# The Relationship Between Acidosis & Cancer

Paul Kern

Naturopath



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## Overview

1. **Introduction to Acidosis**
   - What is chronic metabolic acidosis?
2. **Cancer Causes Acidosis**
   - Understanding how and why tumours produce an acidic microenvironment
3. **Does Acidosis Cause Cancer?**
   - An examination of the evidence surrounding the effects of acidosis on cancer development and progression
4. **Clinical Strategies**
   - Practical advice on assessing and modulating acid-base balance for support of cancer patients



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# Section 1: Introduction to Acidosis



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## What is Acid-Base Balance?

- In chemistry, the pH scale measures how acidic or basic (alkaline) a substance is
- Hydrogen (H+) is the primary acidic ion and 'pH' is an abbreviation for the 'potential of hydrogen' to form acid
- The pH scale ranges from 0 to 14
  - A pH of 7 is neutral
  - A pH less than 7 is considered acidic
  - A pH greater than 7 is basic (alkaline)
- The physiological pH value differs in the various parts of the body



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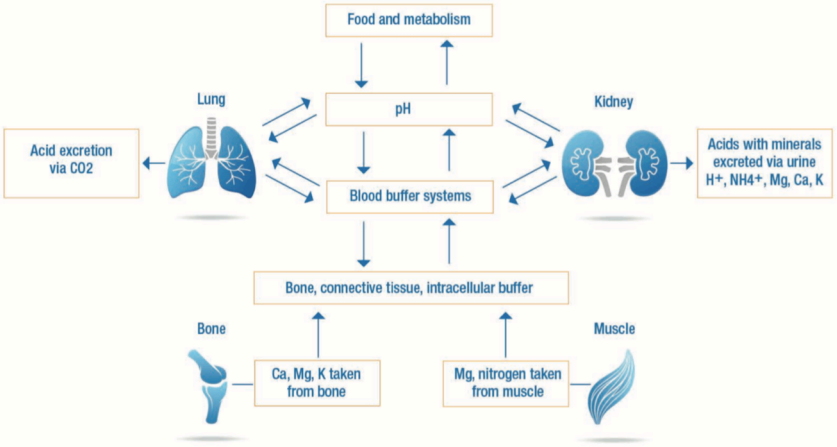
# Control of pH in the Body

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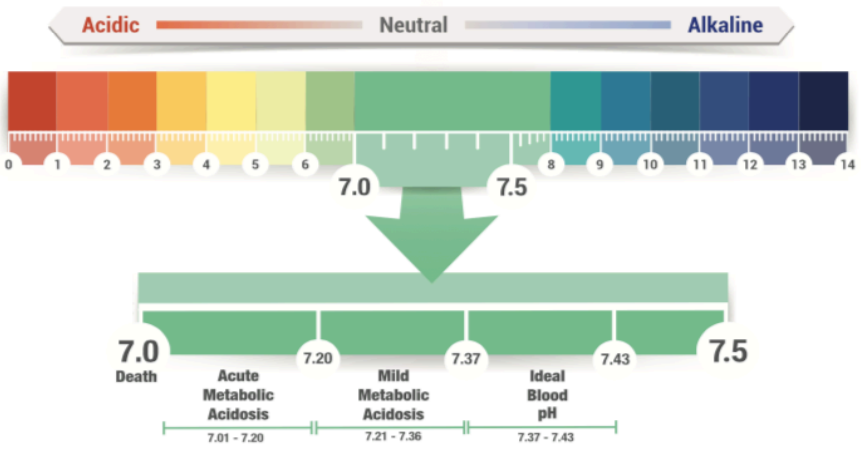
# Chronic Metabolic Acidosis

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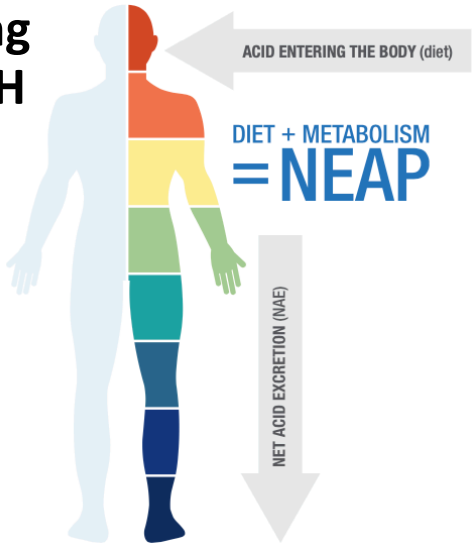
# Factors Affecting Physiological pH

- Diet
- Exercise
- Inflammation
- Stress
- Alcohol
- Ageing
- Impaired buffering capacity
- Mitochondrial dysfunction
- Respiratory disease
- Renal disease

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# Effects of Diet on Physiological pH

- All foods have a net acidifying or alkalising effect on our body
- Food components are ultimately broken down into an acid or a base
- The balance between the acid-forming components and the base-forming components of a food determines its net effect
- This can be measured as the Potential Renal Acid Load (PRAL)
- PRAL is a scientific calculation used to determine the acid production potential of foods based on the content of:
  - Acidifying substances = Sulphur (from the breakdown of amino acids/ protein), phosphorus, sodium chloride
  - Alkalising minerals = Potassium, magnesium, calcium

Robey, I. F. (2012). Examining the relationship between diet-induced acidosis and cancer. *Nutrition & metabolism*, *9*(1), 72.

