preventing cardiovascular disease and cancer. (207) The metabolic effects of intermittent fasting are numerous and include increasing insulin sensitivity, decreasing blood glucose levels, decreasing insulin levels, decreasing insulin-like growth factor, activating the sirtuin pathway, and activating autophagy. Intermittent fasting is the most effective means of activating autophagy and accounts for many of its beneficial effects.

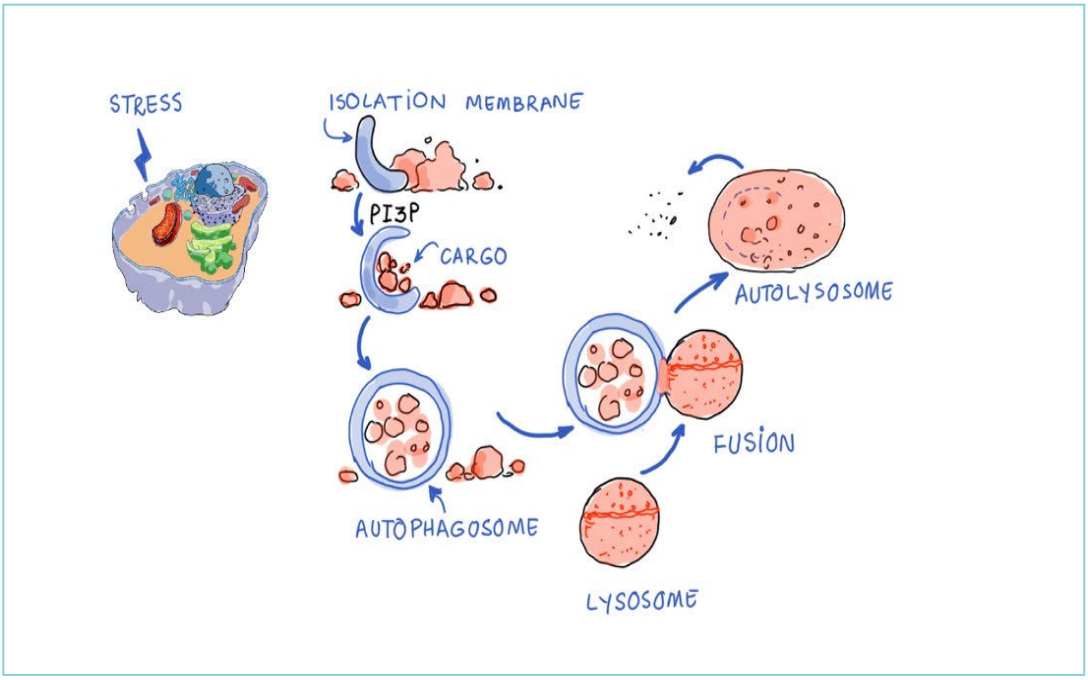

Figure 6. Autophagy pathway (Source: Dr. Mobeen Syed)

While autophagy may play an important role in preventing the development of cancer, it may paradoxically promote cancer cell proliferation. Once a tumor is established, the main function of autophagy is to provide a means to cope with cellular stressors, including hypoxia, nutritional and growth factor deprivation, and damaging stimuli, thus allowing tumor adaptation, proliferation, survival, and dissemination. Autophagy, by degrading macromolecules and defective organelles, supplies metabolites and upregulates mitochondrial function, supporting tumor cell viability even in constantly stressful environments. Cancer cells, which have an increased metabolic demand for energy and macromolecular building blocks to proliferate, show elevated levels of autophagy to recycle nutrients. (208) However, paradoxically, excessive autophagy may lead to cancer cell death. (209) Many of the repurposed drugs listed here (vitamin D, phosphodiesterase inhibitors, etc.) have been demonstrated to enhance tumor cell death by activating the autophagy pathway.

Limited rodent studies and no human studies have evaluated the independent effects of intermittent fasting in modulating cancer progression. In a study of a high-fat driven, postmenopausal breast cancer mouse model, intermittent fasting markedly inhibited tumor initiation, progression, and metastasis compared with mice fed *ad libitum* in the absence of calorie restriction or weight loss. (210) This beneficial effect of intermittent feeding was probably mediated, at least in part, by reduced insulin signaling because systemic insulin infusion through implanted pumps reversed the intermittent fasting-mediated cancer-protective actions. (210) Additional animal models have demonstrated the benefit of intermittent fasting on cancer progression. (211-213)

Recent *in vitro* and *in vivo* models have shown that intermittent fasting improved the chemotherapeutic response to cisplatin, doxorubicin, cyclophosphamide, oxaliplatin, sorafenib, mitoxantrone, gemcitabine, etoposide, temozolomide, and tyrosine kinase inhibitors in models of glioma, neuroblastoma, melanoma, fibrosarcoma and breast cancer, colon cancer, pancreatic cancer, hepatocellular cancer, and lung cancer. (206)

Interestingly, fasting in combination with cytotoxic agents elicited differential responses in normal and cancer cells, a phenomenon known as differential stress resistance (DSR). For DSR, normal cells prioritize maintenance pathways and inactivate growth factor signaling when nutrients are absent. In contrast, cancer cells, due to oncogene activation, do not inhibit stress resistance pathways, thus becoming vulnerable to cytotoxic treatment. Although the results of combining intermittent fasting with anticancer drugs are encouraging, the molecular mechanisms are not completely clear. In a colon cancer model, intermittent fasting inhibited tumor growth without causing permanent weight loss and decreased M2 polarization of tumor-associated macrophages in mice. (214) When intermittent fasting cycles were combined with chemotherapy, tumor growth was slowed and overall survival was prolonged in breast cancer, melanoma, and neuroblastoma animal models. (215)

The role of autophagy in patients with established cancer is controversial as autophagy may be a cell preservation pathway for cancer cells, providing the necessary metabolic substrates for the cancer cell. Indeed, pharmaceutical agents that block autophagy may reduce tumor cell proliferation. (216-220) While intermittent fasting has numerous metabolic effects that may control tumor cell growth, the fact that it activates autophagy in the tumor cell may be problematic. Consequently, the role of intermittent fasting and the enhancement of autophagy is complex in patients with established cancer. While animal models demonstrate a benefit of intermittent fasting in several tumor models, clinical data in humans is lacking. However, in humans, autophagy becomes activated only after about 12-16 hours of fasting, therefore a limited form of intermittent fasting (time-restricted eating) in which fasting does not exceed 12 hours may be an appropriate compromise. Fasting up to 16 hours can be considered in some specific situations, namely: i) in patients undergoing chemotherapy and radiation therapy and ii) in insulin-resistant patients with obesity, metabolic syndrome, and type 2 diabetes. Patients with insulin resistance have high circulating levels of insulin. Insulin is a potent growth factor for tumors and reducing insulin levels may counterbalance the effect on autophagy.

INSULIN POTENTIATION THERAPY FOR CANCER?

In vitro studies suggest that insulin may potentiate the effects of chemotherapeutic drugs.(221) However, there are no clinical studies to support this concept. Furthermore, such treatment may be hazardous (causing severe hypoglycemia) and is counterintuitive, as it may likely promote tumor cell proliferation. Insulin is responsible for cellular glucose uptake and mitogenic signaling cascades in cancer cells and can promote cell proliferation, survival, invasiveness, angiogenesis, immunomodulation, and chemoresistance (as reviewed in this document). (222) Insulin will promote further glycolysis and provide metabolic fuel for the cancer cell! Why then would some medical practitioners claim that the use of insulin and

glucose can improve the outcomes of patients with cancer and facilitate cancer therapy de-escalation? See https://euromedfoundation.com/ and https://donatoperezgarcia.com/, https://contemporarymedicine.net/insulin-potentiation-therapy/. (57, 223)

Supporters of insulin potentiation therapy (IPT) and IPT with low-dose chemotherapy (IPTLD) for patients with cancer claim that insulin increases cancer cells' permeability to chemotherapeutics relative to surrounding healthy tissues, because of the high expression of insulin receptors on these cells. (222) Other supporters suggest anticancer drugs enter cells through the same mechanism as that of glucose, conflating glucose transport with multidrug uptake transport.

There are only two published clinical trials assessing insulin potentiation therapy. Damyanov et al enrolled 16 patients with castration-resistant prostate cancer to receive insulin (0.4 U/kg) and docetaxel or a non-standard drug combination. (222) Those patients who received insulin and chemotherapy had a worse outcome (median survival of 11 months compared with 18.9 months). The second prospective study examined methotrexate response and toxicity in 30 patients with metastatic breast cancer. (224) Stable disease was reported to be more frequent in the group receiving methotrexate plus insulin compared with those receiving methotrexate alone; however, patient-centered outcomes were not provided.

Insulin potentiation therapy cannot be recommended as there is substantial scientific evidence that insulin treatment and increased concentrations of intracellular sugars accelerate both tumor progression and chemoresistance. (222)

CHAPTER 5: REPURPOSED DRUGS FOR METABOLIC CANCER TREATMENT

Remarkably, unlike conventional chemotherapeutic drugs that mostly act via a single cellular biological pathway, almost all the repurposed drugs/nutraceuticals used as adjunctive treatments for cancer have multiple modes of action. These mechanisms can generally be divided into two major groups, namely:

i. those that act directly on cancer cell pathways promoting cell death (apoptosis); and
ii. those that alter the tumor microenvironment (TME) restoring immune function and T cell cytotoxicity, limiting angiogenesis and metastatic spread, and inhibiting cancer stem cells.

Those interventions and repurposed drugs that have been demonstrated to reduce the risk of developing cancer are highly likely to be effective in treating cancer. It is likely that the metabolic pathways involved in cancer prevention play a major role in limiting cancer growth and spread. Consequently, an evaluation of a repurposed drug's efficacy in preventing cancer is important in considering the role of that drug in the treatment of cancer.

Most published studies demonstrating the benefit of nutraceuticals and repurposed drugs are *in vitro* mechanistic experiments and studies performed in animal models. Prospective studies are generally small, focusing on mechanisms of action or surrogate markers of efficacy. Indeed, most of the published clinical data consists of epidemiological studies, small case series, and case reports with few prospective clinical studies. This is not unexpected due to the "war on repurposed drugs" that is being waged by Big Pharma and its supporters; there is little funding to support well-designed clinical studies using cheap, potentially effective, and lifesaving drugs.

A 2014 ProPublica investigation found that "Big Pharma's focus on blockbuster cancer drugs squeezes out research into potential treatments that are more affordable." (225) A researcher at Harvard Medical School who has tried for many years to find funding for a study on the effects of aspirin on breast cancer told the reporter: "For some reason, a drug that could be patented would get a randomized trial, but aspirin, which has amazing properties, goes unexplored because it's 99 cents at CVS." (225)

Large, pharma-funded, randomized, double-blind controlled trials (RCTs) — considered by the medical establishment and those in the ivory towers to be the gold standard — have numerous limitations, however, and frequently don't reflect real-world clinical practice.

Furthermore, there is now strong scientific data and a growing consensus that well-conducted observational studies produce results statistically similar to those of traditional RCTs. (226) It is, therefore, possible, and indeed desirable to design prospective observational studies to study the clinical efficacy of the metabolic approach to cancer and specifically the combined use of multiple repurposed drugs. As the metabolic approach to cancer necessitates a combination of

interventions, including caloric reduction and a ketogenic diet, and multiple off-label anticancer drugs, it would be nearly impossible to design a double-blind randomized study; indeed, such an approach may be considered unethical.

The METRICS study (NCT02201381) is an example of an off-label drug protocol for the treatment of patients with glioblastoma. (157) METRICS is a novel, participant-funded, open-label, non-randomized, single-arm real-world study designed to gather high-quality evidence on the safety, tolerability, and effectiveness of the combination of four off-label metabolically targeted medicines (metformin, atorvastatin, mebendazole, and doxycycline) as an adjunctive cancer treatment for glioblastoma and other tumors. (157) The retrospective arm of the METRICS study has produced very encouraging results, with a significant increase in disease-free survival of patients compared to a control group.

SUMMARY OF TOP METABOLIC INTERVENTIONS TO CONTROL CANCER

Listed in order of priority, stratified based on the quality of evidence (see Appendix 1). Reviewed in detail below.

1. Glucose management: (low-carbohydrate, high-fat, ketogenic diet, coupled with modified time-restricted eating)
2. Green tea catechins: 500-100 mg daily
3. Melatonin: start at 1 mg and increase to 20-30 mg at night (extended/low release)
4. Vitamin D3: 20,000 to 50,000 IU daily – NOTE: dosage should be adjusted according to blood vitamin D levels, aiming for a 25-OH level of at least 55-90 ng/dl
5. Metformin: 1,000 mg twice daily
6. Curcumin (nanocurcumin): 600 mg daily or as per manufacturer's suggested dosing
7. Mebendazole: 100-200 mg daily
8. Berberine: A daily dose of 1000-1500 mg or 500-600 mg two or three times daily (Depending on blood glucose levels, metformin and berberine can be used together or alternating months)
9. Atorvastatin 40 mg BID. Simvastatin 20mg BID is an alternative
10. Exercise (30 minutes/daily): walking, high-intensity interval training, cycling, etc.
11. Sildenafil: 20 mg daily (Tadalafil: 5 mg daily is an alternative)
12. Cimetidine: 400-800 mg twice daily
13. Doxycycline: 100 mg daily (for cycles of 2 weeks)
14. Resveratrol: 1,000 mg daily (bioavailable enhanced formulation)
15. Cyclooxygenase inhibitors: aspirin 325 mg daily or Diclofenac 75-100 mg daily
16. Nigella Sativa: 400-500 mg encapsulated oil twice daily
17. Ganoderma lucidum (Reishi) and other medicinal mushrooms
18. Ivermectin: 12-60 mg twice weekly
19. Dipyridamole: 100 mg twice daily
20. High-dose intravenous Vitamin C (50-75 g IV as per protocol)
21. Dichloroacetate 500 mg two/three times daily

The Repurposing Drugs in Oncology (ReDO) project has cataloged 268 approved drugs with anticancer effects. (227) See Appendix 2 for an abbreviated list of repurposed drugs, nutraceuticals, and botanicals. It would be impossible to review all the drugs in ReDo's database in this monograph; rather, we have focused on and evaluated the drugs that appear to have the greatest clinical utility. These repurposed drugs are listed in priority according to the strength of the supporting clinical and mechanistic evidence (see Appendix 1 which outlines the stratification methodology).

Patients with cancer should consider taking at least the first 10 listed interventions; this can be modified according to the patient's individual clinical response and preferences. Furthermore, it is important to recognize that many of these interventions act additively/synergistically with each other and with conventional chemotherapy. Metronomic chemotherapy dosing is preferred (see below). Patients should monitor the response to treatment with a PET scan (glucose uptake scan) every three months and then at least every 6 months once in remission/cancer stable. Patients should follow their tumor markers concomitantly. Circulating tumor DNA (in blood specimens) is an emerging technology that may poove useful for monitoring tumor progression. (228, 229) Patients and their healthcare providers should dynamically follow their tumor markers and adjust their treatment protocol accordingly. Patients who demonstrate a good clinical response should not stop this protocol abruptly, as this may result in a relapse, (158) but rather reduce the number of interventions dynamically.

As a rule, antioxidant supplements (vitamins A, C, and E; coenzyme Q10, and N-acetyl cysteine) should be avoided in patients undergoing chemotherapy and radiotherapy, as these interventions act largely by increasing oxidant injury. (230, 231) Paradoxically, while oral vitamin C is a potent antioxidant, (232) high-dose intravenous vitamin C generates reactive oxygen species that potentiates the effects of chemotherapy and radiation therapy (see section on intravenous vitamin C).

METRONOMIC DOSING

Metronomic therapy is a new type of chemotherapy in which anti-cancer drugs are administered in a lower dose than the maximum tolerated dose repetitively over a long period to treat cancers with fewer side effects. (233) Metronomic therapy is shown to affect both tumor microenvironment and tumor cells to achieve its therapeutic effects. Metronomic therapy is also cost-effective as a lower dose is used compared to conventional chemotherapy. Metronomic dosing will avoid side effects by administering low doses continuously, and efficacy should be seen as prolonged progression free survival and overall survival, rather than in rapid tumor responses. (234) Metronomic chemotherapy has been most commonly used in patients with metastatic breast cancer, non-small cell lung cancer, and glioblastoma. (234) A meta-analysis of 22 clinical trials reported promising results in patients with advanced breast cancer. (235)

DETAILED DESCRIPTIONS

1. Glucose management

A carbohydrate-restricted diet (less than 25 g of carbs per day) that is high in saturated fat and Omega-3 fatty acids (ketogenic diet) is suggested. Avoid all processed food (see the FLCCC Guide to Fasting and Healthy Eating for more detailed guidance).(143) Contrary to current dogma, saturated fatty acids are "healthy," but you should avoid processed Omega-6 vegetable oils (see below).(236, 237) Avoid foods that are high on the glycemic index and follow the "hacks" to flatten the blood glucose curve (see below).(238)

A continuous glucose monitor (CGM) is essential to track changes in blood glucose levels. Patients must keep accurate records to identify (and avoid) any food that might spike blood glucose. Target a baseline blood glucose of 50-80 mg/dl (2.7 – 4.4 mmol/l) and a postprandial (after a meal) glucose of less than 120 mg/dl (6.6 mmol/l). The ideal is a flat blood glucose curve; the blood glucose should not increase by more than 20 mg/dl after a meal. In addition, a blood ketone meter (blood level of beta-hydroxybutyrate) is recommended to confirm that the patient has entered ketosis (normal level < 0.5 mmol/l). Ideally, the blood ketone level should be over 2 mmol/l. The optimal therapeutic range is between 3 and 5 mmol/l. It is important to track changes in blood glucose and ketones with both fasting and exercise. Therapeutic ketosis requires a blood glucose < 90 mg/dl and a blood ketone > 2 mmol/l, aiming for a Glucose-Ketone Index (GKI) of < 2. (176)

The GKI can be calculated at: https://keto-mojo.com/glucose-ketone-index-gki/ and https://perfectketo.com/glucose-ketone-index-calculator/

The Glycemic Index

The glycemic index is a value assigned to foods based on how quickly those foods cause increases in blood glucose levels and how high they spike. The glycemic index ranks food on a scale from 0 to 100. Pure glucose is arbitrarily given a value of 100, which represents the relative rise in the blood glucose level after two hours (see Figure 7). The glycemic index of a specific food depends primarily on the quantity and type of carbohydrate it contains (see Table 2). Foods that are low on the glycemic index (GI) scale tend to release glucose slowly and steadily. Foods that are high on the glycemic index release glucose rapidly. It should be noted that the glycemic index varies between individuals. (239, 240) A CGM allows for the individual assessment of the glucose excursion (glycemic index) of various foods.

