CANCERCARE

THE ROLE OF REPURPOSED DRUGS AND METABOLIC INTERVENTIONS IN TREATING CANCER

Paul E. Marik, MD, FCCM, FCCP
No Conflicts of Interest
Percentage of U.S. population who has (or ever had) cancer between 1997 and 2019, by age

- **65 years and over**
  - 1997: 14.7%
  - 2000: 15.2%
  - 2005: 17.5%
  - 2009: 18%
  - 2015: 18.9%
  - 2016: 19.5%
  - 2017: 19.2%
  - 2018: 19.5%
  - 2019: 20.1%

- **18 years and over**
  - 1997: 4.8%
  - 2000: 4.8%
  - 2005: 5.7%
  - 2009: 6.1%
  - 2015: 6.6%
  - 2016: 7.1%
  - 2017: 7.1%
  - 2018: 7%
  - 2019: 7.5%
<table>
<thead>
<tr>
<th>Types of Cancer (MALES)</th>
<th># of cases</th>
<th>% of cases</th>
<th>Types of Cancer (FEMALES)</th>
<th># of cases</th>
<th>% of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>61,170</td>
<td>21</td>
<td>Lung &amp; bronchus</td>
<td>59,910</td>
<td>21</td>
</tr>
<tr>
<td>Prostate</td>
<td>34,700</td>
<td>11</td>
<td>Breast</td>
<td>43,170</td>
<td>15</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>28,470</td>
<td>9</td>
<td>Colon &amp; rectum</td>
<td>24,080</td>
<td>8</td>
</tr>
<tr>
<td>Pancreas</td>
<td>26,620</td>
<td>8</td>
<td>Pancreas</td>
<td>23,930</td>
<td>8</td>
</tr>
<tr>
<td>Liver</td>
<td>19,000</td>
<td>6</td>
<td>Ovary</td>
<td>13,270</td>
<td>5</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,900</td>
<td>4</td>
<td>Uterus</td>
<td>13,030</td>
<td>5</td>
</tr>
<tr>
<td><strong>ALL SITES</strong></td>
<td><strong>322,080</strong></td>
<td></td>
<td><strong>ALL SITES</strong></td>
<td><strong>287,740</strong></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Leading sites of cancer deaths - 2023 estimates (Source: American Cancer Society)
Change in Risk of Skin Cancer Over Time

Table 1
Estimated number of new cases of nonmelanoma skin carcinoma in the United States from 1983 to 2012 (Miller and Weinstock, 1994; Rogers et al., 2010, 2015; Scott et al., 1983).

<table>
<thead>
<tr>
<th>Year</th>
<th>New cases of nonmelanoma skin carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>400,000–500,000</td>
</tr>
<tr>
<td>1992</td>
<td>900,000–1,200,000</td>
</tr>
<tr>
<td>2006</td>
<td>3,500,000</td>
</tr>
<tr>
<td>2012</td>
<td>5,300,000</td>
</tr>
</tbody>
</table>
DISCLAIMER

• A review of the published literature.
• Options for repurposed drugs that can be used in cancer treatment.
• Not intended as a stand-alone guide to treating cancer.
• This review should not be taken as a basis to initiate treatment without guidance or avoid any treatment prescribed by your treating physician.
• The treatment interventions outlined should be used as *adjunctive therapy* in addition to the treatment provided by an oncologist.
• Please note that the Cancer Care review is a “living” document -- continuously updated and refined.
Figure 2: "Modern" cancer treatments are expensive and have limited benefit (Source: FLCCC)
Conventional Chemotherapy & Radiotherapy

- Only target rapidly dividing cells
- Cancer Stem Cells allowed to proliferate
- Increases inflammation in TME
- Increases angiogenesis
- Increases metastatic potential
- Highly TOXIC
- Highly COSTLY
Conventional Theory of Cancer

The conventional theory is that cancer is caused by genetic mutations/genomic instability, which drives a population of cells with the following six “classic” biological properties:

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
The Warburg Effect

Anaerobic Glycolysis
Defective Mitochondria
Origins of Cancer

Cancer as a Metabolic Disease
On the Origin, Management, and Prevention of Cancer

Thomas N. Seyfried

PROFESSOR THOMAS SEYFRIED
CANCER AS A METABOLIC DISEASE
Concept Paper

Can the Mitochondrial Metabolic Theory Explain Better the Origin and Management of Cancer than Can the Somatic Mutation Theory?