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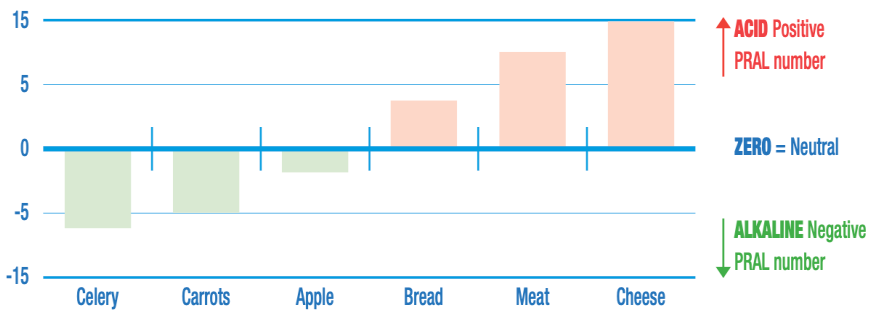
# Assessing Dietary Acid Load




Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. J Am Diet Assoc. 1995 Jul;95(7):791-7.
Pizzorno, J. (2015). Acidosis: An old idea validated by new research. *Integrative Medicine: A Clinician's Journal*, *14*(1), 8.

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# Acidifying & Alkalising Foods

| Acidifying | Alkalising |
|---|---|
| Meat & Meat Products | Fruits |
| Eggs | Vegetables |
| Dairy Products | Herbs & Spices |

Robey, I. F. (2012). Examining the relationship between diet-induced acidosis and cancer. *Nutrition & metabolism*, *9*(1), 72
Pizzorno, J. (2015). Acidosis: An old idea validated by new research. *Integrative Medicine: A Clinician's Journal*, *14*(1), 8

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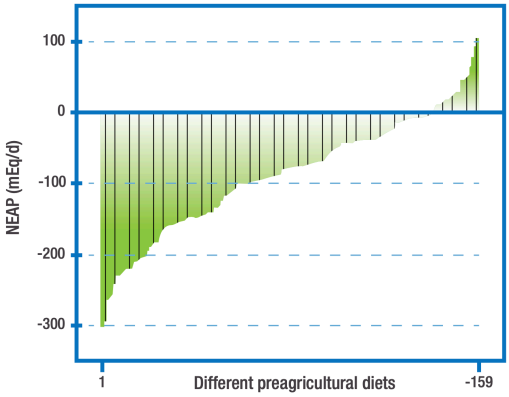
# Ancestral Diets Were Highly Alkaline

The average NEAP (Net Endogenous Acid Production) of preagricultural diets has been calculated to be -88 mEq/day (highly alkaline)




Sebastian, A., Frassetto, L. A., Sellmeyer, D. E., Merriam, R. L., & Morris Jr, R. C. (2002). Estimation of the net acid load of the diet of ancestral preagricultural Homo sapiens and their hominid ancestors. *The American journal of clinical nutrition*, *76*(6), 1308-1316.



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# Modern, Western Diet is Highly Acidic

- Today's Standard Australian Diet (SAD) has an average NEAP (Net Endogenous Acid Production) of about 100mEq/day (VERY acidic)
- This is because the SAD diet contains:
  1. High amounts of acidic animal protein, dairy and grains
  2. Low levels of alkalising, mineral-rich plant matter


Sebastian, A., Frassetto, L. A., Sellmeyer, D. E., Merriam, R. L., & Morris Jr, R. C. (2002). Estimation of the net acid load of the diet of ancestral preagricultural Homo sapiens and their hominid ancestors. *The American journal of clinical nutrition*, *76*(6), 1308-1316.