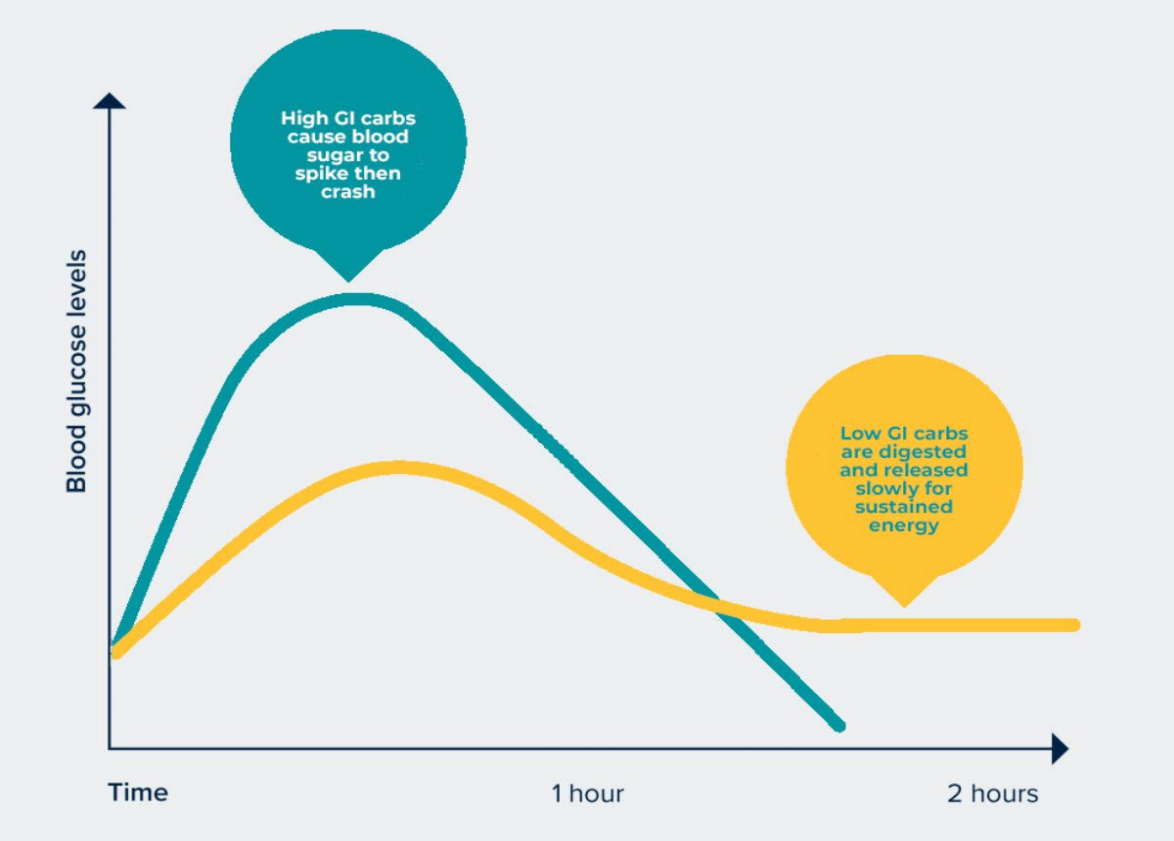

Figure 7: The blood glucose profile of high and low glycemic index foods (Source: adapted from Glycemic Index Foundation)

Food Item	Glycemic Index
White rice	87
Watermelon	76
White bread	75
Orange juice	53
Banana	51
Pineapple	66
Papaya	60
Grape	46
Orange	42
Strawberry	40
Apple	34
Grapefruit	25
Fresh berries	25
Most vegetables	<20
Peanuts	7

Table 2: Glycemic index of selected foods (Source: FLCCC)

What to eat and what not to eat

The most important intervention to reduce obesity, metabolic syndrome, type II diabetes, cancer, cardiac disease, neurodegenerative diseases, autoimmune diseases etc., is to eat real food and not processed food.(143, 182, 241) Telling the difference is quite simple. If it looks like food, it is real. If it comes in a box or has a food label, it's likely processed. The more ingredients listed on a product's label and the more chemicals you see with strange and unpronounceable names, the more processing the product has undergone. Recent evidence suggests that processed foods in themselves can cause insulin resistance.(242)

Healthy foods include:

- All vegetables (especially avocados, and cruciferous and leafy vegetables)
- Nuts (almonds, brazil nuts, cashews, and pistachios)
- Peanut butter (but avoid the white bread and grape jelly!) and chia seeds
- Fish (especially Alaskan salmon and sardines)
- Chicken breast (free range, no hormones, no antibiotics)
- Eggs (they've been giving a bad rap!)
- Meat (grass-fed, no hormones, avoid processed meats)
- Blueberries (limit volume if insulin resistant)
- Grapefruit (limit volume if insulin resistant)
- Coffee with heavy cream or coconut oil; choose Stevia (without erythritol) over sugar or artificial sweeteners

Flattening the glucose curve

Apart from carbohydrate restriction/ketogenic diet and time-restricted eating, several simple interventions (or hacks) prevent the high glucose spikes that fuel cancer. The book "Glucose Revolution" by Jessie Inchauspe is highly recommended and provides more details on interventions to flatten the blood glucose curve, such as. (238)

Eat foods in the right order

Veggies (greens/fiber) should be eaten first, protein and fat second, and starch (sugars) last; this slows gastric emptying, as well as the breakdown and absorption of glucose. Eat fruit last; always preceded by fiber. Don't begin a meal with bread (starch).

- Begin all meals with a salad or green vegetables. Use olive oil and vinegar as salad dressing.
- Avoid starchy foods with no fiber.
- Avoid fruit juices and smoothies, which cause a large glucose spike.
- Skip breakfast. Breakfast is the worst time to eat sugar and starches; this results in a large glucose spike. Cereal for breakfast causes a rapid spike in glucose.

- Avoid snacking throughout the day.
- Drink a tablespoon of vinegar stirred into a tall glass of water before eating starch or something sweet. Apple cider vinegar is recommended. The acetic acid in vinegar decreases the enzymatic breakdown of starch, increases glycogen synthesis (and glucose uptake), and increases fatty acid oxidation. (243-246) Vinegar may be beneficial even if consumed up to 20 minutes after a starchy food. Apple cider vinegar is usually unpasteurized and should be avoided in pregnancy.
- If vinegar is not readily available, consume a few fiber tablets (esp. glucomannan tablets) before eating a starchy/sweet treat.
- Go for a 20-minute walk within an hour of eating/having starchy food. During exercise, muscles take up glucose for energy while increasing mitochondrial oxidative capacity. (247-249) Going to the gym or doing resistance exercise is an alternative. Climbing a few stairs is an option at work. If sedentary, do sitting calf raises (the soleal pump). The soleal pump is strongly recommended; it has been demonstrated to reduce postprandial glucose by about 50%, reduce hyperinsulinemia, and improved lipid metabolism. (250) If you exercise and you have not eaten, i.e., you are engaging in fasted exercise, your liver releases glucose into the bloodstream to fuel the mitochondria in your muscles; this causes a glucose spike. This is mediated by increased release of cortisol, epinephrine, and norepinephrine (with decreased glucagon); i.e., release of harmful stress hormones. If you exercise before eating, we would suggest a shake with 'superfoods,' including a plant protein, super green, Omega-3 fatty acids, vitamins and adaptogenic herbs, probiotics and fiber, super mushrooms and berries (e.g., Ka'Chava ™ https://www.kachava.com/ or 310 Shakes™ https://310nutrition.com/collections/meal-replacement-shakes) instead of a regular protein shake.

Establishing/restoring a "normal" microbiome

The microbiome has a remarkable effect on blood sugar levels and insulin sensitivity. (251-257) Establishing a normal microbiome is important for regulating blood glucose levels and improving insulin sensitivity. Furthermore, alterations in the microbiome play an important role in both tumorigenesis and tumor propagation. Follow these suggestions to help establish a "normal microbiome":

- Eat a diverse range of foods.
- Eat lots of vegetables, legumes, and beans.
- Eat fermented foods like yogurt (unsweetened), kefir, apple cider vinegar, kombucha, pickles, sauerkraut, tempeh, and kimchi.
- Eat foods rich in polyphenols (dark fruits). Include resveratrol supplements.
- Eat prebiotic fiber. Galactomannan is a dietary fiber (soluble and insoluble) made from the root of the konjac plant.
- Eat less sugar and sweeteners.
- Reduce stress.
- Avoid taking antibiotics unnecessarily.

- Stop snacking.
- Exercise regularly.
- Spend time outdoors in the natural world to expose yourself to millions of microbes, many of which can benefit microbiome diversity.
- Get enough sleep.

The saturated fat-cholesterol hoax

The Cholesterol-Saturated fatty acid hoax (236, 258, 259) began to proliferate in the 1960s. Dr. Ancel Keys popularized the notion that saturated fats and high cholesterol were the primary causes of atherosclerotic heart disease — the so-called Diet-Heart Hypothesis. (260, 261) This concept has been vigorously studied, including in many randomized controlled trials, and has been convincingly proven to be false. (236, 262, 263) Indeed, replacing saturated fats with a diet high in vegetable oils (linoleic acid) was associated with higher rates of death, cardiovascular and coronary heart disease as well as a significantly increased risk of cancer. (264)

Healthy and unhealthy oils

Avoid seed oils high in linoleic acid. Linoleic acid is an Omega-6 fatty acid that our bodies require in small amounts. Unfortunately, many people eat up to 10 times the desired amount of linoleic acid, because of excess consumption of foods made with seed oils. Too much linoleic acid is associated with inflammation, obesity, heart disease, and other unfavorable conditions. Therefore, avoid:

- Soybean oil
- Corn oil
- Cottonseed oil
- Sunflower oil
- Sesame oil
- Grapeseed oil
- Safflower oil
- Rice bran oil
- Margarine

Instead, opt for healthy oils and fats such as the ones listed below. Use only high-quality products and check production and expiration dates.

- Olive oil (oleic acid, Omega-9 monounsaturated fatty acids); never heat olive oil to the point where it produces smoke.
- Avocado oil (oleic acid, Omega-9 monounsaturated fatty acids)
- Coconut oil (medium chain fatty acid)
- Flaxseed oil (alpha-linolenic acid, ALA Omega-3)
- Walnut and Pecan oils; should be refrigerated to avoid spoilage
- Butter (saturated fat)

2. Green Tea

Anticancer pathways and mechanisms

Green tea is a significant source of a type of flavonoid called catechin, which includes epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC). The most abundant individual catechin in fresh tea leaves is EGCG, which is more than 40% of the total content of catechins. (137) Green tea catechins (GTCs) have been proven to be effective in inhibiting cancer growth in several experimental models. (265-267) In addition, GTCs may have synergistic anticancer activity when combined with other phytochemicals, particularly resveratrol. (268, 269) GTCs, particularly EGCG, may have a role in both the prevention and treatment of cancers, (270) specifically those dependent on the glutamate pathway as a source of energy. Mitochondrial glutamate dehydrogenase (GDH) catalyzes the oxidative deamination of L-glutamate. Activation of GDH is tightly correlated with increased glutaminolysis. Furthermore, glutamate serves as a mitochondrial intracellular messenger when glucose is being oxidized and the GDH participates in this process by synthesizing glutamate. (271) Li and colleagues demonstrated *in vitro* that EGCG allosterically inhibits GDH in nanomolar concentrations. (180)

GTCs have an important anticarcinogenic role by promoting and/or inhibiting signal transmission through the targeted regulation of multiple links in the signal pathways that are activated or inhibited in cancer cells. (137) EGCG regulates signaling pathways by interacting with membrane receptors. EGCG significantly inhibited the expression of VEGF and reduced VEGF receptors. Inactivation of the VEGF signaling pathway suppresses angiogenesis, a common strategy for inhibiting carcinogenesis. EGCG activates PKA, which dephosphorylates related proteins such as the tumor suppressor Merlin and inhibits the proliferation of cancer cells. (272) EGCG inhibits STAT3 phosphorylation by blocking JAK2 phosphorylation. STAT3 suppresses anti-tumor immune responses and promotes the proliferation and migration of cancer cells. EGCG inhibits the MAPK signaling by competing for the phosphorylation sites of downstream proteins. EGCG inhibits the Wnt pathway by phosphorylating β-catenin and promoting its degradation. EGCG inhibits transcription factors involved in activating the Sonic hedgehog pathway. EGCG inhibited the activities of MMP2 and MMP9 and promoted the expression of tissue inhibitor of MMPs (TIMp1/2) to suppress the invasion and metastasis of tumor cells. (272) Green tea extract has been demonstrated to suppress cancer stem cells.(273, 274)

GTCs have anticancer effects via additional pathways. (137) GTCs exert potent and selective *in vitro* and *in vivo* pro-apoptotic activity in cancer cells via several pathways.(265, 266, 275) GTC inhibits A549 cells by regulating its cell cycle arrest, increasing the expressions of p21 and p27, and inhibiting the expressions of p-AKT and cyclin E1 in a dose-dependent manner in the cancer cells. (276) EGCG inhibited the proliferation of human lung cancer cells by targeting the epidermal growth factor receptor (EGFR) signaling pathway.

GTCs have been demonstrated to alter the tumor microenvironment (TME) thereby attenuating immunosuppression and the risk of metastases. (269) Flavonoids including GTCs

(and resveratrol) are potent modulators of pro-inflammatory gene expression being, therefore, of great interest as agents selectively suppressing molecular targets within pro-inflammatory TME. GTCs have been demonstrated to increase the ratio of active cytotoxic T lymphocytes to Tregs in tumors, indicating a switch of “cold” tumors to “hot” with significantly improved anti-tumor immune therapeutics. (277) GTCs have anticancer effects by enhancing anticancer immunity via PD-1 axis and TLR4 pathways. (278, 279) In addition, GTCs repolarize tumor-associated macrophages (M2 to M1 macrophages), triggering an immune response and limiting metastases. (280) GTCs have been demonstrated to attenuate MDSC-mediated immunosuppression and increased the proportions of CD4+ and CD8+ T cells. (281)

Studies have shown that 20% of cancer-related deaths were directly due to TLR-induced cancer cachexia, in which cancer cells released heat shock proteins that acted as TLR-4 agonists in macrophages, skeletal muscle, and fat cells, causing downstream signal transduction. EGCG effectively downregulates the TLR-4 signal pathway. (282)

GTCs inhibit the accumulation of MDSCs, leading to restoration of the IFN-γ, enhancing the activity of CD8+ T-cells, and improvement of the ratio of CD4(+) to CD8(+) T-cells, which is beneficial to the improvement of the immune system’s attack on tumor cells. (137) In addition, a phytochemical mixture including GTCs exerted anti-tumor activity by repolarization of M2-polarized macrophages and induced the production of IL-12, which recruit cytotoxic T lymphocytes and natural killer cells (NK) with the tumor microenvironment. (280)

In addition to all these beneficial effects, GTCs potentiate the effects of conventional chemotherapeutic agents. Due to their effects on the important signaling pathways in vivo, catechins are often used as sensitizing agents in combination with chemotherapeutic drugs. The combination of anticancer drugs with catechins, whether before or after drug administration, reduced the toxicity of these drugs and enhanced the clinical efficacy by accelerating apoptosis of cancer cells. (137) Importantly, the combination of a number of chemotherapeutic drugs with GTCs will improve the chemotherapeutic sensitivity of cells to the drug, allowing a reduction in the dose of the chemotherapeutic drug. (137)

Clinical studies

Numerous experimental models have explored the mechanistic anticancer effects of GTCs; this data is supported by epidemiologic data, a case series of patients with B cell malignancies,(283) several case reports,(284, 285) and a RCT. A meta-analysis including 18 prospective cohorts and 25 case-control studies showed a significant inverse association between intake of tea catechins and risk of various cancers, with a relative risk (RR) being 0.935 (95% CI = 0.891-0.981). (137) Similarly an umbrella review and meta-analysis by Kim et al, which included 64 observational studies (case-control or cohort) demonstrated that GTC significantly reduced the risk of gastrointestinal cancer (oral, gastric, colorectal, biliary tract, and liver), breast cancer, and gynecological cancer (endometrial and ovarian cancer) as well as leukemia, lung cancer, and thyroid cancer. (146) Lemanne et al reported on a

patient who demonstrated a complete and durable remission of chronic lymphocytic leukemia (CLL) following high dose EGCG.(285) In a randomized, double-blind, placebo-controlled study, treatment with 600 mg/day of green tea catechins reduced the risk of prostate cancer from 30% to 3% in men with high-grade prostate intraepithelial neoplasia. (181)

Types of cancers that green tea may be beneficial for

Green tea catechins may be effective against a range of tumors including cancers of the prostate, breast, uterus, ovary, colorectal, glioma, liver and gallbladder, melanoma, and lung cancers. (137) GTCs appear to be particularly beneficial for prostate cancer as well as breast cancer. (177, 181, 265-268, 281, 286)

Dosing and cautions

Green tea catechins should be taken in a dose of 500-1000 mg/day. Green tea extract should be taken during/after a meal rather than on an empty stomach. (147) Green tea extract has rarely been associated with liver toxicity. (287) The safety of green tea extract was evaluated by the US Pharmacopeia (USP) Dietary Supplement Information Expert Committee (DSIEC). (147) The DSIEC concluded that "*when dietary supplement products containing green tea extracts are used and formulated appropriately the Committee is unaware of significant safety issues that would prohibit monograph development.*" (147) Based on this data we suggest that green tea exacts be taken in the dosages recommended by the manufacturer. Regular liver function tests are suggested in patients taking green tea extract and green tea exact should be avoided/used cautiously in those with underlying liver disease.

3. Melatonin

Melatonin, N-acetyl-5-methoxytryptamine, is a small lipophilic molecule that is secreted by the pineal gland and its synthesis shows a circadian pattern. Melatonin is mainly produced by the pineal gland in response to darkness. (288) At night, melatonin levels increase, then start to decrease in the early morning and throughout the day. Elevated levels of melatonin at night stimulate target organs to enter into suitable homeostatic metabolic rhythms, which help protect the body from developing different diseases. (148)

Exposing the body to light at night may result in disruption of melatonin production and the circadian rhythm. Peak melatonin levels in the blood vary between individuals and depend on age, with levels decreasing rapidly after age 40. (289)

Melatonin has specific receptors to regulate many physiological functions namely MT1 and MT2; both are members of the seven transmembrane G-protein coupled receptor family.(290) Melatonin receptors are found throughout the body, which explains its multiple biological functions. (288) In addition, mitochondria of all cells produce melatonin in an autocrine fashion under the influence of near-infrared irradiation. (291, 292) Melatonin has numerous biological properties acting both directly and indirectly as a potent

antioxidant. (288) Melatonin plays a critical role in normal mitochondrial function, being a strong inducer of oxidative phosphorylation.

Anticancer pathways and mechanisms

Low melatonin levels have been implicated in the etiology of cancer. Several studies have shown reduced levels of melatonin in patients with certain types of cancers, compared with normal, healthy people of the same age. (289) Disruption of nocturnal melatonin secretion in night shift workers has been associated with a modestly increased risk for breast and other cancer types. A meta-analysis of 26 observational studies found significantly increased breast cancer incidence among female airline cabin crew. (293) The International Agency for Research on Cancer reclassified “shiftwork that involves circadian disruption“ from a possible to a probable human carcinogen, in recognition of this relationship. (294)

In experimental models, melatonin has demonstrated a broad spectrum of anticancer activity with multiple underlying mechanisms being proposed (see Figure 8). (127, 148) Melatonin exerts cytotoxic, anti-mitotic, and pro-apoptotic actions in breast cancer cells. The antiproliferative activity of melatonin has been demonstrated in both ER-positive and ER-negative human breast cancer cell lines. In most of these reports, melatonin acted via the MT1 membrane receptor. In addition, melatonin activates cancer cell apoptosis; this may be mediated by PUMA up-regulation. Melatonin increases the expression of pro-apoptotic mediators such as BAX/BAK, Apaf-1, caspases, and p53. (295) Melatonin has been demonstrated to inhibit the proliferation of cancer stem cells and to reduce the expression of Ki67 and matrix metalloproteinase 9. (296) Melatonin can cause cancer cells to switch from anaerobic glycolysis to conventional oxidative phosphorylation via the Krebs cycle. This slows down the proliferative activity of cancer cells, reduces their metastatic potential, and directs the cells to undergo apoptosis. Melatonin stimulates the synthesis of acetyl-CoA from pyruvate by inhibiting the mitochondrial enzyme pyruvate dehydrogenase kinase.(297) A study demonstrated that melatonin altered Ewing sarcoma metabolic profile by inhibiting the Warburg effect. (298) In prostate cancer cells, melatonin was able to reduce glucose metabolism via the downregulation of glycolysis and the pentose phosphate pathway. (299) The antiestrogenic action of melatonin could also enhance the ability of this hormone to limit the proliferation of hormone-sensitive breast cancer. (127)

Anti-angiogenesis is one of the major mechanisms by which melatonin exerts its anticancer effects. Melatonin inhibits hypoxia-induced factor 1-α thereby preventing vascular endothelial growth factor (VEGF) expression. Melatonin also inhibits endothelial cell migration, endothelial cell invasion, and endothelial cell tube formation. It also prevents cancer cell migration via alteration of PI3K and MAPK signaling pathways in both receptor-dependent and independent manner. (296) Melatonin has been demonstrated to stimulate T cell and natural killer (NK) production and reduce regulatory T cells (Tregs). (300, 301)

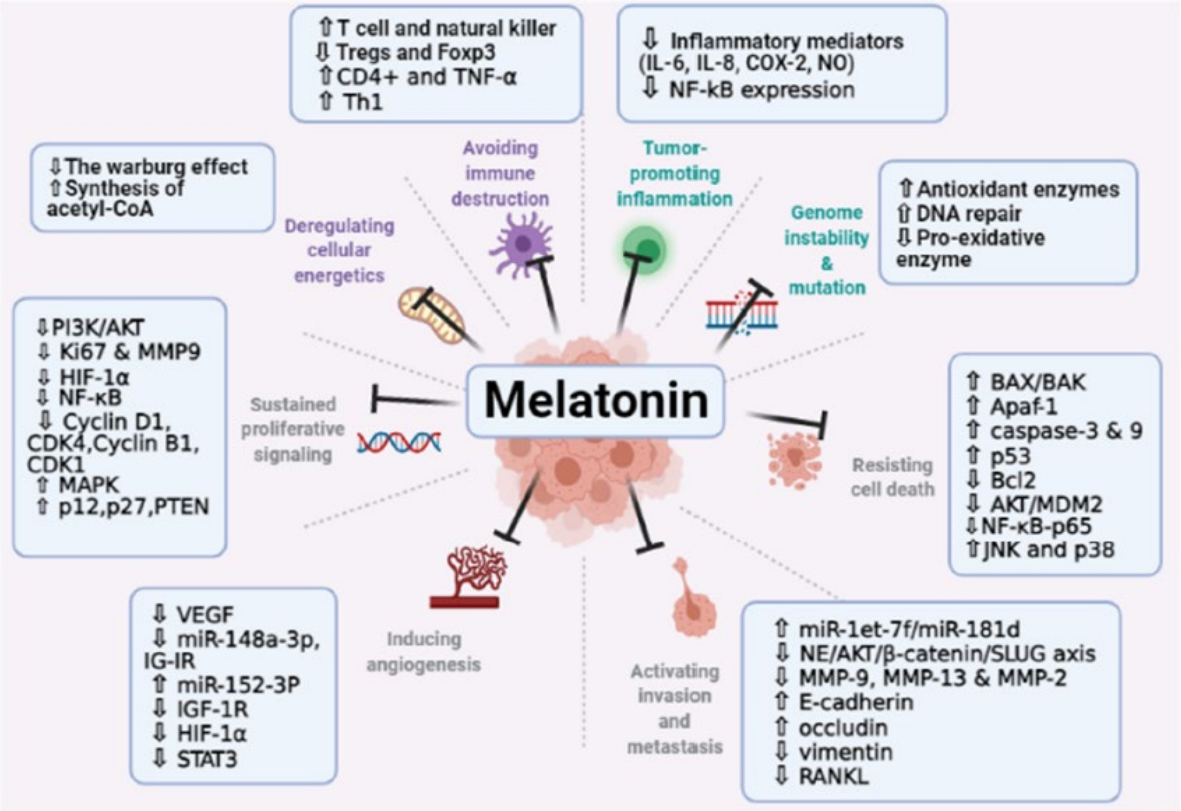

Figure 8. Multiple anticancer pathways affected by melatonin (Source: Reproduced from Talib et al under Creative Commons 4.0 license). (148)

Melatonin may benefit cancer patients who are also receiving chemotherapy, radiotherapy, supportive therapy, or palliative therapy by improving survival and ameliorating the side effects of chemotherapy.

