Energy balance, metabolism, and cancer prevention

MICHAEL POLLAK
McGill University
Montreal
Dealing with the global burden of cancer

Energy balance + metabolism relevant to each of these areas
Caloric restricts protects against experimental carcinogens

The Influence of the Degree of Caloric Restriction on the Formation of Skin Tumors and Hepatomas in Mice

Albert Tannenbaum, M.D., and Herbert Silverstone, Ph.D.

Cancer Res. 1949
Caloric excess raises insulin and accelerates tumor growth.

![Graph showing tumor volume over weeks for high and low carb diets.]

- **High Carb diet**: Red line with error bars.
- **Low Carb diet**: Blue line with error bars.

**Tumor Volume (mm³)** vs **Weeks**

**Serum Insulin**

- **High Carb diet**: *High
data point.
- **Low Carb diet**: *Low data point.

**Association of Diet-Induced Hyperinsulinemia With Accelerated Growth of Prostate Cancer (LNCaP) Xenografts**

Authors: Herman O. Haddad, Nahri E. Rehman, Rong Fan, Linda M. Seger, Rob New, Laurence H. Klotz, Michael Pollak.

<table>
<thead>
<tr>
<th></th>
<th>↑ Risk per 5kg/m²</th>
<th>↑ Mortality Obese vs. not</th>
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<tbody>
<tr>
<td>Breast (postmeno)</td>
<td>1.1</td>
<td>2.1</td>
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<tr>
<td>prostate</td>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Esophagus (adeno)</td>
<td>1.5</td>
<td>2.6</td>
</tr>
<tr>
<td>gallbladder</td>
<td>1.6</td>
<td>2.1</td>
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<tr>
<td>colon</td>
<td>1.1</td>
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<tr>
<td>kidney</td>
<td>1.3</td>
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<td>endometrium</td>
<td>1.6</td>
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<tr>
<td>myeloma</td>
<td>1.1</td>
<td>1.4</td>
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</table>
Energy Balance: Peto’s paradox and Klieber’s law

Within species

Cancer risk / organism

Between species

Cancer risk / organism

BMR

Substantial

Tiny

Lifetime cancer risk for organism as sum of risks for each cell during its life
Obesity increases cancer burden

• Target obesity: implementation science

• Understand underlying mechanisms to identify risk reduction strategies that may be relevant not only to the obese
Whole organism energy balance  Cellular energy balance
Paradigm of hormone dependency of cancer

ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.¹

BY GEORGE THOMAS BEATSON, M.D. EDIN., SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SURGEON GLASGOW WESTERN INFIRMARY; AND EXAMINER IN SURGERY TO THE UNIVERSITY OF EDINBURGH.
Host energy balance

Cellular energy balance in at-risk tissues

Variation in cellular proliferation, survival, and carcinogenesis risk
Variation in cellular proliferation, survival, and carcinogenesis risk
When food intake is reduced, circulating glucose does **NOT** decline significantly until patient is nearly dead: breakdown of stored fat and muscle protects against hypoglycemia.

Also, cancer cells can remove glucose from circulation more effectively than normal cells; this is demonstrated everyday in glucose-labelled PET scans.

depriving cancer of nutrients by restricting calories **cannot work**
Host energy balance

Changes in endocrine and immunologic environment

Variation in cellular proliferation, survival, and carcinogenesis risk

Cellular energy balance
Dietary energy supply influences growth of some tumors by influencing endocrine / immunologic environment rather than energy available to tumor.

The effect of macronutrient intake on cancer biology represents another context of hormonal dependency of neoplastic cells.
Candidate hormonal mediators of effects of energy balance on cancer

- Insulin
- IGFs
- Leptin
- Adiponectin
- Inflammatory cytokines: WAT + systemic *
- Others…

*Iyengar N., …, Dannenberg A. CCR Dec 2015*
Food energy available

↓

Increase insulin secretion

↓

Cells informed:
OK to use energy for proliferation, growth, or to store it

InsR widely expressed in cancers and tissues
not classically considered insulin targets
Higher insulin secretion associated with increased CRC risk

<table>
<thead>
<tr>
<th>C peptide, pmol/ml</th>
<th>.06-.2</th>
<th>.2-.3</th>
<th>.3-.44</th>
<th>.44-.73</th>
<th>.73-2.</th>
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<tbody>
<tr>
<td>RR</td>
<td>1</td>
<td>1.5</td>
<td>2.8</td>
<td>2.5</td>
<td>3.4</td>
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</tbody>
</table>

A Prospective Study of Plasma C-Peptide and Colorectal Cancer Risk in Men

Jing Ma, Edward Giovannucci, Michael Pollak, Azita Leavitt, Yuzhen Tao, J. Michael Gaziano, Meir J. Stampfer
Higher IGF-I associated with increased prostate cancer risk

Chan et al (n=304) Science 1998

Travis et al (n=23,000) Cancer Res. in press, 2016
- Lean: More adiponectin – less cancer
- Adiponectin activates AMPK and inhibits mTOR

Hofmann J et al, *Cancer Res*. In press, 2016 (Multiple Myeloma)
Is there a role for drugs?

BENCH TO BEDSIDE

Repurposing biguanides to target energy metabolism for cancer treatment

Michael Pollak

Metformin is a drug commonly used for treating type 2 diabetes—yet there are more than 100 ongoing trials of metformin at conventional antidiabetic doses for cancer treatment. This situation has arisen in large part because, in contrast to newly synthesized and patented drug candidates where drug supply is controlled and clinical trials are coordinated in a central office, there is a low ‘barrier to entry’ to initiate a clinical trial of an inexpensive generic drug for a potential new indication. When there is an intriguing rationale and a low risk of toxicity, as is the case for treatment of cancer with metformin, many investigators launch clinical trials, but the coordination associated with conventional drug development programs is absent.