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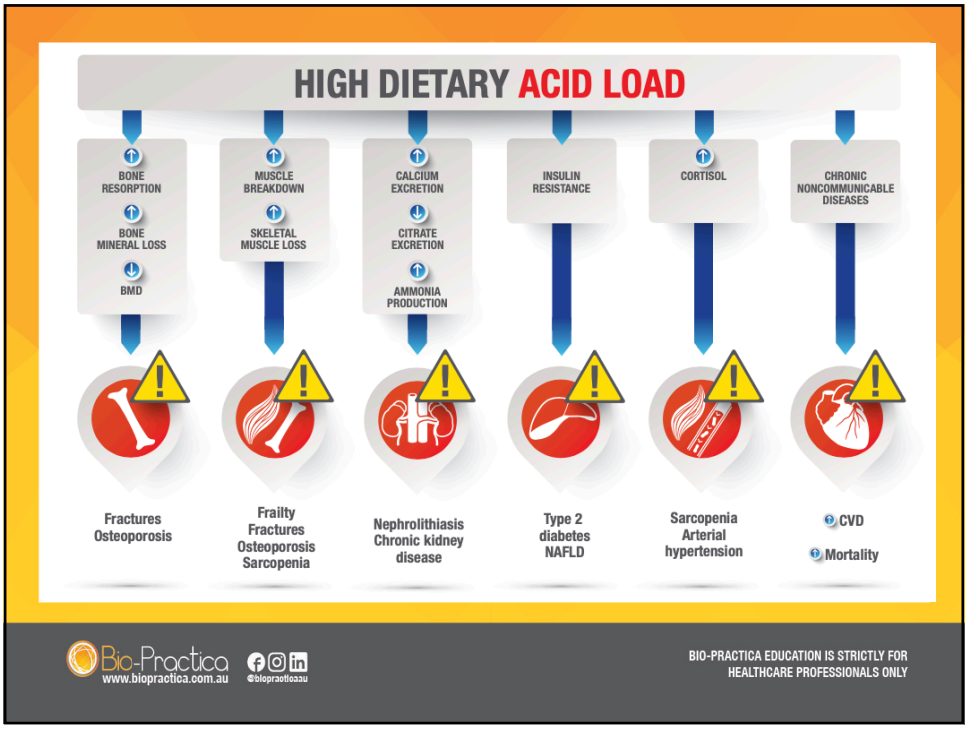
HIGH DIETARY ACID LOAD
BONE RESORPTION
BONE MINERAL LOSS
BMD
MUSCLE BREAKDOWN
SKELETAL MUSCLE LOSS
CALCIUM EXCRETION
CITRATE EXCRETION
AMMONIA PRODUCTION
INSULIN RESISTANCE
CORTISOL
CHRONIC NONCOMMUNICABLE DISEASES
Fractures
Osteoporosis
Frailty
Fractures
Osteoporosis
Sarcopenia
Nephrolithiasis
Chronic kidney disease
Type 2 diabetes
NAFLD
Sarcopenia
Arterial hypertension
CVD
Mortality
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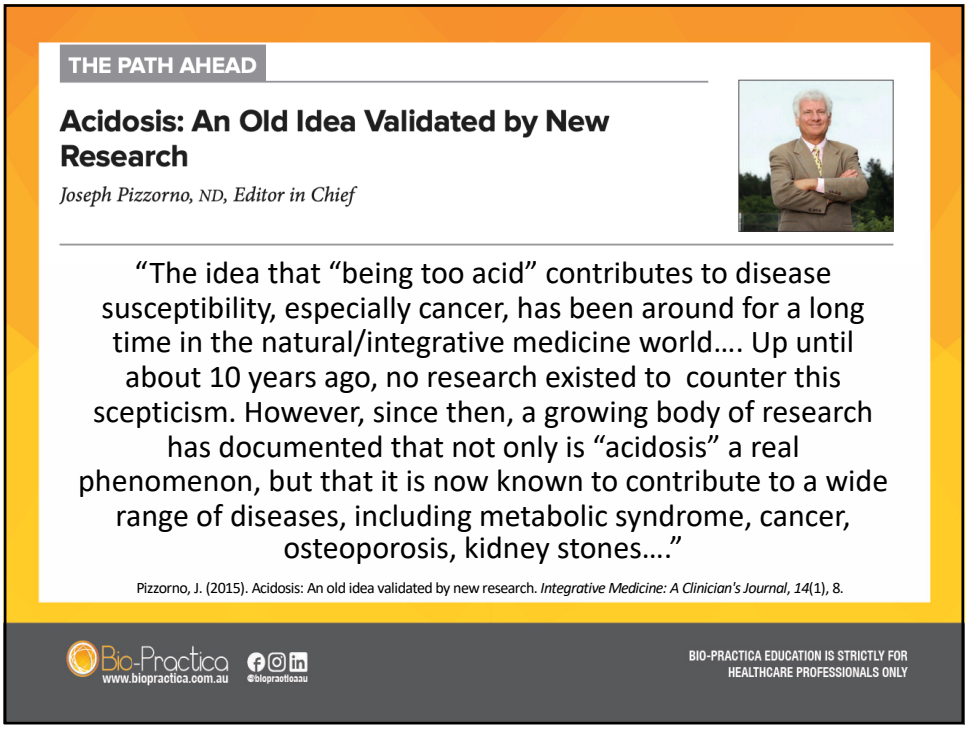
THE PATH AHEAD
Acidosis: An Old Idea Validated by New Research
Joseph Pizzorno, ND, Editor in Chief
"The idea that "being too acid" contributes to disease susceptibility, especially cancer, has been around for a long time in the natural/integrative medicine world…. Up until about 10 years ago, no research existed to counter this scepticism. However, since then, a growing body of research has documented that not only is "acidosis" a real phenomenon, but that it is now known to contribute to a wide range of diseases, including metabolic syndrome, cancer, osteoporosis, kidney stones…."
Pizzorno, J. (2015). Acidosis: An old idea validated by new research. Integrative Medicine: A Clinician's Journal, 14(1), 8.
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# Section 2: Cancer Causes Acidosis



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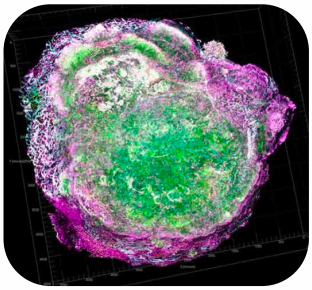
## Tumour Microenvironment Critical

- All aspects of tumour growth and development are affected by the tumour microenvironment, including:
  1. Availability of oxygen and glucose
  2. Growth and regulatory factors
  3. Localised pH
- Tumour cells adapt rapidly to changes in the microenvironment
- Tumour cells deliberately alter the microenvironment to improve their own survival



Fais, S., Venturi, G., & Gatenby, B. (2014). Microenvironmental acidosis in carcinogenesis and metastases: new strategies in prevention and therapy. *Cancer and Metastasis Reviews*, *33*(4), 1095-1108.