Clinical studies

In addition to case studies,(302, 303) the clinical benefit of melatonin in patients with cancer is supported by the highest level of evidence, namely meta-analyses of RCTs.(304, 305) Seely et al systematically reviewed the effects of melatonin in conjunction with chemotherapy, radiotherapy, supportive care, and palliative care on 1-year survival, complete response, partial response, stable disease, and chemotherapy-associated toxicities. (305) This analysis included 21 randomized studies all of which studied solid tumors. The pooled relative risk (RR) for 1-year mortality was 0.63 (95% CI = 0.53-0.74; $P < 0.001$). Improved effects were found for complete response, partial response, and stable disease. In trials combining melatonin with chemotherapy, adjuvant melatonin decreased 1-year mortality (RR = 0.60; 95% CI = 0.54-0.67).

Types of cancers that melatonin may be beneficial for

Melatonin may be active in several cancers including cancers of the breast, ovary, pancreas, liver, kidney, mouth, stomach, colon/rectum, brain, lung, prostate, head and neck, and various leukemias and sarcomas. (127, 148)

Dosing and cautions

Providers should advise patients to begin with 1 mg at night; a slow-release/extended-release preparation is suggested to minimize REM sleep-induced nightmares (best taken an hour before retiring). The dose should be increased up to 20-30 mg, as tolerated. Melatonin is probably the safest medical compound available, with a LD50 of infinity (it is impossible to kill an animal with industrial doses of melatonin). The only side effects reported are early morning drowsiness and "bad dreams" (when the dose is increased too rapidly). (288)

4. Vitamin D

Vitamin D is synthesized in human skin after the photoisomerization of 7-dehydrocholesterol to pre-vitamin D3 under the influence of UV B radiation (wavelength, 280-315 nm).(306) The major factors influencing this process are either environmental (latitude, season, time of day, ozone and clouds, reflectivity of the surface) or personal (skin type, age, clothing, use of sunscreen, genetics). (307) From the skin, parental vitamin D3 (*cholecalciferol*) finds its way into the general circulation, and it is then metabolized in the liver to 25-hydroxyvitamin D3 [25(OH)D3] (*calcifediol*). 25(OH)D3 is an immediate precursor metabolite to the active form of vitamin D3, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] (*calcitriol*), that is the product of the mitochondrial CYP27B1-hydroxylase confined primarily but not entirely to the proximal tubular epithelial cell of the kidney. (307, 308)

As vitamin D has a much shorter half-life than 25(OH)D3 (1-2 days versus 2-3 weeks), 25(OH)D3 is considered the best indicator of vitamin D status; hence 25(OH)D3 is the most widely used test indicating vitamin D status. (307, 308) A vitamin D level > 30 ng/ml is widely considered "normal" while a level between 20-30 ng/l is considered vitamin D insufficient and a level <20 ng/ml is considered vitamin D deficient. (307-309) However, more recent data suggests that a level > 50 ng/ml is desirable, and ideally targeting a level between 55- 90 ng/ml is desirable. (306, 310-312)

It may take many months or even years to achieve optimal levels in patients with low vitamin D levels (< 20 ng/ml) taking the standard recommended dose of 5,000 IU/day. It is therefore important that the optimal regimen for vitamin D supplementation be followed to achieve adequate circulating levels (see Table 3). (311, 312) Since the highest dose of commercially available vitamin D3 is 50,000 IU capsules, and due to its affordability (low cost) and better gastrointestinal absorption, we recommend using 50,000 IU D3 capsules for community setups.(306, 311, 312) Together, a number of these capsules can be taken as a bolus dose [i.e., single upfront doses such as 100,000 to 400,000 IU]. However, the liver has a limited 25-hydroxylase capacity to convert vitamin D to 25(OH)D: thus, taking 50,000 IU capsules over a few days provides better bioavailability. (306, 311, 312)

Vitamin D2 is manufactured through the ultraviolet irradiation of ergosterol from yeast, while vitamin D3 is through the ultraviolet irradiation of 7-dehydrocholesterol from lanolin; both are used in over-the-counter vitamin D supplements. (307) Vitamin D2 has 30% of the biological activity of vitamin D3. It is best to include both Vitamin K2 (Menaquinone [MK7] 100 mcg/day, or 800 mcg/week) and magnesium (250-500 mg/day) when doses of vitamin D > 8 000 IU/day are taken. (313, 314) It should be noted that vitamin K2 itself has anticancer properties and an inverse relationship exists between vitamin K2 (and not K1) intake and cancer mortality. (315-318)

Table 3. Guidance on Upfront Loading Dose Regimens to Replenish Vitamin D Stores in the Body

When serum vitamin D levels are available, the doses provided in this table can be used for the longer-term maintenance of serum 25(OH)D concentration above 50 ng/mL (125 nmol/L). The table provides the initial bolus dose, weekly dose, frequency, and duration of administration of oral vitamin D in non-emergency situations, in a non-obese, 70 kg adult.

Serum Vitamin D (ng/mL) **	Vitamin D Dose: Using 50,000 IU Capsules: Initial and Weekly $		Duration (Number of Weeks)	Total Amount Needed to Correct Vit. D, Deficiency (IU, in Millions) #
	Initial Bolus Dose (IU)	Follow-Up: $$ The Number of 50,000 IU Caps/Week		
<10	300,000	×3	8 to 10	1.5 to 1.8
11–15	200,000	×2	8 to 10	1.0 to 1.2
16–20	200,000	×2	6 to 8	0.8 to 1.0
21–30	100,000	× 2	4 to 6	0.5 to 0.7
31–40	100,000	×2	2 to 4	0.3 to 0.5
41–50	100,000	×1	2 to 4	0.2 to 0.3

Table 3. Replenishing Vitamin D Stores (Source Nutrients – Special Issue: "Vitamin D – Calciferol and COVID" (311) Reproduced with permission from the author.

More than half of human tissues express the gene for the vitamin D receptor, with vitamin D having pleiotropic functions in pathways of energy metabolism, immunity, and cellular growth and differentiation that clearly extend the control of calcium homeostasis. (319) The biologically active form of vitamin D, 1,25(OH)D3, regulates over 1200 genes within the human genome. (306) The most important extra-skeletal function of vitamin D is its role in the modulation of the immune system. Vitamin D receptors are present on immune cells, with this vitamin playing a critical role in both innate and adaptive host immunity. (320, 321)

Vitamin D has anticancer effects both directly *via* controlling the differentiation, proliferation, and apoptosis of neoplastic cells as well as indirectly through regulating

immune cells that affect the microenvironment of malignant tumors. Evidence from observational and randomized controlled studies indicates that low vitamin D status is associated with higher mortality from life-threatening conditions such as cancer and cardiovascular disease. (322, 323) In a real-world analysis of 445,601 participants, aged 40–73 years, from the UK Biobank cohort, both vitamin D deficiency and insufficiency were strongly associated with all-cause mortality. (324) A Cochrane analysis demonstrated that supplementation with vitamin D3 (cholecalciferol) decreased all-cause mortality (RR 0.94, 95% CI 0.91 to 0.98, p = 0.002); however, supplementation with vitamin D2, calcifediol, and calcitriol did not affect mortality. (325)

Vitamin D deficiency has been demonstrated to increase the risk of breast cancer while supplemental vitamin D intake had an inverse relationship with this outcome. (326) Both prospective and retrospective epidemiologic studies indicate that levels of 25-hydroxyvitamin D below 20 ng per milliliter are associated with a 30 to 50% increased risk of incident colon, prostate, and breast cancer, along with higher mortality from these cancers. (307) People living at higher latitudes are at increased risk for vitamin D deficiency and are reported to have an increased risk of Hodgkin's lymphoma as well as colon, pancreatic, prostate, ovarian, breast, and other cancers and are more likely to die from these cancers, as compared with people living at lower latitudes. (209, 307) Vitamin D supplementation likely plays an important role in the prevention of cancer, as highlighted in the prospective study by Bischoff-Ferrari et al (see section on Primary Cancer Prevention). (134, 135) Furthermore, in a meta-analysis of 50 trials with a total of 74,655 participants, Zhang et al reported that Vitamin D supplementation significantly reduced the risk of cancer death (0.85,0.74 to 0.97, 0%). (327) In subgroup analyses, all-cause mortality was significantly lower in trials with vitamin D3 supplementation than in trials with vitamin D2 supplementation. An analysis of 25(OH)D-cancer incidence rates suggests that achieving a vitamin D level of 80 ng/mL vs. 10 ng/mL would reduce cancer incidence rates by 70 ± 10%. (209)

Anticancer pathways and mechanisms

Experimental evidence indicates that vitamin D has diverse antineoplastic activity (see Figure 9). Binding of vitamin D to its target, the vitamin D receptor, leads to transcriptional activation and repression of target genes and results in induction of differentiation and apoptosis, inhibition of cancer stem cells, and decreased proliferation, angiogenesis, and metastatic potential. (328) Vitamin D induces apoptosis of cancer cells, (329) counteracts aberrant WNT-β catenin signaling, (330) and has broad anti-inflammatory effects via downregulation of nuclear factor-Kβ and inhibition of cyclooxygenase expression. (331) In colon, prostate, and breast carcinoma cells, 1,25-(OH)2D3 upregulates several pro-apoptotic proteins (BAX, BAK, BAG, BAD, G0S2) and suppresses survival and anti-apoptotic proteins (thymidylate synthase, survivin, BCL-2, BCL-XL). (332) In this way, it favors the release of cytochrome C from mitochondria and the activation of caspases 3 and 9 that lead to apoptosis. 1,25-(OH)2D3 and metformin have additive/synergistic antiproliferative and proapoptotic effects in colon carcinoma and other types of cells. (333)

In many cancer cell types, 1,25-(OH)2 D3 directly arrests the cell cycle in the G0/G1 phase by downregulating cyclin-dependent kinases and repressing genes that encode cyclins D1 and C. (334) 1,25-(OH)2D3 decreases the expression of epidermal growth factor receptor (EGFR) and interferes with the insulin-like growth factor (IGF)-I/II pathway. (209) Vitamin D has activity against human breast cancer cell lines by targeting Ras/MEK/ERK pathway. (332) In addition, 1,25-(OH)2D3 diminishes the proliferation of breast cancer cells by inhibiting estrogen synthesis and signaling through estrogen receptor (ER)α. (335) In colon carcinoma cells, 1,25-(OH)2 D3 upregulates an array of intercellular adhesion molecules that are constituents of adherens junctions and tight junctions, including E-cadherin, occludin, claudin-2 and -12, and ZO-1 and -2. (336) The Wnt/β-catenin pathway plays an important role in cancer. Antagonism of the Wnt/β-catenin pathway by 1,25-(OH)2 D3 was reported in colon carcinoma cells by a double mechanism: (a) liganded VDR binds nuclear β-catenin, which hampers the formation of transcriptionally active β-catenin/TCF complexes, and (b) induction E-cadherin expression that attracts newly synthesized β-catenin protein to the plasma membrane adherens junctions. In that way, it decreases β-catenin nuclear accumulation. (337)

1,25-(OH)2 D3 is an important modulator of the immune system, as reflected by the expression of vitamin D receptors by almost all types of immune cells. 1,25-(OH)2D 3 is an enhancer of innate immune reactions against tumor cells by activating macrophages, natural killer (NK) cells, and neutrophils. (209) An important mechanism of 1,25-(OH)2D3 is the inhibition of the NF-KB pathway. In turn, this causes the downregulation of multiple cytokines and their effects. 1,25(OH)2 D3 reduces the protumorigenic effect of PG E2 in prostate cancer cells by inhibiting COX-2 and so decreasing the levels of PG E2 and two PG receptors (EP2 and FP). (338)

Autophagy is a process of elimination of cytoplasmic waste materials and dysfunctional organelles that serves as a cytoprotective mechanism but that, when excessive, leads to cell death. (209) In cancer, VDR ligands trigger autophagic death by inducing crucial genes in several cancer cell types. Thus, 1,25-(OH)2 D3 de-represses the key autophagic MAP1LC3B (LC3B) gene and activates 50-AMP-activated protein kinase (AMPK). In Kaposi's sarcoma cells and myeloid leukemia cells, vitamin D compounds inhibit PI3K/AKT/mTOR signaling and activate Beclin-1-dependent autophagy. 1,25-(OH)2D3 has a pro-differentiation effect on several types of carcinoma cells either by direct upregulation of epithelial genes and/or the repression of key epithelial mesenchymal transcription factors (EMT-TFs). (339)

In diverse types of carcinoma cells (colon, prostate, and breast), the antiangiogenic action of 1,25-(OH)2 D3 relies to a great extent on its ability to inhibit two major angiogenesis promoters: it suppresses the expression and activity of hypoxia-inducible factor (HIF)-1α, a key transcription factor in hypoxia-induced angiogenesis, and of vascular endothelial growth factor (VEGF). (209) 1,25-(OH)2D3 also has inhibitory effects on tumor-derived endothelial cells. It reduces their proliferation and sprouting in vitro and diminishes the blood vessel density in cancer models. (340)

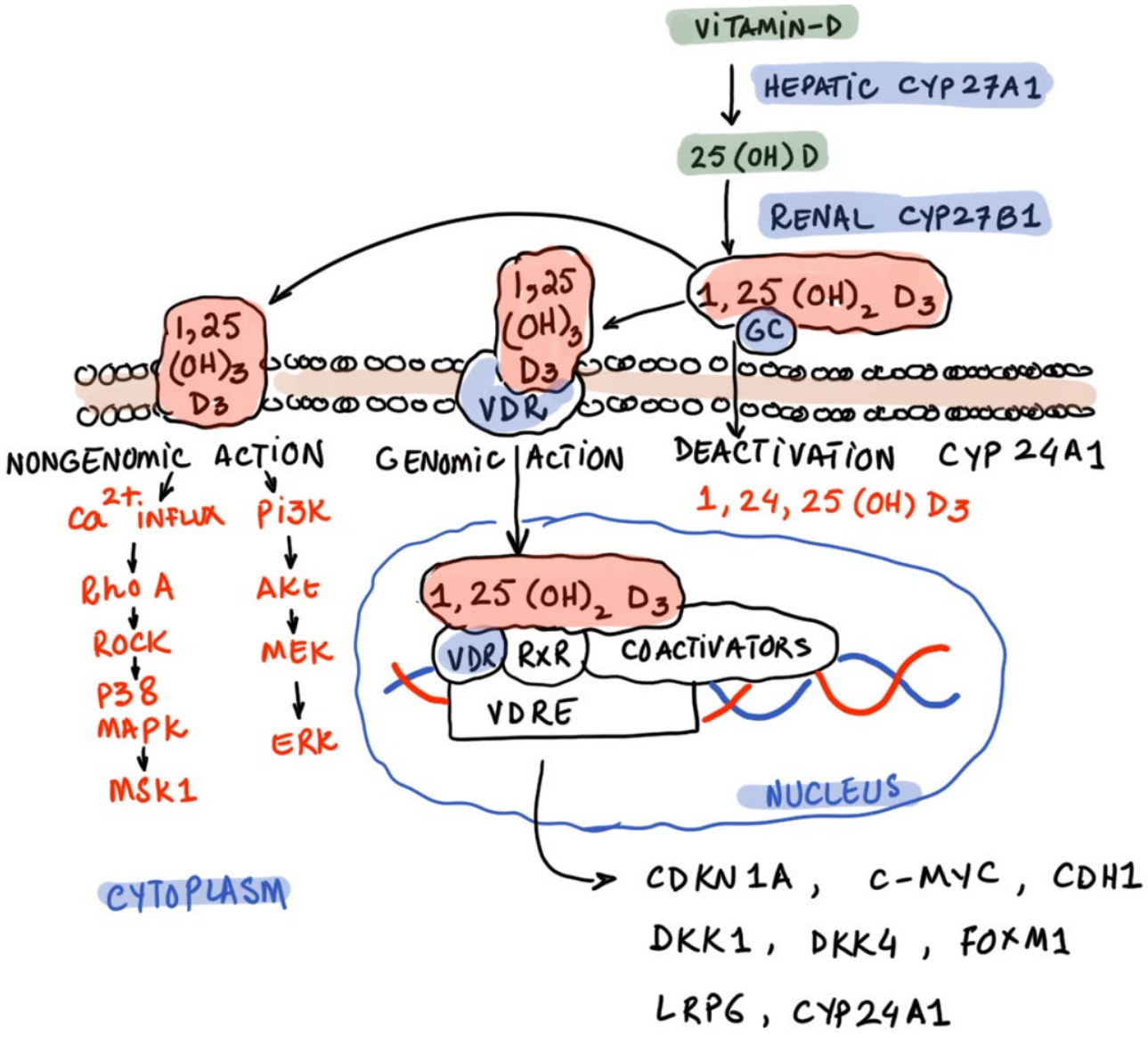

Figure 9. Overview of metabolic pathways of Vitamin D. {Source: Dr. Mobeen Syed}

Footnote for Figure 9: CYP27A1: Cytochrome P450 family 27 subfamily A member 1, CYP27B1: Cytochrome P450 family 27 subfamily B member 1, 25(OH)D: 25-hydroxyvitamin D, 1,25(OH)2 D3: 1,25-dihydroxyvitamin D3, GC: Vitamin D-binding protein (Gc protein), VDR: Vitamin D receptor, RXR: Retinoid X receptor, VDRE: Vitamin D response element, CDKN1A: Cyclin-dependent kinase inhibitor 1A, C-MYC: Cellular Myelocytomatosis oncogene, CDH1: Cadherin-1, DKK1: Dickkopf-1, DKK4: Dickkopf-4, FOXM1: Forkhead box protein M1, LRP6: Low-density lipoprotein receptor-related protein 6, PI3K: Phosphatidylinositol 3-kinase, Akt: Protein kinase B, MEK: Mitogen-activated protein kinase kinase, ERK: Extracellular signal-regulated kinase, Rho A: Ras homolog gene family member A, ROCK: Rho-associated protein kinase, P38: p38 mitogen-activated protein kinase, MAPK: Mitogen-activated protein kinase, MSK1: Mitogen- and stress-activated protein kinase 1

Clinical studies

Data suggest that the majority of patients with cancer are vitamin D deficient (level < 20 ng/ml). (323, 328, 341, 342) Several prospective observational studies have shown that higher levels of plasma 25-hydroxyvitamin D were associated with improved survival among patients with colorectal cancer. (341, 343-345) Similarly, elevated 25-OH D levels were associated with better overall survival in patients with breast and gastric cancer and lymphoma. (346) In a population-based study of patients with cancer of the breast, colon, lung, and lymphoma a 25-OHD level below 18 ng/ml at diagnosis experienced shorter survival. (347) In a meta-analysis of 19 studies Robsahm et al reported an inverse relationship between 25-Hydroxyvitamin D and cancer survival. (348)

Chen performed a meta-analysis of observational cohort studies and randomized trials which assessed the role of post-diagnosis vitamin D supplement intake on survival among cancer patients. (349) The meta-analysis included 11 publications consisting of 5 RCTs and 6 observational cohort studies. The summary relative risk (SRR) for overall survival of vitamin D supplement use vs. non-use, pooling cohort studies and randomized trials, was 0.87 (95% CI, 0.78–0.98; p = 0.02). Vaughan-Shaw et al performed a meta-analysis of 7 studies evaluating the use of supplemental vitamin D in patients with colorectal cancer. (350) The study reported a 30% reduction in adverse outcomes and a beneficial effect on progression-free survival (HR = 0.65; 95% CI: 0.36–0.94). In a meta-analysis by Kuznia et al, subgroup analysis revealed that vitamin D3 administered daily, in contrast to bolus supplementation, reduced cancer mortality by 12 %. (351) It should be recognized that a daily dose of between 800 IU and 4000 IU was administered in the studies included in this meta-analysis and that vitamin D levels were not monitored. A more dramatic reduction in mortality would likely be realized if patients were dosed more appropriately.