Metformin is a biguanide compound known to partially inhibit oxidative phosphorylation,
Retrospective studies of metformin and risk: too good to be true?

Metformin: effect on cancer risk and mortality

Any exposure – Cancer Incidence

Maximum Dose – Cancer Incidence
- Low vs None: 0.51
- Medium vs None: 0.28
- High vs None: 0.99

Any exposure – Cancer Mortality

Adjusted* HR:
- 0.4
- 0.6
- 0.8
- 1
- 1.2

Case-Cohort Study
N=4085 users & 4085 controls
Tayside, Scotland, 1994-2003

Libby et al., Diabetes Care, 2009,32:1620
Metformin causes decline in mitochondrial ATP production in cells that accumulate sufficient concentrations of the drug.
Mitochondrial oxidative phosphorylation

Liver

Metformin

Energetic stress

↑ AMPK

↓ Gluconeogenesis

↓ Glucose if elevated

↓ Insulin if elevated

Reduced growth of the subset of cancers stimulated by the metabolic environment seen in type II diabetes and obesity

Energetic crisis
Cytotoxic effects

Tumor cell sensitive to energetic stress (e.g., loss of function of AMPK, p53, or LKB1)

Energetic stress

↑ AMPK

↓ mTOR

↓ FAS

↓ Energy consumption

Cytostatic effect

Tumor cell capable of responding to energetic stress

Effects on host indirectly influencing target cells require:
- baseline hyperinsulinemia
- neoplasm that is insulin sensitive

Direct effects on target cells require:
- adequate drug concentration in tissue
- expression of cell surface drug transporters such as OCT1

Pollak M. Cancer Discovery 2012
The Effects of Adiponectin and Metformin on Prostate and Colon Neoplasia Involve Activation of AMP-Activated Protein Kinase

Mahvash Zakikhani,1,4 Ryan J.O. Dowling,2,3 Nahum Sonenberg2,3 and Michael N. Pollak1,4
Metformin research agenda 2016

• Pharmaco-epidemiology: older dramatic results now controversial
• Insulin–lowering effect: confirmed, but is magnitude of change biologically significant?
• Direct actions: is drug exposure sufficient? Negative treatment trials
• Effect on urothelium
• Effect on inflammation
• Effect on microbiome
• New biguanides
• Effect on AMPK of GI tract
• Effect on immunometabolism and cancer vaccine efficacy
Modulation of gut microbiota by berberine and metformin during the treatment of high-fat diet-induced obesity in rats

Xu Zhang, Yufeng Zhao, Jia Xu, Zhengsheng Xue, Menghui Zhang, Xiaoyan Pang, Xiaojun Zhang & Liping Zhao

Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-κB activation

Olga Moiseeva, Xavier Deschénes-Simard, Emmanuelle St-Germain, Sebastian Igelmann, Geneviève Huot, Alexandra E. Cadar, Véronique Bourdeau, Michael N. Pollak & Gerardo Ferbeyre

The Primary Glucose-Lowering Effect of Metformin Resides in the Gut, Not the Circulation. Results From Short-term Pharmacokinetic and 12-Week Dose-Ranging Studies

John B. Buse, Ralph A. DeFronzo, Julia Rosenstock, Tera Kim, Colleen Burns, Sharon Skare, Alain Baron & Mark Fineman

Doi: 10.2337/dc15-0488
Division of colon crypt stem cells is reduced by oral metformin

- Sigmoid biopsy → metformin 1.5 g/day x 14 days → sigmoid biopsy

![Graph showing the percentage of P-H3 positive cells/crypt during baseline and after treatment.](image-url)
Metformin improves performance of ov-a antitumor vaccine: immuno-metabolism and prevention

Enhancing CD8 T-cell memory by modulating fatty acid metabolism

Erika L. Pearce¹, Matthew C. Walsh¹, Pedro J. Cejas¹, Gretchen M. Harms¹, Hao Shen², Li-San Wang¹,³, Russell G. Jones¹ and Yongwon Choi¹
Substantial contribution of extrinsic risk factors to cancer development

Song Wu, Scott Powers, Wei Zhu, Yusef A. Henein
Backup slides
A time like no other...not only in historical time, but also evolutionary time

Graphic from Michael Milken, Prostate Cancer Foundation
Evolutionary context:

- Limited nutrient availability and high energy expenditure constrained BMI
- Those best able to avoid starvation in terms of hunger, behavior, intestinal absorption, metabolism are most obesity prone / cancer prone in current environment
Effective education

200 calories  4 hours walk
Change in purchase intent

200 calories: 15%
4 hours walk: 56%

Cancer Prevention Centre, McGill U
Mexico’s Anti-Obesity Policy

November 2013: Mexico’s Congress officially passed a 10% tax on sugar-sweetened beverages and an 8% tax on junk food.

December 2014: 12% reduction in sugary beverages

Worldwide Life Expectancy

Four million years produced an 11-year increase from 20 to 31.

114 years produced a 40-year increase.

James Carey: Longevity; United Nations Development Program

1900  31  1900
2014  71  2014
Obesity prevention vs obesity correction

- Will effective weight loss after decades of obesity lower risks?
- Early interventions preferable