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# Tumour Cells Adapt to Hypoxia by Switching to Anaerobic Glycolysis

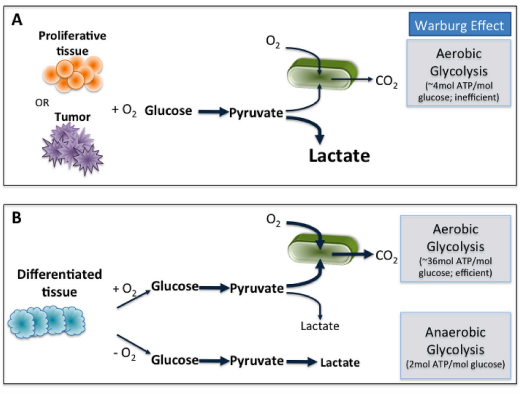
- Tumour cells often exist in hypoxic (i.e. anaerobic) conditions
- Metabolic adaptation to hypoxia involves changes to the way energy is produced within tumour cells
- There is a measurable shift in tumour cells from primarily aerobic cellular respiration to anaerobic cellular respiration
- Tumour cells rely heavily on **anaerobic glycolysis** for energy
- That is, they do not require oxygen but require a plentiful supply of glucose to grow and thrive

Fais, S., Venturi, G., & Gatenby, B. (2014). Microenvironmental acidosis in carcinogenesis and metastases: new strategies in prevention and therapy. *Cancer and Metastasis Reviews*, *33*(4), 1095-1108.



17

# Normal Cellular Respiration vs. Anaerobic Glycolysis in Tumour Cells




https://figshare.com/articles/_Schematics_of_oxidative_phosphorylation_anaerobic_glycolysis_and_aerobic_glycolysis_/371032/1



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# The Warburg Effect in Cancer Cells

- In response to hypoxia, a protein called Hypoxia Induced Factor 1-alpha (HIF1-α) is activated
- This increases the rate of anaerobic glycolysis and decreases aerobic respiration
- In healthy cells this only occurs temporarily (e.g. when exercising intensely – above our cardio-pulmonary capacity to deliver oxygen to muscle cells)
- However, tumour cells preferentially use anaerobic respiration even in the presence of sufficient oxygen
- This phenomenon is known as **The Warburg Effect**

Fais, S., Venturi, G., & Gatenby, B. (2014). Microenvironmental acidosis in carcinogenesis and metastases: new strategies in prevention and therapy. *Cancer and Metastasis Reviews*, *33*(4), 1095-1108.
Corbet, C., & Feron, O. (2017). Tumour acidosis: from the passenger to the driver's seat. *Nature reviews. Cancer*, *17*(10), 577-593.



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# But Why do Tumour Cells Employ the Warburg Effect?

- It is difficult to understand why the Warburg effect occurs:
  - It is less energy efficient than normal cellular respiration
  - It produces large amounts of acid in the form of lactic acid and hydrogen ions (H+)
  - This form of metabolism should be disadvantageous to the tumour
- This seeming contradiction can be explained by the concept of Niche Engineering

Fais, S., Venturi, G., & Gatenby, B. (2014). Microenvironmental acidosis in carcinogenesis and metastases: new strategies in prevention and therapy. *Cancer and Metastasis Reviews*, *33*(4), 1095-1108.



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# Niche Engineering by Tumour Cells

- Niche engineering is an evolutionary strategy to improve a population's survival by altering the environment to decrease the fitness of its competitors
- In this case, cancer cells alter their microenvironment via The Warburg Effect to reduce the survival of healthy surrounding tissue
- The high extracellular acidity produced from The Warburg Effect damages healthy cells, but not cancer cells
- This acidifying effect around tumours is measurable and real

Fais, S., Venturi, G., & Gatenby, B. (2014). Microenvironmental acidosis in carcinogenesis and metastases: new strategies in prevention and therapy. *Cancer and Metastasis Reviews*, *33*(4), 1095-1108.



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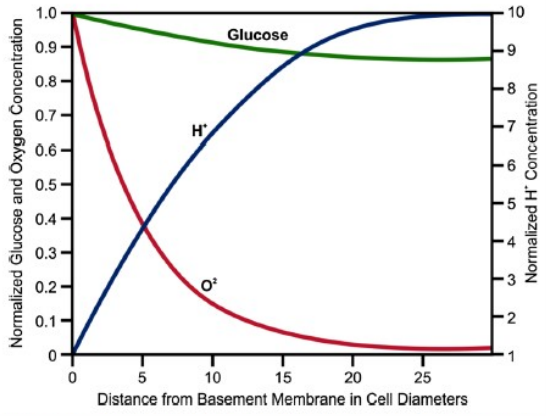
# Less Oxygen Leads to More Acidity in Tumour Microenvironments




Fais, S., Venturi, G., & Gatenby, B. (2014). Microenvironmental acidosis in carcinogenesis and metastases: new strategies in prevention and therapy. *Cancer and Metastasis Reviews*, *33*(4), 1095-1108.