SUNSHINE was a double-blind, multicenter, randomized clinical trial designed to evaluate the efficacy of “high dose” vitamin D3 compared with standard-dose vitamin D3 given in combination with standard chemotherapy in patients with metastatic colorectal cancer. (328) The high-dose group received a loading dose of 8,000 IU per day of vitamin D3 (two 4,000 IU capsules) for cycle 1 followed by 4,000 IU/d for subsequent cycles. The standard dose group received 400 IU/d of vitamin D3 during all cycles. In this underpowered (n=139) RCT, multivariable HR for progression-free survival or death was 0.64 (95% CI, 0-0.90; p = .02) in favor of the high dose group. Comparison of progression-free survival between the high-dose and standard-dose vitamin D3 groups using a log-rank test stratified by ECOG performance status was statistically significant (p = .03). At baseline, median plasma 25-hydroxyvitamin D levels were deficient in both the high-dose vitamin D3 group (16.1 ng/mL [IQR, 10.1 to 23.0 ng/mL]) and in the standard-dose vitamin D3 group (18.7 ng/mL [IQR, 13.5 to 22.7 ng/mL]). Only 9% of the total study population had sufficient levels (≥30 ng/mL) of 25-hydroxyvitamin D at baseline. At treatment discontinuation, patients in the high-dose vitamin D3 group had a median 25-hydroxyvitamin D level of 34.8 ng/mL (IQR, 24.9-44.7 ng/mL), whereas those in the standard-dose vitamin D3 group were still deficient in vitamin D and had a median 25-hydroxyvitamin D level of 18.7 ng/mL(IQR, 13.9-23.0ng/mL) (difference, 16.2 ng/mL [95% CI, 9.9-22.4 ng/mL]; *P* < .001). It is important to note that

based on these levels the “high dose” group was profoundly underdosed. As indicated above, vitamin D dosing should be based on a serum level aiming for a level of > 50 ng/ml (target 55-90 ng/ml). Based on the data from this study we would suggest a daily dose of vitamin D3 of 20,000 to 50,000 IU/day until a vitamin D level is obtained. It is possible that patients with cancer may require an even higher level, approximating 150 ug/dl.

Wang et al demonstrated that postoperative vitamin D supplementation in esophageal cancer patients undergoing esophagectomy was associated with improved quality of life and with improved disease-free survival. (352) Similarly, vitamin D use post-diagnosis was found to be associated with a reduction in breast cancer-specific mortality. (353) Two recent clinical trials in prostate cancer patients suggest that vitamin D supplementation may prevent prostate cancer progression. (354, 355) Vitamin D has additive or synergistic effects when combined with conventional chemotherapy. (333) Zeichner et al demonstrated that use of vitamin D during neoadjuvant chemotherapy in HER2-positive nonmetastatic breast cancer was associated with improved disease-free survival (HR, 0.36; 95% CI, 0.15-0.88; p=0.026). (356)

Types of cancers that Vitamin D may be beneficial for

Vitamin D supplementation is likely beneficial in most cancers, but particularly in patients with breast, colorectal, gastric, esophagus, lung, and prostate cancer as well as those with lymphomas and melanoma.

Dosing and cautions

As almost all patients with cancer are severely vitamin D deficient. A high loading dose of Vitamin D is suggested followed by dose titration according to vitamin D blood levels, aiming for a level of > 50 ng/ml (target 55-90 ng/ml). However current data suggest that levels up to 150 ng/mL are necessary for certain types of cancer to stop growth and metastasis. Vitamin D intoxication is observed when serum levels of 25-hydroxyvitamin D are greater than 150 ng per milliliter (374 nmol per liter). (307) Hypercalcemia will usually not occur until levels exceed over 250 ng/ml. We, therefore, suggest a daily dose of 20,000 to 50,000 IU/day until a vitamin D level is obtained. With the suggested doses, serum 25(OH)D concentrations rise above 100 ng/mL within a week or two, but unless a suitable higher maintenance dose is used (~ 10,000 IU/day), the level will start to drop to baseline after three weeks or so, and the benefit of vitamin D will be lost. If measuring vitamin D levels is not feasible/possible, we would suggest a loading dose of 100,000 IU followed by 10,000 IU/day. Doses of 10,000 IU of vitamin D3 per day for up to 5 months were reported to be safe and without toxicity. (307, 310) It should be noted that dosages of vitamin D up to 80,000 IU/day have been reported to be safe. (357, 358) We recommended vitamin D3 over D2 as vitamin D2 is approximately 30% as effective as vitamin D3 in maintaining serum 25-hydroxyvitamin D levels. (307) Furthermore, vitamin D3 should be dosed daily rather than large intermittent bolus dosing. It is best to include both Vitamin K2 (Menaquinone [MK4/MK7] 100 mcg/day, or 800 mcg/week) and magnesium (250-500 mg/day) when doses of vitamin D > 8 000 IU/day are taken. (313, 314) Patients taking coumadin need to be closely monitored and the need to consult with their PCP before taking vitamin K2. Further,

we suggest measuring PTH (parathyroid) levels and calcium levels and titrating the dose of Vitamin D according to the PTH levels as follows (Coimbra Protocol): (359, 360) i) if the PTH level is below the lower end of the reference range, reduce the dose of Vitamin D ii) if the PTH level is at (or close too) the lower end of the reference range, maintain dose, iii) if PTH is within the reference range but not near to the low end of the reference range increase the dose of Vitamin D.

5. Metformin

Numerous trials have shown that metformin, routinely used to treat diabetes, also inhibits the development of cancer cells and reduces cancer cell proliferation.

Anticancer pathways and mechanisms

Metformin has been shown to have anticancer activity both in vivo and in vitro. (361) It has been proposed that the anticancer properties of metformin result from both direct effects on cancer cells, particularly through inhibition of the AMPK/mTOR pathway, (362) and indirect effects on the host, by its blood glucose-lowering properties and anti-inflammatory effects. Metformin inhibits complex I of the electron transport chain in mitochondria, putting cancer cells under bioenergetic stress and forcing them to rely on glycolysis for ATP synthesis. (363) Metformin's inhibition of GPD2 activity alters the cytosolic redox balance, which prevents redox-dependent substrates from entering the gluconeogenic pathway. (364) Metformin suppresses protein synthesis and cell development by activating ATM (ataxia telangiectasia mutated), LKB1 (liver kinase B1), and adenosine monophosphate-activated kinase (AMPK). This reduces mTOR action. (365) By turning on AMPK, metformin can activate p53, which ultimately stops the cell cycle. (365) Peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1), a distinct molecular pathway, is upregulated due to AMPK activation following metformin exposure. Low levels of PGC-1 have been linked to poorer outcomes, and it is a transcriptional coactivator involved in mitochondrial biogenesis. Metformin boosts PGC-1 and suppresses gluconeogenesis activation. (364) Metformin interacts with the S1RT1 pathway: The sirtuin 1 (SIRT1) route, which is activated by the NAD (+)-dependent protein sirtuin 1 (SIRT1) with deacetylase activity, is another significant mechanism that connects metabolism with cell proliferation. (364) Unlike most standard chemotherapy, metformin suppresses cancer stem cells, the root of cancer. (366)

Metformin regulates the EGFR and IGFR pathways, which are involved in cell growth, proliferation, and the coordination of several metabolic processes. A similar circuit performs profound functions in apoptosis and cell proliferation and is a critical axis for metabolism and cell growth. Additional research has revealed that a poor prognosis, metastasis, and disease progression are linked to elevated IGF-1 and IGF-2 expression and IGFBP-3 abnormalities. Evidence suggests that metformin treatment may prevent some of these alterations and exert an antitumor effect. Both the EGFR and IGFR pathways can boost metabolic cell modifications in a coordinated manner, acting as neoplasm promoters and forming a feedback system. (364)

Clinical studies

Meta-analyses have examined the role of metformin in the primary prevention of cancer, where it was found to significantly reduce overall cancer incidence. (141, 142) Lega et al performed a meta-analysis of 21 observational studies, evaluating the outcomes of diabetic patients with cancer who were receiving metformin. (367) In this study, metformin was associated with a reduction in all-cause mortality [HR, 0.73; 95% confidence intervals (CI), 0.64-0.83] and cancer-specific mortality (HR, 0.74; 95% CI, 0.62-0.88); patients with colorectal cancer demonstrated the greatest benefit. In a similar analysis performed by Yin et al, metformin improved overall survival in patients with lung, breast, and prostate cancer. (368) In diabetic patients with colorectal cancer Mei et al demonstrated that metformin reduced the risk of all causes of death by 44% and the specific risk of colorectal cancer death by 34%. (369) Coyle et al performed a meta-analysis of 27 observational studies which investigated the use of metformin as an adjunctive treatment for cancer. (370) The findings of this study suggested that metformin was associated with significant benefit in the early treatment of patients with colorectal and prostate cancer, particularly in those receiving radical radiotherapy.

Types of cancers that metformin may be beneficial for

Various malignancies can be prevented with the use of metformin. In general, metformin can: i) lower cancer incidence, ii) lower cancer mortality, iii) improve cancer cell response to radiotherapy and chemotherapy, iv) optimize tumor migration and lower malignancy, v) lower relapse risk, and vi) lessen the harmful effects of androgen derivatives. (364, 365) Collective findings show that metformin has a broad spectrum of anticancer activity against breast, pancreatic, gastric, colorectal, endometrial, pancreatic prostate, non-small cell lung cancer (NSCLC), and bladder cancers. (364, 369-375) However, the greatest benefit may be in patients with colorectal and prostate cancer, (369, 375), particularly when used as an adjunctive therapy.

Dosing and cautions

A dose of metformin of 1,000 mg twice daily is suggested. Metformin is a remarkably safe drug with very few side effects. The most common adverse effects include abdominal or stomach discomfort, cough, hoarseness, decreased appetite, and diarrhea. Prolonged use is associated with vitamin B12 deficiency; supplementation with a B complex vitamin is therefore suggested. Metformin may cause very low blood glucose when combined with berberine; hence the blood glucose should be very closely monitored in patients taking this combination; if low glucose does occur, we would suggest alternating metformin and berberine (monthly).

6. Curcumin

Curcumin, popularly called "curry powder" or turmeric, is a polyphenol extracted from Curcuma longa. Curcumin has antioxidant, anti-inflammatory, antimicrobial, antiviral, and anticancer properties. (376)

Anticancer pathways and mechanisms

Curcumin has been shown to interfere with multiple cell signaling pathways in cancer cells, including (see figure 10): (377-394)

i. Cell cycle (cyclin D1 and cyclin E)
ii. Apoptosis (activation of caspases and down-regulation of antiapoptotic gene products), proliferation (HER-2, EGFR, and AP-1)
iii. Survival (PI3K/AKT pathway)
iv. Invasion (MMP-9 and adhesion molecules)
v. Angiogenesis (VEGF)
vi. Metastasis (CXCR-4)
vii. Inflammation (NF-kappa B, TNF, IL-6, IL-1, COX-2, and 5-LOX)

Aberrant activation of NF-κB is characteristic of cancer, with NF-κB playing a major role in cancer angiogenesis, proliferation, metastasis, inflammation, and through the induction of cell survival pathways and inhibition of apoptosis. Phosphorylated NF-KB binds DNA and starts the transcription of oncogenes that block apoptosis and initiates cellular proliferation and angiogenesis. (376) Curcumin suppresses NF-KB activity by inhibiting the phosphorylation by I kappa B kinase and impeding nuclear translocation of the NF-KB p65 subunit. STAT3, is a common target for several signaling pathways regulating oncogenes, as well as modulating the transduction of pro-inflammatory cytokines and growth factors. (376) STAT3 contributes to the growth and survival of the cancer cell, increasing the expression of anti-apoptotic proteins such as Bcl-2 and Bcl-xL, thereby blocking apoptosis. Several factors, such as IL-6, as well as EGFR and PDGF, are reported to be STAT3 activators. (395) STAT3 is reported to be a molecular target of curcumin in several tumors, both directly and indirectly by inhibition of IL-6. (396) The accumulation and activation of immune suppressive cells like Treg, Th17, and MDSCs, the differentiation of macrophages toward the M2 phenotype, and the absence of functional DCs are all caused by STAT3 activation. Curcumin significantly decreases STAT3 phosphorylation. (385) Curcumin inhibits breast cancer cell lines through inhibiting HER2-tyrosine kinase. (397) Curcumin inhibits the phosphorylation of Akt, mTOR, and their downstream proteins, resulting in cell cycle arrest in various breast cancer cell lines. (398)

Curcumin downregulates hexokinase-2 and dissociates HK-2 from the mitochondria inducing apoptosis. (399) Curcumin is also able to interfere with the cell signaling pathway of EGFR, a family of receptor tyrosine kinases, that is reported to be associated with the proliferation, adhesion, migration, and differentiation of cancer cells. (400, 401) Curcumin inhibited the growth and proliferation of breast cancer cells by reducing EGFR signaling and decreasing EGFR and Akt levels. (400) Curcumin has been demonstrated to induce apoptosis of triple-negative breast cancer cells by inhibition of EGFR expression. (401) In pancreatic cancer cells, curcumin potentiates the anticancer activity of gemcitabine via inhibition of NF-κB, proliferation, angiogenesis, and expression of Cdc20, which is associated with enhanced cell proliferation and invasion. (402)

Curcumin has an impact on the tumor microenvironment by inhibiting angiogenesis even under the hypoxic status within the tumor microenvironment. (382) Furthermore, curcumin has activity against cancer stem cells in addition to promoting apoptosis. (382, 386, 393, 403) Curcumin induces apoptosis in tumor cells, (377) through ROS-mediated endoplasmic reticulum (ER) stress and mitochondrion-dependent pathways. (382) In addition, curcumin acts through the Wnt/-catenin pathway. (384, 394)

Clinical studies

Despite the broad anticancer activities of curcumin in experimental models, its clinical use has been limited by its poor bioavailability. Its oral bioavailability is low due to its poor absorption, extensive phase I and II biotransformation, and rapid elimination through the gall bladder. (404) Due to its low solubility in water and poor absorption, it is traditionally taken with full-fat milk and black pepper, which enhance its absorption. To improve the bioavailability, various curcumin analogs and novel drug delivery systems (e.g., phospholipids, lecithinized curcumin, nanoparticles, and liposomes) are under investigation.

While a few case series describing the use of curcumin in cancer have been published, (378, 391, 405-409) the clinical efficacy of curcumin has been evaluated in a limited number of studies. In a pilot randomized clinical trial in patients with multiple myeloma, the addition of curcumin (4 g twice daily for 28 days) to treatment with melphalan and prednisone increased the rates of remission ([75% vs. 33.3%, p=0.009]. (380) In this study NF-KB, VEGF, and TNF levels were significantly lower in the curcumin group with TNF levels being strongly correlated with remission [OR=1.35; 95% CI=1.03-1.76, p=0.03]. In a phase IIa, open-labeled trial patients with metastatic colorectal cancer were randomized to fluorouracil/oxaliplatin chemotherapy (FOLFOX) compared with FOLFOX + 2 g oral curcumin/d (CUFOX). (410) In the intention-to-treat population, the HR for overall survival was 0.34 (95% CI: 0.14, 0.82; P = 0.02) (median of 200 and 502 days for FOLFOX and CUFOX, respectively). In a prospective, single-arm phase II study, Pastorelli et al evaluated the use of a phytosome complex of curcumin (2 g/day) as adjunctive therapy with gemcitabine in patients with advanced pancreatic cancer. (411) The median overall survival of patients treated with gemcitabine as a single agent is 5.7 months. (412) These investigators reported a 27.3% of response rate with 34.1% of cases having stable disease, with a total disease control rate of 61.4%. The median progression-free survival and overall survival were 8.4 and 10.2 months, respectively. Saghatelyan et al randomized 150 women with advanced metastatic breast cancer to receive either paclitaxel plus placebo or paclitaxel plus curcumin once per week for 12 weeks with 3 months of follow-up. (413) In this study, the curcumin was given intravenously. The intention-to-treat analysis revealed that the objective response rate of curcumin was significantly higher than that of the placebo (51% vs. 33%, p<0.01) at 4 weeks of follow-up. The difference between the groups was even greater when only patients who had completed the treatment (61% vs. 38%, odds ratio =2.64, p<0.01) were included.