Thomas N. Seyfried ¹,⋆ and Christos Chinopoulos ²
Can the Mitochondrial Metabolic Theory Explain Better the Origin and Management of Cancer than Can the Somatic Mutation Theory?

- The absence of gene mutations and chromosomal abnormalities in some cancers
- The identification of numerous driver gene mutations in normal human tissue
- The general absence of cancers in chimpanzees despite having about 98% gene and protein sequence identity with humans even at the BRCA1 locus
- Theodor Boveri, the person most recognized as the originator of the SMT never directly studied cancer and was highly apologetic for his general lack of knowledge about the disease
- Normal mitochondria can down-regulate multiple oncogenic pathways and abnormal growth in tumor cells
Cancer is a METABOLIC Disease not a Genetic Disease

“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.”
- Travis Christofferson (Tripping Over The Truth)

“We may have to turn our main research focus away from decoding the genetic instructions behind cancer and toward understanding the metabolism within cancer cells.”
- James Watson, Father of DNA
The Tumor Microenvironment

- Myeloid derived stem cells (MDSC)
- T-regulatory cells (Tregs)
- Tumor associated macrophages
- Platelets
- Natural Killer Cells (NK cells)
- Cytotoxic T cells
The Tumor Microenvironment

Illustration courtesy of Dr. Moeen Syed
Cancer Stem Cells

Figure: Cancer stem cells are the root of cancer (Source: Dr. Justus Hope)
60-80% of Cancers are Preventable

• Tackle insulin resistance (40% of all cancers)
• Quit smoking
• Limit alcohol
• Get enough Vitamin D
• Avoid processed foods
• Avoid sugary drinks and pure fruit juice
• Get enough exercise (aerobic and resistance training)
• Stress reduction
• 8 hours quality sleep
• Limit exposure to carcinogens
### Vitamin D, Omega-3 FA and Home Exercise to Prevent Cancer: An RCT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Event / Total</th>
<th>Event / Total</th>
<th>Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>36 /1076</td>
<td>45 /1081</td>
<td>0.76 (0.49 - 1.18), p= 0.225</td>
</tr>
<tr>
<td>Omega-3</td>
<td>32 /1073</td>
<td>49 /1084</td>
<td>0.7 (0.44 - 1.09), p= 0.115</td>
</tr>
<tr>
<td>SHEP</td>
<td>35 /1081</td>
<td>46 /1076</td>
<td>0.74 (0.48 - 1.15), p= 0.183</td>
</tr>
<tr>
<td>Omega-3 + Vitamin D</td>
<td>15 /529</td>
<td>28 /537</td>
<td>0.53 (0.28 - 1), p= 0.051</td>
</tr>
<tr>
<td>Vitamin D + SHEP</td>
<td>11 /539</td>
<td>21 /539</td>
<td>0.56 (0.3 - 1.04), p= 0.068</td>
</tr>
<tr>
<td>Omega-3 + SHEP</td>
<td>12 /539</td>
<td>26 /542</td>
<td>0.52 (0.28 - 0.97), p= 0.039</td>
</tr>
<tr>
<td>Vitamin D + Omega-3 + SHEP</td>
<td>4 /264</td>
<td>12 /270</td>
<td>0.39 (0.18 - 0.85), p= 0.017</td>
</tr>
</tbody>
</table>