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# Cancer Cells Actively Alter pH to Suit Themselves

- Cancer cells actively pump out lactic acid and protons (H+) into the extracellular space around the tumour via monocarboxylate transporters (MCTs) and Na+/H+ exchange pumps (NHEs)
- They also take in bicarbonate via Na+/$HCO_3$ co-transporters (NBCs)
- This results in an **alkaline intracellular pH**, which promotes cellular proliferation and inhibits apoptosis
- It also causes an **acidic extracellular pH** in the surrounding area, which benefits cancer cells in several ways

Fais, S., Venturi, G., & Gatenby, B. (2014). Microenvironmental acidosis in carcinogenesis and metastases: new strategies in prevention and therapy. *Cancer and Metastasis Reviews*, *33*(4), 1095-1108.



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# Benefits of Acidity for Cancer Cells

- Improves adaptation to hypoxia
- Upregulates cancer cell autophagy
- Increases angiogenesis
- Reduces immune tumour surveillance
- Enhances cancer invasiveness
- Enhances metastatic cancer spread
- Increases resistance to chemotherapy

Corbet, C., & Feron, O. (2017). Tumour acidosis: from the passenger to the driver's seat. *Nature reviews. Cancer*, *17*(10), 577-593.
Fais, S., Venturi, G., & Gatenby, B. (2014). Microenvironmental acidosis in carcinogenesis and metastases: new strategies in prevention and therapy. *Cancer and Metastasis Reviews*, *33*(4), 1095-1108.



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# Section 3: Does Acidosis Cause Cancer?



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## Acidogenic Diet & Cancer Risk

**Higher diet-dependent acid load is associated with risk of breast cancer: Findings from the sister study**

Yong-Moon Mark Park[1], Susan E. Steck[2,3], Teresa T. Fung[4,5], Anwar T. Merchant[3], M. Elizabeth Hodgson[6], Jean A. Keller[7] and Dale P. Sandler[1]

[1]Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC
[2]Cancer Prevention and Control Program, University of South Carolina, Columbia, SC
[3]Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC
[4]Department of Nutrition, Simmons College, Boston, MA
[5]Department of Nutrition, Harvard TH Chan School of Public Health, Boston, MA
[6]Social and Scientific Systems, Inc., Durham, NC
[7]Westat, Durham, NC

Dietary factors that contribute to chronic low-grade metabolic ac
epidemiologic study has examined diet-dependent acid load and
participants who completed a validated food frequency question
criteria. The Potential Renal Acid Load (PRAL) score was used to
consumption of protein and phosphorus, and lower consumption
between PRAL and breast cancer was evaluated using multivaria
invasive breast cancers diagnosed at least 1 year after enrollme
reflecting greater acid-forming potential, was associated with in
CI, 1.04–1.41], $p_{trend}$ = 0.04). The association was more pronour
1.67 [95% CI, 1.07–2.61], $p_{trend}$ = 0.03) and triple-negative brea
$p_{trend}$ = 0.02). Negative PRAL scores, representing consumption
negative and triple-negative breast cancer, compared to a PRAL
load may be a risk factor for breast cancer while alkaline diets m
with meat consumption and negatively correlated with fruit and
and vegetables and low in meat may be protective against horm

*"An acidogenic diet, as measured by PRAL value, was associated with an increased risk of breast cancer, while an alkaline diet reduced the risk of breast cancer."*

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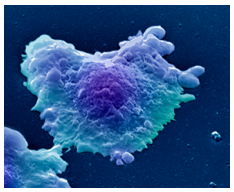
# Acidogenic Diet Drives Tumorigenesis

- An acidogenic diet can cause the pH of intracellular and extracellular spaces in tissues to become more acidic
- Raised intracellular and extracellular pH in the tumour microenvironment enhances tumour invasion and metastasis



- Thus an acidogenic diet could enhance the effects of Niche Engineering by tumours – i.e. Chronic Metabolic Acidosis may make it easier for tumours to thrive

Pizzorno, J. (2015). Acidosis: An old idea validated by new research. *Integrative Medicine: A Clinician's Journal*, *14*(1), 8.
Fais, S., Venturi, G., & Gatenby, B. (2014). Microenvironmental acidosis in carcinogenesis and metastases: new strategies in prevention and therapy. *Cancer and Metastasis Reviews*, *33*(4), 1095-1108.



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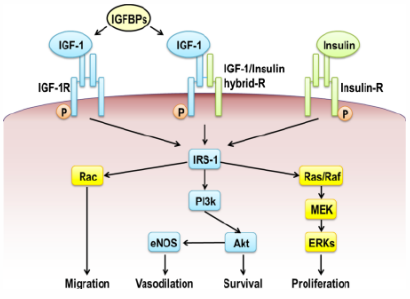
# Chronic Metabolic Acidosis Drives Carcinogenesis Via IGF-1

- Long term consumption of an acidogenic diet increases Insulin-like Growth Factor 1 (IGF-1)




- IGF-1 binding to the insulin receptor has been shown to inhibit apoptosis and increase cellular proliferation
- Elevated IGF-1 has been associated with an increased risk of several cancers

Robey, I. F. (2012). Examining the relationship between diet-induced acidosis and cancer. *Nutrition & metabolism*, *9*(1), 72.