In dose escalation studies, up to 10 g of curcumin taken daily has been shown to be well tolerated. Patients with breast cancer taking 6 g/day of curcumin for 7 weeks, and patients with prostate cancer who took 3 g/day of curcumin for 9 weeks exhibited adverse effects. [301,353,389]

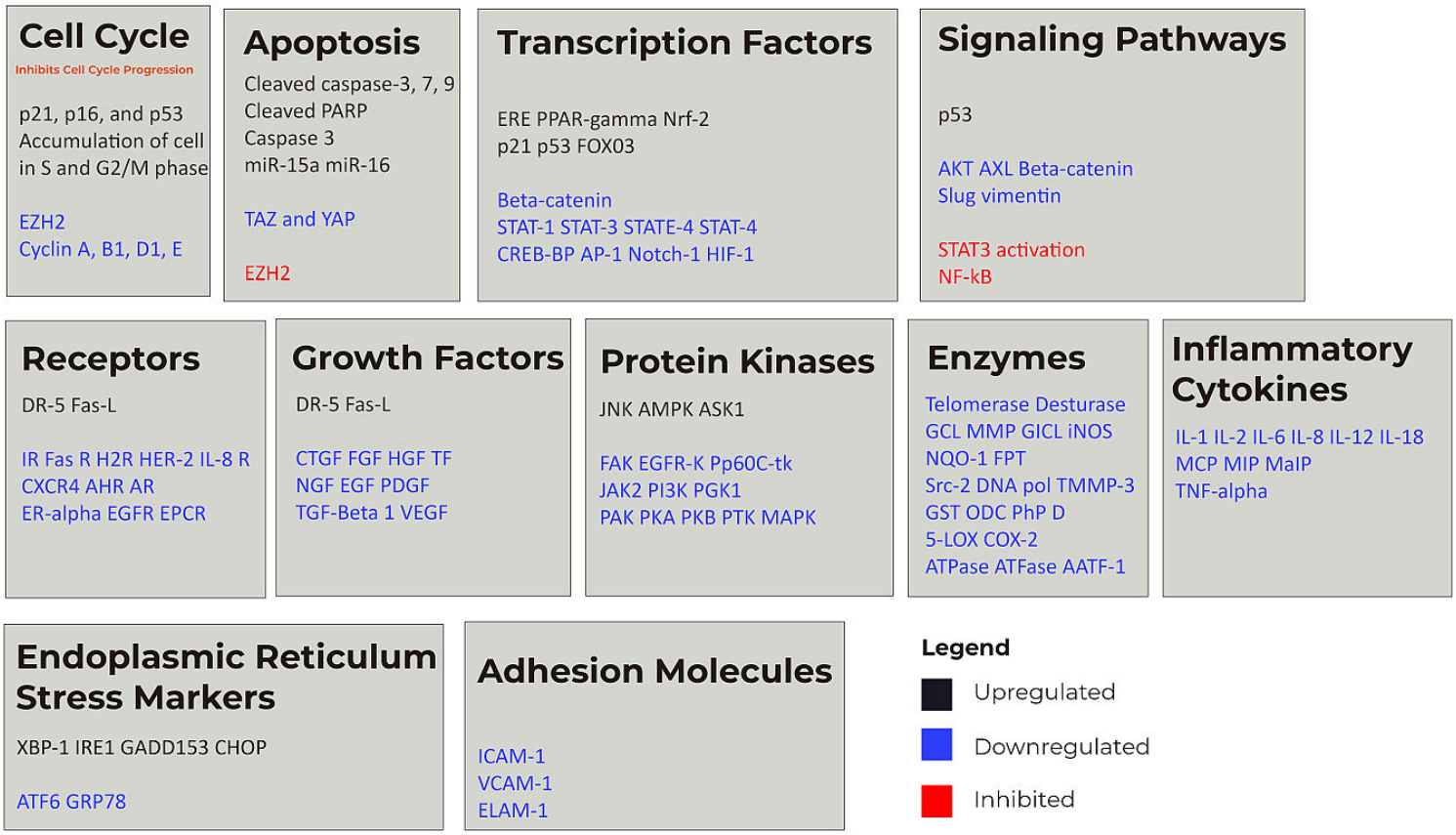

Figure 10. Curcumin - a multifaceted anticancer agent [Source: Dr. Mobeen Syed]
Footnote for Figure 10. See Appendix 3.

Types of cancers that curcumin (turmeric) may be beneficial *for*
Colorectal, lung, pancreatic, breast, prostate, chronic myeloid leukemia, liver, gastric, brain tumors, ovarian, skin, head and neck, lymphoma, esophageal cancer, and myeloma. (376, 394)

Drug formulations and cautions
The use of curcumin has been limited by its poor solubility, absorption, and bioavailability. The manipulation and encapsulation of curcumin into a nanocarrier formulation can overcome these major drawbacks and potentially may lead to a far superior therapeutic efficacy. In a murine Hodgkin's Lymphoma model, formulating curcumin in solid lipid nanoparticles exhibited greater anticancer activity compared to curcumin alone. (414) Nano-curcumin preparations or formulations designed to enhance absorption are therefore recommended. (415-418)

In the U.S., a large share (55%) of the turmeric dietary supplement market is comprised of products formulated to enhance curcumin bioavailability, including proprietary products where curcuminoid extracts are often combined with some type of lipophilic carrier to increase absorption, or products combining curcumin with piperine to decrease metabolism. (419) However, as the quality of these products may vary, we would recommend the use of USP-grade supplements. Furthermore, nanoformulation-based combination therapy has emerged as a potent approach for drug delivery systems. (420) A nanodrug co-delivery system incorporating chemotherapeutic agents has demonstrated greater cancer cell sensitivity. (421, 422)

Curcumin has been characterized as "generally safe" by the US Food and Drug Administration (FDA). (423) No toxicity is seen for doses of up to 8–10 g/day. (391, 392, 394, 408, 424, 425) However, diarrhea can be a frequent side effect, especially if the daily dose exceeds 4 g. (391) Hepatic injury (hepatitis) is a rare complication and therefore liver function tests should be monitored during long-term use. (426)

Curcumin does not appear to have any overt negative effects, but it has been noted that this compound can inhibit several cytochromes P450 subtypes, including CYP2C9 and CYP3A4. (394, 427) Consequently, curcumin has been reported to interact with several different drugs, including antidepressants, antibiotics, and anticoagulants like coumadin and clopidogrel. (394, 428) Curcumin has anticoagulant effects and may prolong bleeding in people using anticoagulants. (394, 429)

7. Mebendazole/ Fenbendazole/Albendazole

Anticancer pathways and mechanisms
A compound originally developed as a treatment for parasitic worms, mebendazole (MBZ) works by fatally disrupting the cellular microtubule formation in abnormal cancer cells that occurs as the cell is attempting to divide. Like the other benzimidazoles, Mebendazole binds to the tubulin colchicine-binding domain and appears to act by both p53-dependent and

independent mechanisms. (430) MBZ inhibits many factors involved in tumor progressions such as tubulin polymerization, angiogenesis, pro-survival pathways, matrix metalloproteinases, and multi-drug resistance protein transporters. (431) MBZ inhibits cancer stem cells; this mechanism of action is critical in preventing metastasis. (128, 431)

MBZ decreases the activity of the Hedgehog pathway, which is common in gliomas, melanomas, lung cancers, ovarian cancers, and colorectal cancer. (64) MBZ inactivates Bcl-2 and activates caspases to promote apoptosis in cancer cells and the release of cytochrome c which has also been shown to trigger apoptosis in malignant cells. Benzimidazole modulates the typically overactivated MAPK pathway, switching it to activate the apoptotic pathway, rather than the anti-apoptotic pathway; it also destabilizes microtubules, structural proteins required to maintain a cell's integrity during the process of mitosis, among other functions; it *also* interferes with cancer cells' glycolysis-dependent metabolism, upon which *most* cancers are heavily preferentially dependent, as well as functioning as an inhibitor of mitochondrial oxidative phosphorylation, or OXPHOS, which reduces the residual energy available via the ordinary metabolic ATP production pathway.

MBZ can cross the blood-brain barrier and has been demonstrated to slow the growth of gliomas by targeting signaling pathways involved in cell proliferation, apoptosis, invasion, and migration, as well as by making glioma cells more susceptible to conventional chemotherapy and radiotherapy. (432)

MBZ can also sensitize cancer cells to conventional therapy, such as chemotherapeutics and radiation, enhancing their combined antitumor potential, confirming that MBZ may be useful as an adjuvant therapeutic combined with traditional chemotherapy. (432) When combined with low-dose chemotherapy there is also evidence these drugs help to destroy the tumor-associated macrophage cells that may help maintain a favorable environment for the cancer to flourish.

Clinical studies

The use of benzimidazoles in cancer is limited to a few case reports (433, 434) and a small case series. (435) Mebendazole is a component of the multidrug cocktail used in the METRICS study. (157) The use of benzimidazoles, and in particular fenbendazole, has achieved much attention as a repurposed drug for cancer due to the reported experience of Joe Tippens. (57) In 2016, Tippens was diagnosed with non-small-cell lung cancer with extensive metastatic disease. At the advice of a veterinarian friend, he took Fenbendazole together with nanocurcumin, and three months after starting these drugs his PET scan was completely clear. He remains alive and disease-free up until the present; however, some questions surround his apparent cure.

Types of cancers that mebendazole may be beneficial for

A wide variety of cancers, including NSCLC, adrenocortical, colorectal, chemo-resistant melanoma, glioblastoma multiforme, colon, leukemia, osteosarcoma/soft tissue sarcoma,

acute myeloid sarcoma, breast (ER+ invasive ductal), kidney, and ovarian carcinoma, have been shown to be responsive to benzimidazoles, including MBZ. (155, 430-432, 436-445)

Dosing and cautions

We suggest Mebendazole 100-200 mg/day. The cost of mebendazole in the U.S. skyrocketed once this drug was discovered to have activity against cancer ($555 for a single 100 mg tablet). However, mebendazole is available from international compounding pharmacies (India) at about 27c for a 100 mg tablet.

8. Berberine

Depending on the patient's blood glucose levels, providers can consider using metformin and berberine together or alternating (switching back and forth for one month at a time).

Anticancer pathways and mechanisms

Berberine's anticancer mechanisms include reducing the growth of cancer cells, preventing metastasis, inducing apoptosis, activating autophagy, controlling the microbiota in the gut, and enhancing the effects of other cancer treatments by focusing on antibacterial action, which includes controlling the microbiota in the gut and preventing intratumoral microbes. (446-450)

Berberine may prevent the growth of cancer cells through the upregulation of miR-214-3p, the downregulation of SCT protein levels, the regulation of catenin, the inhibition of telomerase activity, and the deactivation of MAPK signaling pathways. (451-453) By increasing p21, p27, and p38 and lowering CDK1, CDK4, cyclin A, and cyclin D1, berberine may inhibit the growth of cancer cells. (446, 454) Through the AMPK-p53, PI3K/AKT/mTOR, miR19a/TF/MAPK signaling pathways, and modulation of the CASC2/ AUF1/B-cell/Bcl-2 axis, berberine promotes cancer cells apoptosis. (448, 455-457) Berberine downregulates many TME-related genes, including PDGFRB, COL1A2, and BMP7, and upregulating E-cadherin, thereby inhibiting metastatic spread. (458-460)

Berberine has anticancer effects by influencing the gut microbiota. For example, berberine increases the Firmicutes/Bacteroidetes ratio and the relative abundance of Clostridiales, Lactobacillaceae, Bacteroides, and Akkermansia muciniphila. (449, 450)

Berberine increases radiation sensitivity and enhances the effects of anticancer medications such as cisplatin, 5-fluorouracil, doxorubicin, niraparib, and icotinib. (461-464)

Clinical studies

While there is limited clinical data on the benefits of berberine, a randomized, double-blind study demonstrated that berberine in a dose of 300 mg twice daily significantly reduced the risk of recurrent colorectal adenomas following polypectomy. (465)

Types of cancers that berberine may be beneficial for

Berberine shows anticancer effects on various cancers, such as breast, lung, gastric, liver, colorectal, ovarian, cervical, and prostate. (446-448, 451-457, 459-464, 466)

Dosing and cautions

A total daily dose of 1000-1500 mg (take 500 mg two or three times daily or 600 mg twice daily) is suggested. As insulin release is glucose-dependent hypoglycemia has not been reported with this herb; however, blood glucose should be monitored and the additive/synergistic effect of metformin on the blood glucose profile should be determined. Berberine should not be taken in patients taking cyclosporine as this combination will increase cyclosporine levels (absolute contraindication). Berberine may alter the metabolism of the following drugs, which should be used with caution (monitor effects): anticoagulants, dextromethorphan, tacrolimus (Prograf), phenobarbitone, losartan (inhibits effect) and sedative drugs (see https://www.webmd.com/vitamins/ai/ingredientmono-1126/berberine). If you are scheduled for surgery, please notify your anesthesia team if you are taking Berberine. You may need to stop taking Berberine one week prior to surgery.

9. **Atorvastatin** or simvastatin. The lipophilic statins appear to be highly effective in the management of several cancers.

Anticancer pathways and mechanisms

Statins may affect tumor cells directly in four main ways: i) growth suppression, ii) apoptosis induction, iii) anti-invasive and anti-metastatic effects, and iv) anti-angiogenic effects. A primary effect is that statins block activity of the cholesterol-producing enzyme HMG CoA, which means less cholesterol is available to produce new cell walls in rapidly proliferating tumors. Rapidly multiplying cancer cells require more cholesterol to allow the creation of cell membranes. (467, 468) A reduction in the availability of cholesterol may limit the cellular proliferation required for cancer growth and metastasis. In addition, statins alter the expression of genes regulating the balance between life-promoting and death-promoting proteins in cancer and may have a number of benefits in killing cancer cells. Studies have shown statins also reactivate caspases and upregulate the production of PPARγ, another protein that programs cell death. Statins also reduce the number of cell surface GLUT-1 glucose receptors, thus reducing cancer cell activity by limiting the amount of energy available. Additionally, statins' direct inhibition of HMGCR depletes the body's stores of isoprenoids, which play a crucial role in controlling the growth and spread of cancer cells. (469)

Clinical studies

Lipophilic statins have been demonstrated to reduce the incidence and all-cause mortality from a number of cancers. A 10-year retrospective cohort study by Farwell et al compared statin use in a veteran population taking antihypertensive medications and found that, on average, statin users had a 31% lower risk of prostate cancer incidence. (470) NSAIDs have been found to significantly reduce prostate cancer risk and may act synergistically with statins to prevent prostate cancer. (471)

Nielsen et al assessed mortality among patients from the entire Danish population who had received a diagnosis of cancer between 1995 and 2007. (472) In this study multivariable-adjusted hazard ratios for statin users, as compared with patients who had never used statins, was 0.85 (95% CI, 0.82 to 0.87) for death from cancer. The reduced cancer-related mortality among statin users as compared with patients who had never used statins was observed for 13 cancer types. Zhong et al demonstrated that patients who used statins after a diagnosis of cancer had an HR of 0.81 (95% CI: 0.72–0.91) for all-cause mortality compared to non-users; the benefit was most marked for colorectal, prostate, and breast cancer. (473)

In a population-based retrospective cohort study that looked at the usage of statins after a prostate cancer diagnosis, (474) the post-diagnostic use of statins was associated with a decreased risk of prostate cancer mortality (HR, 0.76; 95% CI, 0.66 to 0.88) and all-cause mortality (HR, 0.86; 95% CI, 0.78 to 0.95); longer and higher dosages led to a lower incidence in mortality, as well as distant site metastasis.

In a meta-analysis of 10 studies, statin use was associated with improved recurrence-free survival (RFS; HR 0.64; 95% CI 0.53–0.79) in women with breast cancer. (475) Furthermore, this survival benefit appeared to be confined to use of lipophilic statins. Similarly, Ahern et al performed a population study of women with stages I–III breast cancer; they reported a 10% reduction in breast cancer recurrence among women who were prescribed a lipophilic statin (most commonly simvastatin). (476) Similarly, in colorectal and hepatocellular cancer, statin usage reduces cancer-specific mortality, in particular when used either prior to diagnosis or prior to recurrence. (477-479) In lung cancer, retrospective studies have shown that statins reduce cancer-specific mortality. (480)

Types of cancers that statins may be beneficial for
Breast, prostate, colorectal, hepatocellular, lung, testicular, pancreatic, gastric, ovarian, leukemia, brain, and kidney. (372, 469, 472, 481)

10. Stress Reduction and Exercise (aerobic and resistance training)

Regular exercise combining both aerobic activity and resistance training is recommended in patients undergoing treatment for cancer. Aerobic exercises such as walking, high-intensity interval training (HIIT), cycling, swimming, etc., improve overall cardiovascular fitness with improved indicators of quality of life including better cognition and mood with less fatigue and reduced anxiety and depression. (482-486)

Resistance training preserves lean body mass (muscle mass), which reduces insulin resistance and improves glucose control and may be an important factor in increasing overall survival as sarcopenia is a major negative prognostic factor in patients with cancer. (487)

The Combined Aerobic and Resistance Exercise (CARE) Trial compared different types and doses of exercise performed during breast cancer chemotherapy. (488) In this study a combined dose of 50-60 minutes of aerobic and resistance exercise performed three times weekly was significantly associated with better patient-reported outcomes and health-related compared to performing aerobic exercise alone. Meta-analyses that focused on specific types of cancer reported benefits in breast cancer treated with adjuvant chemotherapy and/or radiotherapy, colorectal cancer treated with chemotherapy, lung cancer treated with chemotherapy, prostate cancer treated with radiation therapy, and hematologic malignancies. (482)

It is critically important that patients engage in activities that reduce stress (meditation, yoga, mindfulness exercises etc) and have at least 8 hours of high-quality sleep (ensure adequate sleep hygiene). (149-154, 489)

11. Phosphodiesterase 5 inhibitors: sildenafil, tadalafil, and vardenafil

Selective phosphodiesterase 5 inhibitors, including sildenafil, tadalafil, and vardenafil, are widely used in the treatment of erectile dysfunction and pulmonary arterial hypertension. These drugs may also be effective cancer treatments.

Anticancer pathways and mechanisms
Inhibition of PDE5 by sulindac sulfide (an NSAID) selectively induces apoptosis and attenuates oncogenic Wnt/β-catenin mediated transcription in human breast tumor cells. (490) Sildenafil treatment affects HSP90 expression, a chaperone protein that promotes degradation of PKD2, a serine threonine kinase with an important role in cancer cell proliferation and viability. (491)

Sildenafil and tadalafil were shown to inhibit the development and progression of aflatoxin B1 induced hepatocellular carcinoma. (492)

PDE5 inhibitors can reduce the incidence of intestinal cancer by altering epithelial homeostasis via cGMP. In a rodent model, sildenafil-treated mice showed less polyp formation with greater differentiation, less proliferation, and less inflammation. (493)

Booth et al demonstrated that PDE5 inhibitors interacted in a greater than additive fashion with numerous cytotoxic agents to cause cell death. (494) The most potent PDE5 inhibitor was sildenafil. In this study, treatment with PDE5 inhibitors and chemotherapy drugs promoted autophagy with knock out of Beclin1 reducing the drug combination lethality by about 50%. Furthermore, these authors demonstrated that celecoxib (an NSAID) and PDE5 inhibitors interacted in a greater than additive fashion to kill multiple tumor cell types including human glioma cells. (495) The effects of celecoxib were COX2 independent. The drug combination inactivated mTOR and increased the levels of autophagy and activated the JNK pathway. The combined use of platinum-based chemotherapeutic agents and PDE

inhibitors have a higher antiproliferative effect on lung cancer cells than platinum monotherapy. (496) Sildenafil combined with curcumin increases the efficacy of 5-Fluorouracil in controlling colorectal tumors. (497)

Sildenafil could inhibit colonic tumorigenesis via blocking the recruitment of MDSCs. (498) Treatment with sildenafil reduced MDSC numbers infiltrating primary tumors and metastatic lesions and increased CD8+ T cells. (499) PDE5 inhibitors reduce Tregs and cancer stem cells and impair MDSC function. (499, 500) Klutzny et al demonstrated that PDE5 inhibition eliminates cancer stem cells via induction of PKA signaling. (501)

Clinical studies

In a study of 192,661 patients, the use of PDE5 inhibitors was shown to be associated with a decreased risk of developing colon cancer. (502) The use of PDE5 inhibitors is associated with a lower risk of colorectal cancer in men with benign colorectal neoplasms. (156) Two recent clinical trials, conducted among patients with head and neck squamous cell carcinoma, reported that tadalafil can enhance systematic immune responsiveness as well as tumor-specific immunity by reducing MDSCs, regulatory T cells, and improving T-cell function. (503, 504) Huang et al demonstrated that in patients with colorectal cancer, the post-diagnostic use of PDE5 inhibitors was associated with a decreased risk of cancer-specific mortality (adjusted HR = 0.82, 95% CI 0.67-0.99) as well as a decreased risk of metastasis (adjusted HR = 0.85, 95% CI 0.74-0.98). (505) In a retrospective cohort analysis of 3100 patients with prostate cancer treated with radical prostatectomy between 2003 and 2015, patients were divided into those receiving a PDE-5 inhibitor or non-recipients (controls). In this study, multivariate analysis documented that PDE-5 inhibitor administration was associated with a lower risk of biochemical recurrence and death. (506)

Types of cancers that phosphodiesterase 5 inhibitors may be beneficial for

Prostate, breast, hepatocellular, colorectal, lung, head and neck, glioblastoma, and leukemias. (499)

Dosing and cautions

Sildenafil 20 mg daily or tadalafil 5mg daily. PDE5 inhibitors are contraindicated in patients receiving nitrates or with a previous history of non-arteritic anterior ischemic optic neuropathy. Despite its wide therapeutic window, sildenafil may show serious cardiovascular side effects in patients.