*Bischoff-Ferrari et al. Front Aging 2022;3:852643*
Vitamins and Nutrients

• Vitamin D3:
  o 5000 u/day and adjusted according to Vitamin D3 (25OH D3 > 60 mg/dl ~ 100mg/dl)

• Omega 3 fatty acids:
  o 2-4 g/day

• Green tea catechins:
  o 500-1000 mg/day

• Melatonin:
  o 0.75 – 5 mg (extended/slow release) at night

• Metformin:
  o 250 mg - 2000 mg daily
Hierarchy of evidence for the stratification of repurposed drugs/nutraceuticals

(reviewed > 1,200 peer reviewed papers)

- Meta analysis of observational and/or randomized controlled trials.
- RCTs and/or prospective observational studies.
- Epidemiological studies
- Case reports and case series
- In Vivo/in Vitro models
  - Killing cancer cells
  - Killing stem cells
  - Synergy with chemotherapeutic drugs
  - Improvement in tumor microenvironment
If the only tool you have is a hammer the world looks like a nail!
Metabolic Interventions to Control Cancer: TOP 12

1. A low-carbohydrate, high-fat, ketogenic diet + time-restricted eating
2. Exercise, stress reduction, and quality sleep
3. Vitamin D3: 20,000 to 50,000 IU daily
   - Dosage should be adjusted by blood vitamin D levels aiming for a 25-OH vitamin D level of ~ 100 ng/ml.
4. Melatonin: start 1 mg and increase to 20-30 mg nightly (extended/slow release)
5. Green tea catechins: 500-1,000 mg daily
6. Metformin: 1,000 mg twice daily
7. Curcumin: (nanocurcumin) 600 mg twice daily
8. Mebendazole: 100-200 mg daily
9. Omega-3 fatty acids: 4 g daily
10. Berberine: 500-600 mg twice daily
    - Metformin and berberine can be used together or alternating (for one month then switching) depending on blood glucose levels.
11. Atorvastatin: 40 mg twice daily or Simvastatin 20 mg twice daily
12. Disulfiram: 80 mg three times daily or 500 mg once daily

Over the Counter
Requires a prescription
Warburg Phenomenon

(A) Normal cell
- Glucose → Glycolysis → Pyruvate → LDHA → Lactate
- Oxidative phosphorylation: ~38 mol ATPs/mol glucose
- Anaerobic glycolysis: 2 mol ATPs/mol glucose
- Extracellular component: CO₂ and O₂

(B) Cancer cell
- Glucose → Glycolysis → Pyruvate → LDHA → Lactate
- Anaerobic glycolysis (Warburg effect): 2 mol ATPs/mol glucose
- Extracellular components: CO₂, Lactate
- Cell proliferation: Biomass incorporation

Wikimedia license: https://commons.wikimedia.org/wiki/File:Differences_in_glycolysis_pathways_between_normal_cells_and_cancer_cells.webp
Glucose Management

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

High GI carbs cause blood sugar to spike then crash

Low GI carbs are digested and released slowly for sustained energy
Glucose Management

ARTICLE

Dietary Insulin Load and Cancer Recurrence and Survival in Patients With Stage III Colon Cancer: Findings From CALGB 89803 (Alliance)

Conclusion:
Patients with resected stage III colon cancer who consumed a high-insulinogenic diet were at increased risk of recurrence and mortality

Chemotherapy

Over 50 chemotherapeutic drugs
All target actively dividing cell

Chemotherapeutics

- Antimetabolites
  - purine analogs
  - purine antagonists
  - pyrimidine antagonists
  - antifolates
  - ribonucleotide reductase inhibitors

- Alkylating agents
  - hydrazine
  - oxazaphosphorines
  - nitrogen mustards
  - platinum-based agents

- Others
  - enzymes
  - antibiotics
  - proteasome inhibitors
  - tyrosine kinase inhibitors

Mitotic spindle inhibitors
  - taxanes
  - vinca alkaloids

Topoisomerase inhibitors I and II
Traditional “chemo” fails for solid tumors because:

• Solid tumors are composed of heterogeneous population of cells many of which are slowly growing.
• Most of the tumor cells are in the rest phase of the cell cycle.
• Chemotherapy does not improve the cancer. microenvironment (which promotes cancer cell proliferation) and likely makes it worse.
• Chemotherapy enhances rather than kills cancer stem cells.
• Cancer cells become resistant to the chemotherapeutic agent.
# Chemotherapy vs Repurposed Drugs

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Repurposed Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor Cell population</strong></td>
<td>Actively dividing cells only (~ 10% of cells)</td>
<td>All malignant cells</td>
</tr>
<tr>
<td><strong>Tumor selectivity</strong></td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Tumor Stem Cells</strong></td>
<td>Enhances</td>
<td>Suppresses/kills</td>
</tr>
<tr>
<td><strong>Effect on adaptive immunity</strong></td>
<td>Suppressive</td>
<td>Enhances</td>
</tr>
<tr>
<td><strong>Effect on Tumor Microenvironment</strong></td>
<td>Negative effect</td>
<td>Improves/enhances</td>
</tr>
<tr>
<td><strong>Myelotoxic</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Severe systemic side effects</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Tumor cell resistance develops</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>+++++</td>
<td>+</td>
</tr>
</tbody>
</table>
## Chemotherapy “Curable” Cancer

<table>
<thead>
<tr>
<th>Cancer Curable</th>
<th>Improves Survival</th>
<th>Palliation Only (metastatic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choriocarcinoma</td>
<td>Breast cancer</td>
<td>Colorectal, gallbladder</td>
</tr>
<tr>
<td>Acute lymphatic leukemia</td>
<td>Ovarian Cancer</td>
<td>Pancreatic, stomach</td>
</tr>
<tr>
<td>Chronic lymphatic leukemia</td>
<td>ALL in adults</td>
<td>Esophageal, liver</td>
</tr>
<tr>
<td>Acute promyelocytic leukemia</td>
<td>AML</td>
<td>Prostate, bladder, kidney</td>
</tr>
<tr>
<td>Testicular cancer</td>
<td>Thyroid Cancer</td>
<td>Endometrial and cervical</td>
</tr>
<tr>
<td>Ovarian germ cell tumor</td>
<td>Small cell lung cancer</td>
<td>NSCLC (lung cancer)</td>
</tr>
<tr>
<td>Hodgkin's lymphoma</td>
<td>Multiple myeloma</td>
<td>Brain, adrenal, melanoma</td>
</tr>
<tr>
<td>High Grade non-Hodgkin's lymphoma</td>
<td>Osteosarcoma</td>
<td>Adenocarcinoma primary unknown</td>
</tr>
<tr>
<td>Rare childhood malignancies</td>
<td>Wilms tumor</td>
<td>H&amp;N cancer</td>
</tr>
</tbody>
</table>
Role of Chemotherapy and Repurposed Drugs

Illustration courtesy of Dr. Mobeen Syed
Surgically “Curable” Disease. Five-year survival for local disease* with surgical removal

<table>
<thead>
<tr>
<th>Cancer</th>
<th>5-year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>99</td>
</tr>
<tr>
<td>Prostate</td>
<td>99</td>
</tr>
<tr>
<td>Thyroid</td>
<td>99</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>99</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>95</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>93</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>92</td>
</tr>
<tr>
<td>Uterine Cervix</td>
<td>93</td>
</tr>
<tr>
<td>Colorectal</td>
<td>91</td>
</tr>
</tbody>
</table>

* Local disease; An invasive malignant cancer confined entirely to the organ of origin
Personalized Management of Cancer

- Repurposed Drugs & Metabolic Rx
- Chemotherapy
- Surgery
- Stress Management & sleep
Review the CANCER CARE monograph

- Go to FLCCC.net
- Select “Medical Evidence” on main menu
- Under “Reviews & Monographs”

flccc.net/cancer-care
Thank you