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# Acidosis Indirectly Drives Carcinogenesis Via Endocrine System

Mild metabolic acidosis increases serum cortisol levels; elevated cortisol may then drive to cancer via several mechanisms:

1. **Androgen Metabolism:** Cortisol may stimulate androgen receptors and alter androgen metabolism, stimulating growth of certain cancers.
2. **Tryptophan Metabolism:** Cortisol directly and indirectly enhances the metabolism of tryptophan to kynurenine. Kynurenine promotes tumorigenesis by impairing immune tumour surveillance.
3. **Insulin Resistance:** Cortisol promotes insulin resistance and hyperinsulinaemia. Hyperinsulinaemia increases the risk of cancer development and progression, independent of obesity and diabetes.

Robey, I. F. (2012). Examining the relationship between diet-induced acidosis and cancer. *Nutrition & metabolism*, *9*(1), 72.



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# Chronic Metabolic Acidosis Dangerously Alters Adipokine Profiles

- An acidogenic diet can alter levels of adipokines, elevating leptin and lowering adiponectin
- Elevated leptin may increase cancer incidence
- Leptin enhances cellular proliferation, promotes angiogenesis, inhibits apoptosis, enhances cellular migration and increases oestrogen biosynthesis
- Adiponectin is protective against cancer development, impairing proliferation by binding growth factors
- Low adiponectin levels have bee observed in several cancers

Robey, I. F. (2012). Examining the relationship between diet-induced acidosis and cancer. *Nutrition & metabolism*, *9*(1), 72.



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# Acidosis-Induced RANK/NFATc1 Activation Drives Carcinogenesis

- Acidosis triggers osteoclast activation and bone resorption in order to liberate buffering minerals
- This involves stimulation by Receptor Activator of NF-κB Ligand (RANKL) and Nuclear Factor of Activated T-cells 1 (NFATc1)
- These proteins are involved in several mitogenic pathways
- Chronic activation of RANK/NFATc1 due to Chronic Metabolic Acidosis could contribute to cancer risk

Robey, I. F. (2012). Examining the relationship between diet-induced acidosis and cancer. *Nutrition & metabolism*, *9*(1), 72.



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# Official Guidelines Recommend an Alkaline Diet for Cancer Prevention

- A diet low in fruit and vegetables and high in red meat, processed foods, refined grains and soft drinks (i.e. an acidogenic diet) significantly increases the risk of developing cancer, and of dying from that cancer
- Official guidelines from the American Cancer Society recommend a diet that is high in fruit and vegetables, and low in red meat, processed foods, and refined grains and sugars (i.e. an alkaline diet) to reduce the risk of cancer

Kushi, L. H., Doyle, C., McCullough, M., Rock, C. L., Demark-Wahnefried, W., Bandera, E. V., ... & American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee. (2012). American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA: a cancer journal for clinicians*, *62*(1), 30-67.



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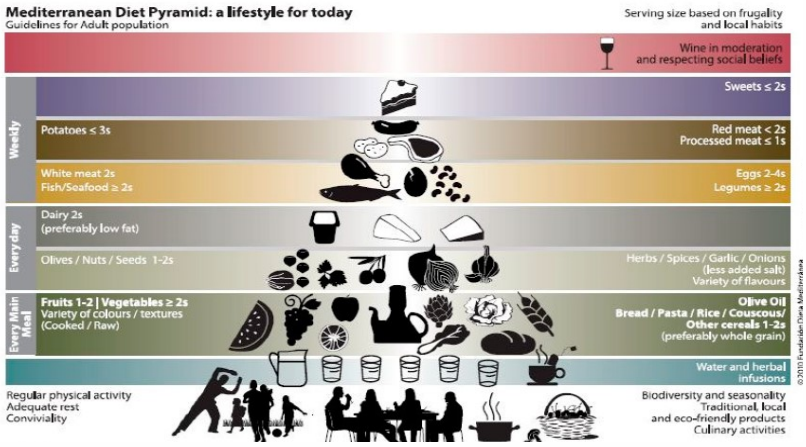
# Mediterranean Diet is Alkaline




Chauveau, P., et al. (2018). Mediterranean diet as the diet of choice for patients with CKD. *Neph Dialysis Transplantt 33*(5), 725-735.
Huang, X., et al. (2013). Mediterranean diet, kidney function, and mortality in men with CKD. *Clin J Am Soc Neph. 8*(9), 1548-1555.