12. Cimetidine

Anticancer pathways and mechanisms

Cimetidine, commonly used to treat ulcers and gastroesophageal reflux disease, has been demonstrated to have four different anti-tumor effects, namely: Anti-proliferative, immunomodulatory, anti-cell adhesion, and anti-angiogenic effects on cancer cells. (507)

Anti-proliferative: Histamine, the principal mast cell mediator, and its receptors (HR1-HR4) were increased in several malignancies and associated with cancer survival, metastasis, and recruitment of suppressive cells to the TME. Mast cells and their mediators have previously been linked with tumor progression and metastasis. (508)

L-histidine decarboxylase (HDC), an enzyme that produces histamine, is expressed by a variety of tumor types both in vitro and in vivo. Tumors are also capable of secreting large amounts of histamine in a paracrine and/or autocrine manner. Histamine has a wide range of actions, including inflammatory and immunological effects. Four histamine receptors, of which H2 and H4 are involved in cancer cell proliferation, invasion, and angiogenesis, mediate these physiological effects. By blocking H2 receptors, cimetidine reduces cancer cell proliferation. (507, 509-511) In addition, cimetidine upregulates Caspase 3 level to induce apoptosis of cancer cells and has synergistic activity when combined with vitamin C. (509)

Immunomodulation: Cimetidine has been demonstrated to kill myeloid-derived stem cells (MDSCs), decrease Tregs, and increase natural killer cells (NKs). Histamine has been linked to an immunosuppressive tumor microenvironment in cancer, which includes increased CD4+CD25+ regulatory T cell (Treg) activity, decreased dendritic cell (DC) antigen-presenting activity, decreased NK cell activity, and increased myeloid-derived suppressor cell (MDSC) activity. (507, 512, 513). MDSCs express H_1–H_3 receptors, and there is in vitro and in vivo evidence that blockade of H_1 (using the H_1RA cetirizine) or H_2 (using cimetidine), can reverse the immunosuppressive action of these cells. (507, 513) Cimetidine causes an increase in NK activity compared to non-cimetidine-treated controls in patients undergoing cardiopulmonary bypass surgery. (507, 514)

Additionally, it has been demonstrated that in patients with colorectal and gastric cancer, perioperative cimetidine reverses the histamine-induced suppression of lymphocyte proliferation and increases the number of tumor-infiltrating lymphocytes (TIL). (515, 516) Increased tumor-infiltrating lymphocytes were linked to improved prognosis in these studies and are also thought to be significant in several other cancer types, such as breast, ovarian, brain, and head and neck cancers. (507)

The heterodimeric cytokine interleukin-12, which is mostly produced by monocytes and macrophages, is a crucial inducer of cell-mediated immunity because it promotes the growth, proliferation, and activity of Th1 cells. (507) IL-12 overproduction may have a role in the etiology of autoimmune disease. Histamine binding to the H2 receptor, which is connected to the suppression of IL-12 and enhancement of IL-10 production, is associated with a shift in the Th1/Th2 balance toward Th2-dominance of the immune response. Studies showed that cimetidine prevented this effect in human peripheral blood mononuclear cells. (507, 517-519)

Anti-cell adhesion: It has been demonstrated that cimetidine inhibits cancer cells' ability to adhere to endothelial cells without affecting their H2RA activity. (507)

Anti-angiogenesis: Angiogenesis accelerates the development and progression of tumors. (509) Evidence from mouse and rat bladder cancer models suggested that the anti-angiogenic impact of cimetidine may be connected to a decreased expression of platelet-derived endothelial growth factor (PDECGF) and vascular endothelial growth factor (VEGF) via the H2R/cAMP/PKA pathway. (507, 509, 515, 520, 521) TNF-α plays a variety of roles within the TME and promotes tumor growth through several methods. Cimetidine has anti-angiogenic effects by downregulating TNF-α. (509)

Clinical studies

There is limited data on the clinical benefits of cimetidine in patients with cancer. Most of the studies have been performed in the post-operative period in patients undergoing colorectal surgery. (507) In a Cochrane meta-analysis of five studies (n=421) that prescribed cimetidine as an adjunct to curative surgical resection of colorectal cancers, a statistically significant improvement in overall survival (HR 0.53; 95% CI 0.32 to 0.87) was demonstrated. (522) In two small series of patients with melanoma, the combination of cimetidine and interferon was associated with a clinical response ranging from complete regression to partial regression and prolonged disease stabilization. (523, 524) A report from Denmark assessed overall survival of gastric cancer patients treated with oral cimetidine 400 mg twice daily for 2 years. In this double-blinded study, 181 patients were randomized to cimetidine or placebo immediately after surgery. Median survival in the cimetidine group was 450 days and 316 days in the placebo group (p = 0.02). (525) Relative survival rates (Cimetidine/placebo) were 45%/28% at 1 year.

Types of cancers cimetidine may be beneficial for

While cimetidine appears to be beneficial in patients with colorectal cancer (507, 515, 519, 526-528), melanoma (507, 529), and gastric cancer (507, 510, 515, 516, 527), this drug may have some benefit in patients with pancreatic cancer (507, 530), ovarian carcinoma (507, 531), prostate cancer (507), Kaposi's Sarcoma (507), salivary gland tumors (507, 532), renal cell carcinoma (507, 529, 533, 534), breast cancer (507, 509, 535), glioblastoma (507, 536) and bladder cancer (507, 521).

Dosing and cautions

Most studies used a standard dose of 400 mg twice daily. Cimetidine has few side effects, with the most frequent being gynecomastia.

13. Doxycycline

Anticancer pathways and mechanisms

Doxycycline and minocycline were introduced into medicine as more potent, active, and stable semisynthetic tetracycline antibiotics. In general, the incidence of adverse effects caused by minocycline and doxycycline is very low. In addition, they show many non-

antibiotic properties, including anti-inflammatory, antioxidant, neuroprotective, immunomodulatory, and anticancer effects. (537, 538) Recently published studies and analyses considered the repurposing of minocycline and doxycycline as anti-melanoma agents. (539, 540)

Mechanisms of the anticancer activity of doxycycline and minocycline involve reduction of STAT3 phosphorylation, prevention of NF-KB activation, repression of tumor necrosis factor (TNF) - α expression and inhibition of matrix metalloproteinases. (538, 541) Minocycline and doxycycline have been demonstrated to exert anti-melanoma effects. (539, 540) These drugs inhibited cell proliferation, decreased cell viability, and induced apoptosis. Rok et al demonstrated similar findings in amelanotic melanoma cells. (537) In this study, the treatment caused changes in the cell cycle profile and decreased the intracellular level of reduced thiols and mitochondrial membrane potential. In addition, exposure of melanoma cells to minocycline and doxycycline triggered the release of cytochrome c and activated initiator and effector caspases. In this study, doxycycline was a more potent drug than minocycline in mediating these anticancer effects.

Doxycycline blocks the activity of metalloproteinases, which would otherwise be involved in the breakdown of the extracellular matrix that allows individual cancer cells to break free and seed new metastatic cancer growth around the body. Considering the potent inhibitory effects of tetracyclines against metalloproteinases, their anticancer potential has been studied in a variety of cancers, including melanoma, lung, breast, and prostate cancers. (542) When combined with celecoxib, minocycline inhibited the osseous metastasis of breast cancer in nude (hairless) mice, by increasing tumor cell death and decreasing tumor expression of MMP-9 and VEGF. (543) Minocycline has been shown to inhibit *in vitro* invasion and experimental pulmonary metastasis in mouse renal adenocarcinoma. In addition, these drugs have been demonstrated to inhibit angiogenesis in vitro by a non-metalloproteinase-dependent mechanism. (544)

Weiler et al demonstrated that minocycline inhibited the TNF-α-induced fusion of cancer cells with breast epithelial cells; (541) this may have an important role in limited metastatic cancer spread. Minocycline has been demonstrated to act synergistically with cisplatin in the treatment of hepatocellular carcinoma. (545) Anti-proliferative and anti-metastatic properties of minocycline have also been demonstrated in various other types of cancer, including renal adenocarcinoma, (546) breast cancer, (543) and malignant gliomas. (547)

Clinical studies

Despite the numerous experimental models, there are no published reports that have investigated the clinical benefits of these drugs in patients with cancer.

Types of cancers doxycycline may be beneficial for

Despite the absence of clinical data, doxycycline may have clinical efficacy in the following cancers: melanoma, renal adenocarcinoma, breast cancer, prostate, and malignant gliomas.

Dosing and cautions
The standard dose of doxycycline is 100 to 150 mg daily. The duration of therapy in patients with cancer has not been studied; therefore, a course lasting no longer than 2 weeks is suggested. Serious adverse effects are uncommon, with the most common adverse effects being headache and nausea. Due to the effect of antibiotics on the microbiome a prolonged course of doxycycline should be avoided.

14. Resveratrol

Resveratrol (3,40,5-trihydroxy-trans-stilbene) is a non-flavonoid polyphenol that occurs naturally in many species of plants, including peanuts, grapes, and berries. (548) Pterostilbene is a naturally occurring analog of resveratrol.

A significant amount of research, including preclinical, clinical, and epidemiological studies, has indicated that dietary consumption of polyphenols, found at high levels in vegetables and fruits, may prevent the evolution of an array of diseases, including cancer. (548) Resveratrol and other flavonoids (quercetin, turmeric) have numerous anticancer activities.

Anticancer pathways and mechanisms
Resveratrol has also been reported to possess a significant anticancer property in various preclinical animal models. (548) Resveratrol affects a variety of cancer stages, from initiation and promotion to progression, by affecting the diverse signal-transduction pathways that control cell growth and division, inflammation, apoptosis, metastasis, and angiogenesis. It has been shown that resveratrol has in vitro cytotoxic effects against a large range of human tumor cells, including myeloid and lymphoid cancer cells, and breast, skin, cervix, ovary, stomach, prostate, colon, liver, pancreas, and thyroid carcinoma cells. (548-551)

Studies conducted in vitro have discovered that resveratrol exerts an anti-proliferative activity by inducing apoptosis. Resveratrol modifies the balance of cyclins as well as cyclin-dependent kinases (CDKs), resulting in cell cycle inhibition at G0/G1 phase. (552) Resveratrol causes activation of the p53-dependent pathway. (553) The inhibition of anti-apoptotic proteins of the Bcl-2 family, and activation of pro-apoptotic proteins such as Bad, Bak or Bax, by resveratrol has also been shown to be a mechanism for caspase activation and cytochrome c release. (554) It has also been shown that resveratrol induces apoptosis via inhibiting the PI3K/Akt/mTOR pathway, modulating the mitogen-activated protein kinase pathway (MAPK) and inhibiting NF-KB activation. (548) Resveratrol also causes inhibition of signal transducers and activators of transcription 3 (STAT3), which adds to its pro-apoptotic and anti-proliferative potential. (555) In addition, resveratrol may inhibit cancer stem cells. (556)

Flavonoids, as antioxidants, inhibit regulatory enzymes and transcription factors important for controlling inflammatory mediators. Moreover, they modulate cellular oxidative stress by interacting with DNA and enhancing genomic stability. (269) Resveratrol also augments

the activity and expression of antioxidant and phase-II detoxifying enzymes through the activation of nuclear factor E2–related factor 2 (Nrf2).

Preclinical research has demonstrated the effectiveness of flavonoids against inflammation-associated cancer progression. (269) Due to the association between inflammation and angiogenesis in tumor cells, experimental models demonstrate that flavonoids decrease angiogenesis and tumor metastasis. Resveratrol has been suggested to inhibit metastatic spread by inhibiting the expression of MMP (mainly MMP-9) and angiogenesis markers such as VEGF, EGFR or FGF-2. (548, 557). Luteolin showed a potent capacity to target HIF-1α/VEGF signaling and angiogenesis. (558)

It has been reported that resveratrol can reverse multidrug resistance in cancer cells, and, when used in combination with clinically used drugs, it can sensitize cancer cells to standard chemotherapeutic agents. (548) In addition, it is likely that resveratrol has synergic activity against cancers when combined with GTCs.

Clinical studies
Although it is clear that resveratrol has shown excellent anticancer properties, most of the studies were performed in cell culture and pre-clinical models. Furthermore, resveratrol's poor bioavailability is a significant issue with regard to extrapolating its effects on humans. (548)

Types of cancers that resveratrol may be beneficial for

Resveratrol likely has anticancer effects in patients with breast, prostate, colorectal, hepatocellular, pancreatic, lung, and ovarian cancer. (548)

Dosing and cautions
Various approaches have been created to enhance the bioavailability of resveratrol, including consuming it with various foods, using it in combination with an additional phytochemical — piperine — and using a prodrug approach, micronized powders, or nanotechnological formulations. (548) A resveratrol dose of 500 mg twice daily is suggested. A bio-enhanced formulation containing trans-resveratrol from Japanese Knotweed Root appears to have improved bioavailability.

15. Cyclooxygenase inhibitors – Aspirin (ASA) and NSAIDs (Diclofenac)

There are more than 20 different nonsteroidal anti-inflammatory drugs (NSAIDs), from six major classes determined by their chemical structures; they differ in their dose, drug interactions, and side effects. The primary effect of NSAIDs is to inhibit cyclooxygenase (COX), thereby impairing the transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. COX inhibition is central to the mechanism of action of both aspirin and the non-salicylate NSAIDs.

Two related isoforms of the COX enzyme have been described, namely COX-1 and COX-2. COX-1 is expressed in most tissues but variably and is described as a "housekeeping" enzyme, regulating normal cellular processes. COX-2 is a highly regulated enzyme that is constitutively expressed in the brain, kidney, and bone. Its expression is increased during states of inflammation. The extent of enzyme inhibition varies among the different NSAIDs. The degree to which a particular NSAID inhibits an isoform of cyclooxygenase affects both its activity and toxicity.

NSAIDs have additional modes of action beyond that of COX inhibition, including Inhibition of neutrophil activation, Inhibition of the expression of inducible nitric oxide synthase (iNOS), Inhibition of the activation of nuclear factor (NF)-kappa β, and inhibition of Erk kinase activation. While there has long been an interest in the use of aspirin (ASA) and NSAIDs in chemoprevention, there is now emerging evidence that such drugs may have activity in a treatment setting.

Aspirin

Aspirin, also known as acetylsalicylic acid (ASA), is an NSAID that exhibits a broad range of pharmacologic activities, including analgesic, antipyretic, and antiplatelet properties. Low doses (typically 75 to 81 mg/day) irreversibly acetylate cyclooxygenase (COX)-1. This effect inhibits platelet generation of thromboxane A2, resulting in an antithrombotic effect. Intermediate doses (650 mg to 4 g/day) inhibit COX-1 and COX-2, blocking prostaglandin production, and have anti-inflammatory, analgesic, and antipyretic effects. High doses (between 4 and 8 g/day) are effective as anti-inflammatory agents in rheumatic disorders; however, the usefulness of aspirin at these high doses is limited by toxicity, including tinnitus, hearing loss, and gastric intolerance. ASA 325 mg daily appears to be at least as effective as 75 mg daily in terms of cardiovascular and cerebrovascular protection. Furthermore, there does not appear to be a difference in safety across the low dose range of 75-325 mg. (559)

Leukocytes, endothelial cells, mucosal cells, and vascular smooth muscle cells express COX-2. Selective targeting of COX-2 suppresses the prostaglandins, particularly prostacyclin, at sites of vascular inflammation. In cancer, the possible mechanisms by which aspirin may provide benefit range from a direct inhibitory effect on cancer cells themselves to antiplatelet effects, including reducing platelet–tumor cell interactions or reducing platelet secretion of proangiogenic and growth factors, cytokines, and chemokines. (560) Malignant tumors within the proinflammatory and antiapoptotic tumor microenvironment have been shown to aberrantly express COX-1 and COX-2. (561, 562) Therefore, aspirin may exert an antitumor effect by way of a COX-related inhibition of inflammation and apoptosis. (563) The extent of this effect would likely vary by tumor subtype; for instance, the relative expression of COX-1 and COX-2 in ovarian cancer was shown to vary by the histological grade and subtype of the cancer. (562) In addition, COX-independent mechanisms have

been suggested, including the suppression of signaling by IκB kinase β and extracellular signal regulated kinase, leading to reduced inflammation and proliferation. (564, 565)

Clinical studies

The Cancer Prevention Study II, published in 1991, showed a 40% reduction in colon cancer mortality associated with the regular use of aspirin in a cohort of 662,424 patients. (566) Subsequently, two trials published in the *New England Journal of Medicine* in 2003 demonstrated clear benefits of low-dose aspirin (81 -325 mg/day) in secondary prevention of colorectal cancer. (567, 568) The issue becomes more complex as these trials were followed by negative studies, (569, 570) and in 2007 the U.S. Preventive Services Taskforce (USPSTF) recommended against the routine use of aspirin for any cancer prevention. (571)

Shortly after the USPSTF recommendation, large meta-analyses of prospective trials of aspirin for cardiovascular disease were published, which found a clear benefit of aspirin in reducing both cancer incidence and mortality. (118, 572) In 2016, the USPSTP reversed its position, stating that adults between the ages of 50 and 69 years would in fact derive cancer benefits from the preventive use of low-dose aspirin, defined as ≤325 mg per day. (573) However, the benefit in patients without a history of cancer was small and outweighed by the risk of major bleeding. (574)

This was followed by the ARRIVE trial, which was published in 2018. The ARRIVE trial enrolled nearly 13,000 patients with a mean age of 64 years. Patients in ARRIVE were randomly assigned to 100 mg of enteric-coated aspirin or placebo and followed up for an average of 5 years. Differences in cancer incidence were not significant but favored placebo. (575) Published one month later, the ASPREE trial was larger than ARRIVE and enrolled an older population, presumably at higher risk for cancer; 19,114 patients were randomly assigned to 100 mg of enteric-coated aspirin vs placebo. (576, 577) Surprisingly, aspirin was associated with an increase in all-cause mortality (HR, 1.14; 95% CI, 1.01-1.29), which was driven largely by an increase in deaths resulting from cancer (HR, 1.31; 95% CI, 1.10-1.56).

In the most recent USPSTF guideline, the use of aspirin was not associated with reductions in cardiovascular disease mortality or all-cause mortality. (578) While the studies for colorectal cancer were highly heterogenous, for events occurring within the RCT periods only, low-dose aspirin had no statistically significant association with colorectal cancer incidence at 5 to 10 years of follow-up. In summary, the role of aspirin for the prevention of colorectal cancer is uncertain.

Clinical evidence supporting the role of aspirin in cancer prevention is greatest in those at high risk of colorectal cancer, as was demonstrated in the CAPP2 trial for patients with Lynch syndrome. (579) However, there is suggestive evidence in several other cancer types as well. Hepatocellular carcinoma rates were lower among patients with chronic viral hepatitis with low-dose aspirin use. (580) The use of aspirin may be associated with a lower risk of pancreatic cancer. (581, 582) Until additional studies are available, the use of aspirin for cancer prevention is limited to specific high-risk patients.

The role of ASA in the treatment of cancer is equally as contradictory as for the prevention of cancer. Observational studies tend to demonstrate a survival advantage with the use of ASA; however, this benefit has not been replicated in prospective studies. In an observational study that included 70 studies with 18 different cancers, Elwood reported aspirin to be associated with a 20% reduction in cancer deaths (HR of 0.79; 95% confidence intervals: 0.73- 0.84). (583) Wang et al evaluated 13 published cohort studies with 65,768 patients in order to estimate the overall risk of cancer-specific mortality associated with post-diagnosis low-dose aspirin use. (584) The authors reported a significant decreased cancer-specific mortality with an odds ratio (OR) of 0.84 (95% CI 0.75-0.93). However, these findings have not been replicated in prospective clinical trials. (585, 586) The ABC trial was a randomized, phase III, double-blind placebo-controlled trial of aspirin as adjuvant therapy for high-risk, HER2-2 negative breast cancer. In this study, 3,021 patients were randomized to 300 mg aspirin or placebo daily for 5 years. (586) The HR for invasive disease-free survival comparing aspirin to placebo was 1.27, which exceeded the prespecified HR of futility.

NSAIDS (Diclofenac)

Diclofenac (DCF) is a well-known and widely used non-steroidal anti-inflammatory drug (NSAID), with a range of actions of interest in an oncological context. (587) There is considerable variation in COX-1/COX-2 selectivity between different NSAIDs, and some evidence that DCF binds to COX-2 via a different mechanism than other commonly used drugs. (588) DCF was developed by Ciba-Geigy and is now available globally as a generic medication. Common trade names include Voltaren, Voltarol, Cataflam, Cambia, Zipsor, and Zorvolex. In some countries, low-dose formulations of oral DCF (typically 25 mg tablets) are available over the counter. In the U.S., DCF requires a prescription and is available as 25, 50, 75, and 100 mg delayed-release tablets.

DCF, which is a potent inhibitor of COX-2 and prostaglandin E2 synthesis, displays a range of effects on the immune system, the angiogenic cascade, chemo- and radio-sensitivity, and tumor metabolism. PGE2 are found in a range of different cancer types and are associated with the chronic inflammation that is found in a pro-tumor microenvironment. (589)

Anticancer pathways and mechanisms

There are multiple mechanisms of action postulated to explain the diverse anticancer effects of DCF. These include anti-angiogenic, immunomodulation, pro-apoptotic, effect on platelet function, effects on Myc and glucose metabolism, and increasing treatment sensitivity. In addition, NSAIDs are associated with phosphodiesterase (PDE) 5 inhibition and activation of cGMP signaling which are closely associated with its ability to induce apoptosis of tumor cells. (490)

Experimental models demonstrate DCF decrease in tumor angiogenesis, which was associated with a reduction of PGE2 synthesis. (590) One mechanistic explanation is that PGE2 upregulates the production of VEGF. (591) In experimental models, DCF decreased the expression of both VGEF and monocyte chemoattractant protein (MCP-1). (592) PGE2 has

been shown to induce the differentiation of bone marrow stem cells into MDSCs in a number of animal models of cancer. Decreases in PGE2 break the positive feedback loop of PGE2-MDSC expansion. (593) It has been shown in autochthonous tumor models that blockade of PGE2 synthesis results in the downregulation of ARG1 expression and ROS production by MDSCs, followed by improved antitumor T-cell function and cancer chemoprevention. (594, 595)

Fujita and colleagues showed that in a mouse model of glioma, COX-2 blockade inhibited PGE2 production and delayed tumor progression. (596) This was associated with reduced accumulation of MDSCs and an increased presence of cytotoxic T lymphocytes. Reduction of tumor-induced PGE2 using both selective and non-selective COX inhibitors has been shown to reduce T-reg populations and activity. (597) DCF was able to reduce the intra-tumoral accumulation and activation of T-regs in a murine glioblastoma model. (598) In addition to modulation of angiogenesis and immune suppression, there is some evidence for a pro-apoptotic mechanism of action for DCF in cancer. (587, 599) There is also some evidence that DCF has an impact on tumor metabolism that is independent of its action as a COX-inhibitor. Gottfried and colleagues showed that DCF downregulated Myc gene expression and glucose metabolism in a number of leukemia, prostate cancer, and melanoma cell lines in vitro and in an in vivo melanoma model. (600)

Dysregulation of Wnt β-catenin/Tcf signaling pathway contributes to tumor progression. Sareddy et al demonstrated that diclofenac and celecoxib are potential therapeutic agents against glioblastoma cells by suppressing the activation of Wntβ-catenin/Tcf signaling. (601) It is likely that DCF act synergetically with convention chemotherapeutic agents as well as with other adjunctive therapies. Indeed, Gerhofer demonstrated synergistic anti-migratory and anti-proliferative effects of the combined treatment with metformin and diclofenac on brain tumor initiating cells. (602)

Clinical studies

In contrast to the wide range of in vitro and in vivo results, there is a relative paucity of clinical data with respect to the use of DCF as an anticancer agent. Forget and colleagues reported on a retrospective analysis of breast cancer patients treated with conservative surgery, with and without intraoperative NSAIDs (DCF or ketorolac). (603) Patients treated pre-incisionally with ketorolac (20 mg -30 mg) or DCF (75 mg) showed improved disease-free survival (HR = 0.57, 95% CI: 0.37–0.89, *P* = 0.01) and an improved overall survival (HR = 0.35, CI: 0.17–0.70, *P* = 0.03), compared to patients not treated with NSAIDs. (604) The findings of this study were, however, not replicated in a prospective RCT. (605)

Types of cancers diclofenac may be beneficial for

While there is limited data, diclofenac may be effective against the following tumors; (587) desmoid tumors, inflammatory myofibroblastic tumors, neuroblastoma, osteosarcoma, head and neck cancers, esophageal cancer, breast cancer, ovarian cancer and non-small cell lung cancer.

Dosing and cautions

A dose of 75 to 100 mg/day diclofenac is suggested. As a potent COX2 inhibitor, DCF can increase the risk of peptic ulcer disease. For this reason, we suggest that DCF be combined with cimetidine, which is used to treat/prevent peptic ulcers; this drug combination likely has synergistic anticancer properties. NSAIDs cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. Diclofenac is contraindicated in the setting of coronary artery bypass graft surgery. DCF should be used cautiously in patients with known coronary artery disease; however, interventions that manage metabolic syndrome (and optimize the TG/DHL ratio) may mitigate against this risk.

16. Nigella sativa

Anticancer pathways and mechanisms

The primary bioactive substance in Nigella sativa, thymoquinone (TQ), has anti-inflammatory and chemotherapeutic properties and can limit cell proliferation, increase cancer cell death, prevent cell invasion and metastasis, and inhibit angiogenesis. TQ disrupts the phosphorylation and subsequent activation of a few upstream tyrosine kinases (such as MAPK, Akt, mTOR, and PIP3) implicated in signaling pathways for tumor cell growth. (606-608)

TQ's anticancer effects predominantly involve the nuclear factor (NF)-κB, phosphoinositide 3 kinases (PI3K)/Akt, Notch, transforming growth factor (TGF)-β, c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK) signaling pathways as well as the regulation of the cell cycle, matrix metallopeptidase (MMP)-9 expression, and pyruvate kinase isozyme type M2 (PKM2) activity. (606, 607, 609-613) Additionally, TQ exhibits chemopreventive properties by upregulating cytoprotective enzymes (such as glutathione S-transferase, superoxide dismutase, and oxidoreductase), downregulating carcinogen metabolizing enzymes (such as CYP 1A2, CYP 3A4), and attenuating the production of pro-inflammatory mediators (e.g., cytokines, chemokines, and prostaglandins). (607, 609, 614)

Clinical studies

Unfortunately, there are no published clinical studies that have investigated the effects of Nigella sativa in patients with cancer.

Types of cancers that Nigella sativa may be beneficial for

In vitro and in vivo experimental findings suggest that Nigella sativa may have anticancer action against a variety of malignancies, including ovarian, (607, 615, 616) myeloblastic leukemia and other blood cancers, (617) cervical, (608, 618, 619) colon, (608, 614, 620-622) hepatic, (614, 623-626) prostate, (606, 627) breast, (606, 620, 622) renal, (608, 628) pancreatic, (606, 613, 629) and lung carcinomas. (606, 620, 630, 631)

Dosing and cautions
Patients can be directed to take seeds (80 mg/kg once daily) or encapsulated oil (400 to 500 mg twice daily). The safety of Nigella sativa in pregnancy has not been established and it should probably be avoided.

17. Ganoderma lucidum (Reishi) and other medicinal mushrooms

More than 50 different types of mushrooms — such as Ganoderma lucidum (Reishi), G. tsugae, Sparassis crispa, Pleurotus tuberregium, P. rhinoceros, Trametes robiniophila Murill, Coriolus versicolor, Lentinus edodes, Grifola frondosa, Flammulina velutipes and others — have produced potential immunoceuticals with anticancer and immunomodulatory effects in vitro, in vivo, and in human malignancies. (632)

The most research has been done on G. lucidum (Reishi). Beta-glucan polysaccharides and triterpenes are the bioactive compounds in Reishi mushroom. (633)

Anticancer pathways and mechanisms
Antroquinonol, cordycepin, hispolon, lectin, krestin, polysaccharide, sulfated polysaccharide, lentinan, and Maitake D Fraction are the main anticancer compounds found in mushrooms. (632) The therapeutic effects of these compounds include suppression of cancer cell growth, induction of autophagy and phagocytosis, improved immune system response, and induction of apoptotic cell death through upregulation of pro-apoptotic factors and downregulation of anti-apoptotic genes. (634) The expression of caspase-3, -8, and -9, AKT, p27, p53, BAX, BCL2, NF-kB pathway, and mTOR (635) were significantly implicated in these activities. (634, 636)

Bioactive substances derived from mushrooms stimulate and/or regulate the immune system by influencing the maturation, differentiation, and proliferation of immune cells, hence preventing the spread and growth of cancer cells. (633) The strongest anticancer and immunomodulatory chemicals found in mushrooms are polysaccharides. (633) By attaching to pathogen recognition receptors, chemicals produced from mushrooms stimulate immune cells to cause either cell-mediated or direct cytotoxicity in cancer cells. (633, 637, 638) In addition, mushroom-derived compounds induce innate and adaptive immunity by enhancing immune surveillance against cancer by affecting monocytes, macrophages, NK cells, and B cells (633, 636-641) which leads to cancer cell apoptosis, cell cycle arrest, and prevention of angiogenesis and metastasis. (632) Consumption of mushroom compounds also boosts the secretion of antitumor cytokines by Directed Cytotoxic T Lymphocytes (CTLs) and activation of immune organs, thereby eliminating cancer cells and strengthening the weakened immune system. (633, 639)

By controlling a single molecule of a particular signaling pathway or by having many targets in the same or different signaling route(s), such as the PI3K/Akt, Wnt/-catenin, and MAPK pathways, mushroom compounds exhibit anticancer potential. Studies have demonstrated the effectiveness of components derived from mushrooms as standalone and adjunctive

treatment agents in reversing multidrug resistance (MDR) by focusing on interactions between PD-1/PD-L1 and CTLA-4/CD80. (633) Furthermore, the prebiotic benefits of medicinal mushrooms may help restore the gut microbiome. (633)

A new, inflammatory type of programmed cell death called pyroptosis is defined by the executive protein gasdermin creating pores in the plasma membrane, which causes the cells to lyse and expel their contents. (639, 642) By activating caspase 3 and further cleaving the gasdermin E (GSDME) protein to create pores on the cell membrane, Ganoderma lucidum extract (GLE) causes pyroptosis, which releases many inflammatory factors into breast cancer cells. (639) GLE blocks multi-steps of tumor metastasis including adhesion, migration, invasion, colonization, and angiogenesis. (639)

Clinical studies

In a trial of patients with colorectal adenomas, a water-soluble Reishi extract (1.5 g/d, administered for 12 months) significantly reduced the number and overall size of adenomas in the intervention group as compared to the control group. (643) G. lucidum (Reishi) at a dose of 5.4 g/day was demonstrated to have immuno-modulating properties in patients with advanced colorectal cancer. (644) Patients with advanced-stage cancer who consumed a Reishi polysaccharide preparation showed increased natural killer cell activity. (645) In a review of the literature, Huber et al reported that medicinal mushrooms improve the quality of life during and after conventional cancer therapy. (646)

Types of cancers that Reishi and other medicinal mushrooms may be beneficial for

Noteworthy that mushroom extracts have the strongest anticancer effects against breast cancer. (632, 633, 647) Mushrooms may also have activity against colorectal carcinoma, (632, 633, 635, 646, 647) cervical, ovarian and endometrial cancers, (632, 646, 647) lung cancer, (632, 646) astrocytoma, (647) bladder cancer, (632, 647) esophageal cancer, (647) fibrosarcoma, (647) gastric cancer, (632, 647) glioblastoma, (647) hepatocellular carcinoma, (632, 633, 647) kidney cancer, (647) laryngeal cancer, (647) leukemia, (632, 647) melanoma, (633, 647) neuroblastoma, (647) oral cancer, (647) pancreatic cancer, (647) prostate cancer, (632, 647) sarcoma, (647) and skin epidermoid cancer. (647)

Dosing and cautions

It is suggested that 6 to 12 g of Reishi extract be taken daily. (648) Reishi has antiplatelet properties; hence it may increase the risk of bleeding, especially when taken in conjunction with anticoagulants.

18. Ivermectin

Ivermectin is a macrolide antiparasitic drug that is widely used for the treatment of many parasitic diseases, such as river blindness, elephantiasis, and scabies. Satoshi Omura and William C. Campbell won the 2015 Nobel Prize in Physiology or Medicine for the discovery of the excellent efficacy of ivermectin against parasitic diseases. Ivermectin was approved by the FDA for use in humans in 1978. Recently, scientists have discovered that ivermectin

has strong anticancer effects. Ivermectin has been reported to inhibit the proliferation of several tumor cells by regulating multiple signaling pathways. (649, 650)

Anticancer pathways and mechanisms

Experimental data demonstrated that ivermectin inhibited the proliferation of multiple breast cancer cell lines. (651) The mechanism involved the inhibition by ivermectin of the Akt/mTOR pathway to induce autophagy Ivermectin has been demonstrated to inhibit the proliferation of canine breast tumor cell lines by blocking the cell cycle related to the inhibition of the Wnt pathway. (652) In a study that screened Wnt pathway inhibitors, ivermectin inhibited the proliferation of multiple cancers, including the colorectal cancer cell, and promoted apoptosis by blocking the Wnt pathway. (653) Other cancers that show an active WNT pathway and are inhibited by ivermectin include carcinomas of the lung, stomach, cervix, endometrium, and lung, as well as melanomas and gliomas. (653)

Triple-negative breast cancer (TNBC) refers to cancer that is negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) and is the most aggressive subtype of breast cancer with the worst prognosis. (654) In addition, there is also no clinically applicable therapeutic drug currently available. A drug screening study of TNBC showed that ivermectin resulted in impairment of clonogenic self-renewal in vitro and inhibition of tumor growth and metastasis in vivo by blocking the SIN3-interaction domain. (655)

Ivermectin exerts an antitumor effect through the autophagy pathway. Using the autophagy inhibitors chloroquine and wortmannin or knocking down Bclin1 and Atg5 by siRNA to inhibit autophagy, the anticancer activity of ivermectin reduced significantly. (651)

Ivermectin induces cancer cell apoptosis mainly through the mitochondrial pathway. (649) Chen et al demonstrated that ivermectin inhibited the viability and induced apoptosis of esophageal squamous cancer cells through a mitochondrial-dependent pathway. (656) Heat shock protein-27 (HSP27) is highly expressed in and supports oncogene expression of many cancers. Ivermectin inhibits MAPKAP2-mediated HSP27 phosphorylation and depolymerization, thereby blocking HSP27-regulated survival signaling and client-oncoprotein interactions. (657) Chen et al demonstrated that ivermectin inhibited the viability and induced apoptosis of esophageal squamous carcoma cells through a mitochondrial-dependent manner. In addition, Sharmeen et al demonstrated that ivermectin induced chloride-dependent membrane hyperpolarization and cell death in leukemia cells. (658)

Ivermectin has anticancer activity by influencing the tumor microenvironment. Ivermectin decreases MDSC and Tregs and targets cancer stem cells. (130, 659) Furthermore, ivermectin acts to suppress the action of TAMs, which otherwise produce aberrant cytokine signals that act to suppress tumor apoptosis via a number of pathways, particularly TGF-β, and also upregulates the expression of the p53 tumor suppressor gene.

Clinical studies
While many in vitro studies have demonstrated the effectiveness of ivermectin against multiple cancers, the clinical effectiveness is limited to small case series. (660, 661)

Types of cancers ivermectin may be beneficial for
Ivermectin has shown in vitro activity against breast cancer (including TNBC), as well as lung, stomach, cervix, esophageal, endometrium, liver, prostate, kidney and ovarian cancer as well as cholangiocarcinoma, melanomas, leukemia, lymphoma and gliomas. (649)

Dosing and cautions
The optimal dosing strategy with ivermectin is unclear. De Castro et al reported the use of 1mg/kg/day for up to 6 months in three pediatric patients with refractory AML without untoward side effects. (660) Ishiguro et al reported the use of ivermectin 12 mg twice weekly. (661)

19. Dipyridamole

Anticancer pathways and mechanisms
Dipyridamole is a vasodilator and antithrombotic drug. Its major effects involve the blocking of nucleoside uptake and phosphodiesterase inhibition, leading to increased levels of intracellular cAMP. Dipyridamole is a non-selective phosphodiesterase 5 inhibitor. (499) Several studies have shown that, in vitro, dipyridamole can significantly increase the cytotoxic and antitumor activities of a variety of chemotherapeutic agents. (662) Furthermore, there is evidence for a contribution of platelets in metastasis formation with platelets interacting with tumor cells to form aggregates. The interaction of cancer cells with platelets leads to platelet activation and the pro-metastatic activities of platelets. (663) Consequently, agents that interfere with platelet aggregation could prevent tumor metastases. (664)

In a murine triple negative breast cancer model dipyridamole significantly reduced primary tumor growth and metastasis formation. (662) In this study dipyridamole effects were mediated by Wnt, ERK1/2-MAPK and NF-kB pathways. Moreover, dipyridamole significantly decreased the infiltration of tumor-associated macrophages (TAM) and myeloid-derived suppressor cells (MDSC) in the primary tumors. Molecular chaperone HSP90 has been considered as a promising target for anticancer drug development. Dipyridamole inhibits the growth and proliferation of human cancer cells by downregulating cell cycle regulators and upregulating apoptotic cell signaling, which are mediated by the binding of dipyridamole to HSP90 and phosphodiesterase. (665)

Clinical studies
Dipyridamole has been used in combination with cytotoxic drugs in a number of small clinical trials. (666-669) The benefit or lack thereof of dipyridamole in these studies is difficult to ascertain.

20. High dose intravenous vitamin C

The use of high dose vitamin C for the treatment of cancer dates back to the 1970s, largely due to the work of Nobel laureate Linus Pauling. (670) In the early 1970s, Cameron and Pauling published a thesis claiming that ascorbic acid is able to potentiate the intrinsic production of serum physiological hyaluronidase inhibitor, thereby protecting against the spreading of cancer cells. (671) In 1976, these authors published the results of an observational case-control study in which 100 terminal cancer patients were given supplemental ascorbate (10 g IV for 10 days then 10 g orally) as a part of their routine management and were compared to 1,000 matched controls. (672) The study showed that the mean survival time was more than four times longer for the ascorbate treated subjects. In response to the data obtained by Cameron and Pauling, Creagan et al conducted in 1979 a randomized, controlled double-blind trial to evaluate the effect of vitamin C (10 g daily by oral route) on the severity of symptoms and survival rate in 123 patients with advanced and preterminal cancer. (673) The study proved a lack of vitamin C effect, with no difference in survival time between ascorbate and control groups. Similarly, Moertel et al. in a double-blind placebo-controlled study with 100 advanced colorectal cancer patients failed to demonstrate a benefit of vitamin C (10 g orally). (674)

The studies by Creagen et al and Moertel et al essentially ended the use of vitamin C for cancer at that time. It should, however, be appreciated that these studies used oral vitamin C and therefore did not replicate the work of Cameron and Pauling. It has subsequently been established that vitamin C is absorbed by the gut through vitamin C transporters that are saturated at a dose of about 500 mg.

In 2004 Padayatty et al demonstrated that 1.25 g vitamin C given orally produced a peak concentration of 180 umol/l where the same dose given IV resulted in a peak plasma concentration of about 1,000 umol/l. (675) In this study, 50 g of vitamin C given intravenously produced a peak serum concentration of 12 mmol/l. It has subsequently been demonstrated that millimolar concentrations of vitamin C are toxic to cancer cells and that such concentrations can only be achieved through intravenous administration. (676-679)

Paradoxically, vitamin C has potent antioxidant effects when given orally, however, the millimolar concentration achieved with intravenous vitamin C has pro-oxidant effects, which are largely responsible for the cytotoxic effects on cancer cells. (232) While liposomal vitamin C is widely touted to produce serum levels similar to intravenous use, this contention is false, with liposomal formulations producing serum levels almost identical to that of regular vitamin C given orally. (680-683)

Anticancer pathways and mechanisms

Benade et al were the first to propose that the main cytotoxic mechanism of ascorbate was connected with intracellular generation of hydrogen peroxide (H_2O_2) produced upon oxidation of vitamin C. (684) This occurs because cancer cells selectively take up more ascorbate compared to normal cells through the facilitated transport with participation of

glucose transporters (GLUTs) due to an increased metabolic need for glucose. Catalase decomposes H_2O_2 to oxygen and water. Catalase activity in cancer cells is 10- to 100-fold lower than in normal cells, making them over-sensitive to ascorbate. (684)

Yun et al reported that cultured human colorectal cancer cells with KRAS or BRAF mutations were selectively killed when exposed to high concentrations of vitamin C, and that effect resulted from an increased dehydroascorbate (DHA) uptake via the GLUT1 glucose transporter. (685) Inside the cell, DHA is reduced by GSH, NADH, and NADPH-dependent enzymes leading to the depletion of glutathione, thioredoxin, and NADPH, thus increasing the intracellular oxidative stress. ROS accumulation inside cells inactivates glyceraldehyde 3-phosphate dehydrogenase (GAPDH), which leads to a decreased formation of glycolytic adenosine 5'-triphosphate (ATP) and pyruvate, causing an energetic crisis that triggers cell death. (685) In experimental rodents after parenteral administration of vitamin C, not only the increased production of H2O2 was observed, but also the altered expression of genes involved in protein synthesis, cell cycle progression and angiogenesis, and reduced levels of HIF-1 and VEGF. (670)

Clinical studies

While case reports of complete cancer remission or reduction in metastatic lesions have been reported, (686-688) case series which have administered high-dose IVC as a single anticancer treatment have not demonstrated beneficial results. (670, 689, 690)

In vitro and animal studies have demonstrated that concomitant administration of vitamin C with many chemotherapeutic agents and radiotherapy works synergistically, resulting in a decreased tumor size and increased survival. (691) These findings have not been reproduced in the small clinical trials conducted to date. (670, 692, 693) In a phase III RCT, high-dose vitamin C plus chemotherapy failed to show superior progression-free survival compared with chemotherapy in patients with metastatic colorectal cancer as first-line treatment. (694) In summary, high-dose intravenous vitamin C represents a promising and inexpensive anticancer therapeutic option that currently has limited supportive clinical data but should be further explored in clinical trials.