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# Mediterranean Diet Reduces Risk of Developing Cancer

UICC global cancer control
IJC International Journal of Cancer

**Adherence to Mediterranean diet and risk of cancer: A systematic review and meta-analysis of observational studies**

Lukas Schwingshackl and Georg Hoffmann

Department of Nutritional Sciences, Faculty of Life Sciences, University of Vienna, Vienna, Austria

*"Following a Mediterranean Diet significantly reduces the risk of developing or dying from cancer."*

The aim of this research study risk, and different cancer type EMBASE until January 10, 201 pooled using a random effect including 1,368,736 subjects and 12 case–control studies with 62,725 subjects met the objectives and were enclosed for meta-analyses. The highest adherence to MD category resulted in a significantly risk reduction for overall cancer mortality/incidence (cohort; RR: 0.90, 95% CI 0.86–0.95, $p < 0.0001$; $I^2 = 55\%$), colorectal (cohort/case–control; RR: 0.86, 95% CI 0.80–0.93, $p < 0.0001$; $I^2 = 62\%$), prostate (cohort/case–control; RR: 0.96, 95% CI 0.92–0.99, $p = 0.03$; $I^2 = 0\%$) and aerodigestive cancer (cohort/case–control; RR: 0.44, 95% CI 0.26–0.77, $p = 0.003$; $I^2 = 83\%$). Nonsignificant changes could be observed for breast cancer, gastric cancer and pancreatic cancer. The Egger regression tests provided limited evidence of substantial publication bias. High adherence to a MD is associated with a significant reduction in the risk of overall cancer mortality (10%), colorectal cancer (14%), prostate cancer (4%) and aerodigestive cancer (56%).



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# The Optimal Chemo-Preventative Diet

*nutrients*

*Review*

**Cancer and Mediterranean Diet: A Review**

**Maria Chiara Mentella [1,*], Franco Scaldaferri [2], Caterina Ricci [3], Antonio Gasb and Giacinto Abele Donato Miggiano [1]**

1 UOC di Nutrizione Clinica, Area Me
Scienze Gastroenterologiche, Endocr
Universitario A. Gemelli IRCCS, Uni
2 UOC di Medicina Interna e Gastroen
Medica, Dipartimento di Scienze Gas
Fondazione Policlinico Universitario
00168 Rome, Italy
3 UOC di Ginecologia Oncologica, Are
del Bambino e di Sanità Pubblica, Fo
Università Cattolica del Sacro Cuore,
* Correspondence: mariachiara.mente

Received: 24 July 2019; Accepted: 29 Au

> *"The regular consumption of fruits and vegetables with a low intake of meat, and a moderate intake of alcohol may be considered an optimal combination in the prevention of cancer."*

**Abstract:** The Mediterranean diet is considered one of the most worldwide healthy dietary patterns thanks to a combination of foods rich mainly in antioxidants and anti-inflammatory nutrients. Many studies have demonstrated a strong and inverse relationship between a high level of Mediterranean diet adherence and some chronic diseases (such as cardiovascular diseases, diabetes, etc.) and cancer. Given its protective effects in reducing oxidative and inflammatory processes of cells and avoiding DNA damages, cell proliferation, and their survival, angiogenesis, inflammations and metastasis, the Mediterranean diet is considered a powerful and manageable method to fight cancer incidence. The aim of this narrative review was to determine the magnitude of interaction between the Mediterranean diet and more widespread types of cancer so as to give a first and useful overview on this relationship identifying, with a nutritional approach, those nutrients of Mediterranean diet able to reduce cancer incidence.

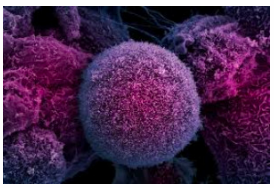
**Keywords:** Mediterranean diet; cancer incidence; cancer



# Alkalisation May Slow Cancer Progression & Support Treatment

Animal studies show that oral alkalising supplementation can:

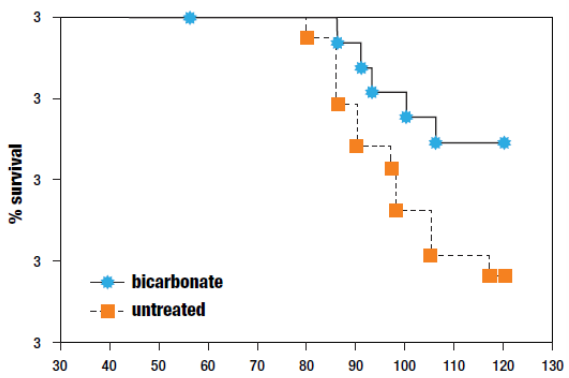
- Increase the extracellular pH around tumours, without significantly altering blood pH
- Delay the transition of cancer from *in situ* to invasive
- Hamper development of metastases
- Increase the efficacy of certain chemotherapy agents
- Improve the anti-tumour effects of immunotherapy



Corbet, C., & Feron, O. (2017). Tumour acidosis: from the passenger to the driver's seat. *Nature reviews. Cancer*, *17*(10), 577-593.

Fais, S., Venturi, G., & Gatenby, B. (2014). Microenvironmental acidosis in carcinogenesis and metastases: new strategies in prevention and therapy. *Cancer and Metastasis Reviews*, *33*(4), 1095-1108.

# Alkalising Treatment Improves Survival in Rodent Model of Breast Cancer




Robey, IF & Martin, NK (2011) Bicarbonate and dichloroacetate: evaluating pH altering therapies in a mouse model for metastatic breast cancer. *BMC cancer*, *11*(1), 235.