Dosing and cautions

High-dose IV vitamin C is considered to have a relatively good safety profile providing that appropriate precautions are taken, although it also can cause serious side effects in some patients. (670) Vitamin C in gram doses is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, due to a risk of developing intravascular hemolysis.

21. Dichloroacetate (DCA)

The Warburg effect is mediated in part by cancer cells inactivating a key enzyme complex called the pyruvate dehydrogenase complex (PDC), which acts as the control point for the entry of pyruvate into the mitochondria. Pyruvate is derived from glucose (glycolysis) and is

the main fuel for mitochondrial oxidative phosphorylation. The mitochondrial PDC irreversibly decarboxylates pyruvate to acetyl coenzyme A, thereby linking glycolysis to the tricarboxylic acid cycle and a defining step in cellular bioenergetics. (695) Cancer cells turn off PDC by upregulating pyruvate dehydrogenase kinase (PDK). Inhibition of PDC in the cancer cell is the key step in metabolic reprogramming.

The glycolysis inhibitor dichloroacetate (DCA) inhibits PDK. The inhibition of PDK by DCA results in diminished glycolysis in the cancer cell, forcing the cancer cell to use oxidative phosphorylation in the mitochondria as the main source of ATP. (695, 696) DCA has other anticancer effects, including the induction of protective autophagy, reduction of hypoxia-inducible factor (HIF-1) and angiogenesis, and eradication of cancer stem cells. (695) Metformin, curcumin, fenbendazole, ivermectin, and doxycycline act synergistically to increase the efficacy of DCA. (661, 697) Both thiamine and alpha lipoic acid are cofactors for PDC and are routinely recommended with DCA.

Clinical studies
A phase II study of dichloroacetate in combination with chemoradiotherapy for unresected, locally advanced head and neck squamous cell carcinoma reported an end-of-treatment complete response rate that was significantly higher in the DCA group compared to placebo (71.4% vs 37.5%, p=0.03); however, survival outcomes were not significantly different between groups. (698) Case reports have demonstrated “long-term stabilization” of patients with metastatic melanoma, colon cancer, and non-Hodgkin’s lymphoma treated with DCA. (699-701)

Types of cancers dichloroacetate may be beneficial for
Non-Hodgkin’s lymphoma, colorectal cancer, endometrial cancer, breast cancer, glioblastoma, lung cancer, pancreatic cancer, gastric cancer, hepatocellular cancer, and multiple myeloma.

Dosing and cautions
An oral dose of 1,000 mg daily or 500 mg three times daily has been recommended. Neurotoxicity is a well-known reversible adverse effect of DCA, with peripheral neuropathy the most common symptom. Severe encephalopathy has also been described, (702) suggesting that patients being treated with DCA be closely monitored.

DCA is available as a dietary supplement, though its use as a compounded medication has been discontinued by the FDA based upon a review in which it determined that there was insufficient evidence for its use in cancer. The Agency expressed the view that the evidence of benefit and concerns about potential toxicity if not properly dosed, did not outweigh the evidence favoring the use of approved chemotherapies or other agents for cancer.

CHAPTER 6: POTENTIAL ADJUNCTIVE THERAPIES

TUMOR TREATING FIELDS

Tumor treating fields (TTF) are a non-invasive antimitotic therapy that delivers alternating electric fields via the Optune® system. (703) TTF are 100 – 400 kHz alternating current (AC) electric fields transmitted transdermally to tumors using two orthogonal sets of transducer arrays. Transducer arrays are activated sequentially each second, effecting a direction change of the incident field on the target. (704) TTF mechanism of action involves polarizable intra-cellular structures and mitotic disruption. TTF induces mitotic spindle assembly checkpoint arrest leading to a cell-cycle arrest, followed by mitotic slippage, and subsequent cell death or senescence. In addition, TTF promotes autophagy by inducing AMPK, miR29b and other drivers of autophagy. TTF has immunological effects including activation of the STING pathway, increased expression of MHC ll, CD80, and CD40 on dendritic cells and M1 macrophage polarization. (704) TTF has been shown to suppress the migration and invasion of LN-18 glioma cells in experimental models. TTF do not have a systemic half-life like oral or intravenous therapies and exert their therapeutic effect while the electric fields are being applied only on actively dividing cancer cells but not on healthy cells. Thus, compliance with treatment is critical to maximize effectiveness. (703)

TTF has been studied most extensively in patients with glioblastoma multiforme (GBM) .TTF is currently undergoing evaluation as adjunctive treatment in patients with NSCLC, pancreatic and ovarian cancer. (704) In patients with GBM, TTF is delivered to the region of the tumor via transducer arrays placed on the patient's scalp. The Phase III EF-14 RCT (n=695) in newly diagnosed GBM patients demonstrated significantly improved progression-free survival (HR, 0.63; 95%CI, 0.52-0.76; $P < .001$) and overall survival (HR, 0.63; 95%CI, 0.53-0.76; $P < .001$) when TTF were used together with maintenance temozolomide (TMZ) compared with TMZ alone. (705, 706) The National Comprehensive Cancer Network (NCCN) recommends TTF in combination with TMZ for the treatment of patients with both newly diagnosed and recurrent glioblastoma. (707) Based on this information patients with GBM should consider TTF, when feasible, as an adjunctive treatment option. (708)

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is a treatment approach that causes tissue destruction by visible light in the presence of a photosensitizer and oxygen. (709) When sensitizer molecules are exposed to light energy, electrons at low-energy singlet states jump to high energy singlet states, and some spontaneously convert to excited triplet states. The excited triplet state interacts with oxygen producing reactive oxygen species. Reactive oxygen species cause cell death locally through a complex interplay of apoptosis, necrosis, and autophagy-associated cell death. (710)

Light has been known to provide a therapeutic potential for several thousands of years. Over 3,000 years ago, since the ancient Indian and Chinese civilizations, it has been used for the treatment of various diseases mainly in combination with reactive chemicals, for example, to treat conditions like vitiligo, psoriasis, and skin cancer. Sunshine has enormous therapeutic effects both due to ultraviolet-B (UVB) and the synthesis of vitamin D in the skin and near infrared (NIR) radiation (about 40% of solar radiation), which has enormous health benefits including mitochondrial melatonin synthesis. (711, 712) Due to our modern lifestyle, modern man has a profound deficiency of NIR exposure. (712)

Of all the wavelengths of sunlight, NIR-A radiation has the deepest penetration into tissues, up to 23 cm. During the 1918 influenza pandemic, “open-air treatment of influenzae” (sunshine) appears to have been the most effective treatment for seriously ill patients. (713) A more recent prospective study demonstrated that avoiding sun exposure is a risk factor for all-cause mortality. (714) In this study, the mortality rate amongst avoiders of sun exposure was approximately twofold higher compared with the highest sun exposure group.

Dermatologists commonly use PDT with a topical photosensitizing agent for the treatment of actinic keratoses and early nonmelanoma skin cancers, but the potential applications for PDT are far broader, including solid tumors. (709) When PDT is utilized to treat malignant and premalignant tumors, a patient is administered a sensitizer agent that preferentially accumulates in neoplastic lesions and is activated by light to produce cell death. (710)

PDT for cutaneous indications commonly utilizes a topical photosensitizer, such as 5-aminolevulinic acid or methyl aminolevulinate, which are precursors of protoporphyrin IX. (709) Treatment of visceral tumors requires an intravenous or oral photosensitizer, and the most commonly used photosensitizing agent for this indication is porfimer sodium. Porfimer sodium absorbs light at 630 nm (red light). PDT has been performed with various light sources including lasers, incandescent light, laser-emitting diodes, transcutaneous fiberoptic devices, and daylight. (715)

While the efficacy of PDT in killing cancer cells has been demonstrated in experimental models, (716) clinical studies demonstrating the benefit of this modality in patients with non-cutaneous malignancies is limited. (715, 717-719) The role of PDT and photobiomodulation in patients with non-cutaneous cancer requires further evaluation. However, to improve mitochondrial function we suggest that all patients expose themselves to about 30 minutes of midday sunshine whenever possible (at least 3 times a week); this is best achieved with a brisk midday walk.

HYPERBARIC OXYGEN THERAPY

Hypoxia is a critical hallmark of solid tumors and involves enhanced cell survival, angiogenesis, glycolytic metabolism, and metastasis. Hyperbaric oxygen treatment (HBOT) has for centuries been used to improve or cure disorders involving hypoxia and ischemia, by enhancing the

amount of dissolved oxygen in the plasma and thereby increasing O2 delivery to the tissue. (720)

HBOT leads to hyperoxia and elevated levels of reactive oxygen species (ROS), which overwhelm the cancer cells' antioxidant defense and lead to cell death. (721, 722) The molecular mechanisms behind hyperoxia-induced cell death involve a complex signaling system including protein kinases and receptors such as RAGE, CXCR2, TLR3, and TLR4. (723) Furthermore, contrary to what would be expected, HBOT has been shown to induce an antiangiogenic effect in tumor models. (721, 724)

While HBOT appears to have limited effects on cancer growth, it may potentiate the effects of other treatment modalities. Hoff et al demonstrated that a ketogenic diet combined with HBO had significant anticancer effects in a natural model of systemic metastatic cancer. (725) Hypoxia has been described as an important factor for chemotherapeutic resistance. (720) Studies on HBOT as a chemotherapeutic adjuvant have shown augmented effects both in vitro and in vivo. (720) However, it is important to emphasize Mayer et al. list five chemotherapeutic agents (doxorubicin, bleomycin, disulfiram, cisplatin, and mafenide acetate) which are strongly contradictory in combination with HBOT due to potential potentiation of toxicity. Radiotherapy in combination with HBOT has been used clinically in two different applications: (a) as a therapeutic agent for treating late radiation injury and (b) as a radiosensitizer, aiming to increase the effect of radiotherapy. (720) An updated Cochrane systematic review concluded that "there is some evidence that HBOT improves local tumor control and mortality in tumors of the head and neck; however, the outcomes seem to be related to the use of unusual fractionation schemes, and thereby conclude that the benefits of HBOT should be interpreted with caution." (726) While HBOT may have promise as an anticancer intervention, especially when combined with other treatment modalities, the clinical data to support this intervention is limited at this time.

APPENDIX 1. Hierarchy of evidence for the stratification of repurposed drugs/nutraceuticals

1. Meta analysis of observational and/or randomized controlled trials (RCTs).
2. Prospective RCTs and/or observational studies.
3. Epidemiological data demonstrating that the agent reduces the risk of cancer and/or improves survival in those with cancer.
4. Case series (≥ 3 cases).
5. Individual case reports (at least 2).
6. *In Vivo* model demonstrating favorable effect on tumor microenvironment.
7. *In Vivo*/*In Vitro* model demonstrating synergistic/additive cancer cell killing in presence of cancer chemotherapeutic agent(s).
8. *In Vivo* model demonstrating killing of tumor cells and/or cancer stem cells.
9. *In Vitro* model (cell culture) demonstrating killing of cancer cells.

APPENDIX 2. Other potential agents with limited evidence of anti-cancer activity

These listed drugs/nutraceuticals/botanicals* have *in-vitro, in-vivo,* and (in most cases) limited human data demonstrating anti-cancer activity. This list is adapted from the ReDO database. (227)

In order for a "medication" to be recommended for clinical use it requires *in vitro* data demonstrating that the compound kills cancer cells (apoptosis) and that this killing is enhanced in the presence of chemotherapeutic drugs, that the agent kills/inhibits cancer stem cells (CSC), that the compound kills cancer cells in animal models (*in vivo*) and that in these models the agent favorably alters the tumor microenvironment. Furthermore, to be recommended in humans there needs to be *sufficient scientific evidence* that the agent is both "safe and effective". This *does not* require the "gold standard" RCT, but *sufficient and reproducible* data from case reports, case series and observational studies. This is a dynamic process and when sufficient evidence accumulates the medication can then be included in the list of recommended agents.

The criteria used for the stratification of the listed agents is provided in **Appendix 1**. It should be noted that while "anecdotes" are important in the totality of evidence, anecdotes do not represent objective scientific evidence and are not listed in Appendix 2. If a practitioner claims to have *"cured hundreds of patients*" with a particular intervention, it should be relatively simple to publish this data in a peer reviewed medical journal.

Acetaminophen (727)
Allopurinol
Alpha-Lipoic Acid
Aminophylline
Amiodarone
Annona muricata (soursop, graviola or guanabana) (728)
Aprotinin
Artesunate
Atovaquone
Atrial Natriuretic Peptide
Azithromycin
Bezafibrate
Bosentan
Bromocriptine
Caffeine (729)
Cannabidiol
Captopril
Carvedilol
Chloroquine (730)
Clarithromycin (731)
Clopidogrel
Colchicine
Cyproheptadine
Dandelion extract (732-734)
Dapagliflozin

Deferoxamine
Digoxin
Enalapril
Enoxaparin
Esomeprazole
Famotidine
Fenofibrate
Finasteride
Gallic Acid (tea other plants) (735)
Ganciclovir
Hydroxychloroquine (730)
Imipramine
Irbesartan
Itraconazole (736)
Ketoconazole
Levofloxacin
Licorice root (737, 738)
Loratadine
Losartan
Meclizine
Metoclopramide
Miconazole
Naltrexone (low dose-LDN) (739-742)
Nicardipine
Nifedipine
Niclosamide
Nitroglycerine (743)
Omega 3 fatty acids (135, 744-746)
Omeprazole
Pao Pereira (flavopereirine) (747-754)
Pentoxifylline
Phenytoin
Propranolol (755)
Propolis (*honeybee extract)* (756)
Pyridoxine (Vitamin B6)
Rauwolfia vomitoria (747-752, 757, 758)
Spironolactone
Sulfasalazine
Sulforaphane (broccoli) (759-761)
Valproic Acid

* Nutraceuticals/Botanicals indicated by *italics.*

APPENDIX 3. Footnote for Figure 10

Cell Cycle. p21: Protein 21, p16: Protein 16, p53: Protein 53, EZH2: Enhancer of Zeste Homolog 2, Cyclin A: Cyclin A, Cyclin B1: Cyclin B1, Cyclin D1: Cyclin D1, Cyclin E: Cyclin. **Apoptosis.** Cleaved caspase-3, 7, 9: Cleaved caspase-3, 7, 9, Cleaved PARP: Cleaved Poly (ADP-ribose) polymerase, Caspase 3: Caspase-3, miR-15a: microRNA-15a, miR-16: microRNA-16, TAZ: Transcriptional coactivator with PDZ-binding motif, YAP: Yes-associated protein, EZH2: Enhancer of Zeste Homolog 2. **Transcription Factors.** ERE: Estrogen Response Element, PPAR-gamma: Peroxisome Proliferator-Activated Receptor Gamma, Nrf-2: Nuclear factor erythroid 2-related factor 2, p21: Protein 21, p53: Protein 53, FOX03: Forkhead box O3, Beta-catenin: Beta-catenin, STAT-1: Signal Transducer and Activator of Transcription 1, STAT-3: Signal Transducer and Activator of Transcription 3, STATE-4: Signal Transducer and Activator of Transcription 4, STAT-4: Signal Transducer and Activator of Transcription 4, CREB-BP: cAMP Response Element-Binding Protein Binding Protein, AP-1: Activator Protein 1, Notch-1: Notch receptor 1, HIF-1: Hypoxia-Inducible Factor 1. **Signaling Pathways.** AKT: Protein Kinase B (also known as Akt), AXL: AXL Receptor Tyrosine Kinase, Beta-catenin: Beta-catenin, Slug: Snail Family Transcriptional Repressor 2, Vimentin: Vimentin (an intermediate filament protein), STAT3: Signal Transducer and Activator of Transcription 3, NF-kB: Nuclear Factor-kappa B, **Receptors.** DR-5: Death Receptor 5, Fas-L: Fas Ligand, IR: Insulin Receptor, Fas: Fas Receptor, R: Receptor, H2R: Histamine H2 Receptor, HER-2: Human Epidermal Growth Factor Receptor 2, IL-8: Interleukin-8, CXCR4: C-X-C chemokine receptor type 4, AHR: Aryl Hydrocarbon Receptor, AR: Androgen Receptor, ER-alpha: Estrogen Receptor-alpha, EGFR: Epidermal Growth Factor Receptor, EPCR: Endothelial Protein C Receptor. **Growth Factors.** DR-5: Death Receptor 5, Fas-L: Fas Ligand, CTGF: Connective Tissue Growth Factor, FGF: Fibroblast Growth Factor, HGF: Hepatocyte Growth Factor, TF: Transcription Factor, NGF: Nerve Growth Factor, EGF: Epidermal Growth Factor, PDGF: Platelet-Derived Growth Factor, TGF-Beta 1: Transforming Growth Factor-Beta 1, VEGF: Vascular Endothelial Growth Factor. **Protein Kinases.** JNK: c-Jun N-terminal Kinase, AMPK: AMP-activated Protein Kinase, ASK1: Apoptosis Signal-regulating Kinase 1, FAK: Focal Adhesion Kinase, EGFR-K: Epidermal Growth Factor Receptor-Kinase, Pp60C-tk: Protein Tyrosine Kinase p60c-src, JAK2: Janus Kinase 2, PI3K: Phosphoinositide 3-Kinase, PGK1: Phosphoglycerate Kinase 1, PAK: p21-Activated Kinase, PKA: Protein Kinase A, PKB: Protein Kinase B (Akt), PTK: Protein Tyrosine Kinase, MAPK: Mitogen-Activated Protein Kinase. **Enzymes.** Telomerase: Telomerase, Desaturase: Desaturase, GCL: Glutamate-Cysteine Ligase, MMP: Matrix Metalloproteinase, GICL: Glutathione Induced Cancer-like Protein, iNOS: Inducible Nitric Oxide Synthase, NQO-1: NAD(P)H Quinone Dehydrogenase 1, FPT: Farnesyl Protein Transferase, Src-2: Steroid Receptor Coactivator 2, DNA pol: DNA Polymerase, TMMP-3: Tissue Matrix Metalloproteinase-3, GST: Glutathione S-transferase, ODC: Ornithine Decarboxylase, PhP: Phosphohexose Isomerase, D: D-aminopeptidase, 5-LOX: 5-Lipoxygenase, COX-2: Cyclooxygenase-2, ATPase: Adenosine Triphosphatase, ATFase: Adenosine Triphosphatase (ATPase) Activator, AATF-1: Apoptosis Antagonizing Transcription Factor 1. **Inflammatory Cytokines.** IL-1: Interleukin-1, IL-2: Interleukin-2, IL-6: Interleukin-6, IL-8: Interleukin-8, IL-12: Interleukin-12, IL-18: Interleukin-18, MCP: Monocyte Chemoattractant Protein, MIP: Macrophage Inflammatory Protein, MaIP: Macrophage-activating Inflammatory Protein, TNF-alpha: Tumor Necrosis Factor-alpha. **Endoplasmic Reticulum Stress Markers.** XBP-1: X-Box Binding Protein 1, IRE1: Inositol-Requiring Enzyme 1, GADD153: Growth Arrest and DNA Damage-Inducible Protein 153, CHOP: C/EBP Homologous Protein, ATF6: Activating, Transcription Factor 6, GRP78: Glucose-Regulated Protein 78. **Adhesion Molecules.** ICAM-1: Intercellular Adhesion Molecule-1, VCAM-1: Vascular Cell Adhesion Molecule-1, ELAM-1: Endothelial Leukocyte Adhesion Molecule-1.

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