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# Alkalising Therapy Inhibits Tumour Progression

*"Oral alkalising mineral therapy prevented the progression of in situ tumours to invasive cancer in this mouse model."*

Published in final edited form as:
*J Urol*. 2012 August ; 188(2): 624–631. doi:10.1016/j.juro.2012.03.113.

**Systemic Buffers Inhibit Carcinogenesis in TRAMP Mice**

**Arig Ibrahim-Hashim**, **Heather H. Cornnell**, **Dominique Abrahams**[*], **Mark Lloyd**, **Marilyn Bui**[†], **Robert J. Gillies**[‡], and **Robert A. Gatenby**[§]
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**Abstract**

**Purpose**—Hypoxia and acidosis develop in in situ tumors as cellular expansion increases the diffusion distance of substrates and metabolites from blood vessels deep to the basement membrane. Prior studies of breast and cervical cancer revealed that cellular adaptation to microenvironmental hypoxia and acidosis is associated with the transition from in situ to invasive cancer. We hypothesized that decreased acidosis in intraductal tumors would alter environmental selection pressures for acid adapted phenotypes and delay or prevent evolution to invasive cancer.

**Materials and Methods**—A total of 37 C57BL/6 TRAMP mice were randomized to a control group or to 1 of 4 treatment groups. In the latter groups 200 mM sodium bicarbonate were added to drinking water starting between ages 4 and 10 weeks.

**Results**—In all 18 controls prostate cancer developed that was visible on 3-dimensional ultrasound at a mean age of 13 weeks. They died within 52 weeks (median 37). When sodium bicarbonate therapy commenced before age 6 weeks in 10 mice, all reached senescence (age 76 weeks) without radiographic evidence of prostate cancer. Histological sections of the prostates in this cohort showed hyperplasia but no cancer in 70% of mice and minimal well differentiated cancer in the remainder. When therapy commenced after age 6 weeks in 9 mice, prostate cancer development was no different from that in controls.

**Conclusions**—Immunohistochemical staining for carbonic anhydrase 9 in regions of ductal hyperplasia showed increased expression in controls vs the early treatment group. Regional pH perturbation in in situ tumors may be a simple, inexpensive and effective cancer prevention strategy.



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# Alkalising Therapy Inhibits Metastases

Research Article

**Bicarbonate Increases Tumor pH and Inhibits Spontaneous Metastases**

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**Abstract**

**The external pH of solid tumors is acidic as a consequence of increased metabolism of glucose and poor perfusion. Acid pHe has been shown to stimulate tumor cell invasion and metastasis *in vitro* and in cells before tail vein injection *in vivo*. The present study investigates whether inhibition of this tumor acidity will reduce the incidence of *in vivo* metastases. Here, we show that oral $NaHCO_3$ selectively increased the pH of tumors and reduced the formation of spontaneous metastases in mouse models of metastatic breast cancer. This treatment regimen was shown to significantly increase the extracellular pH, but not the intracellular pH, of tumors by $^{31}P$ magnetic resonance spectroscopy and the export of acid from growing tumors by fluorescence microscopy of tumors grown in window chambers. $NaHCO_3$ therapy also reduced the rate of lymph node involvement, yet did not affect the levels of circulating tumor cells, suggesting that reduced organ metastases were not due to increased intravasation. In contrast, $NaHCO_3$ therapy significantly reduced the formation of hepatic metastases following intrasplenic injection, suggesting that it did inhibit extravasation and colonization. In tail vein injections of alternative cancer models, bicarbonate had mixed results, inhibiting the formation of metastases from PC3M prostate cancer cells, but not those of B16 melanoma. Although the mechanism of this therapy is not known with certainty, low pH was shown to increase the release of active cathepsin B, an important matrix remodeling protease.** [Cancer Res 2009;69(6):2260–8]

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effectively reverse pH gradients in tumors and not affect the pHe of normal tissues (14). This was confirmed in the current study using $^{31}P$ magnetic resonance spectroscopy (MRS) and fluorescence ratio imaging of SNARF-1 in a dorsal skin-fold window chamber. Notably, bicarbonate did not affect the systemic pH or the growth rate of primary tumors but had significant effects on the formation of spontaneous metastases. In two of three experiments, $NaHCO_3$ therapy reduced the colonization of lymph nodes, but in no experiment did it significantly affect the levels of circulating tumor cells. The lymphatic results notwithstanding, these results indicate that inhibition of end-organ metastasis did not occur by a reduction of intravasation. In contrast, the formation of liver metastases following intrasplenic injection of MDA-MB-231 cells was significantly reduced, indicating that end-organ colonization of metastatic sites was

*"Oral bicarbonate therapy selectively increased the pH of tumours and reduced the formation of metastases in mouse models of breast cancer."*



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# Alkalising Therapy Improves Efficacy of Some Chemotherapy

- Most chemotherapy agents are either alkaline or acidic
- The acidic extracellular environment around tumours prevents the uptake of alkaline chemotherapy drugs through a phenomenon known as **ion trapping**
- **Ion trapping** reduces the efficacy of the drug
- *In vitro* and *in vivo* studies show that alkalising therapy given alongside alkaline chemotherapeutic drugs enhances their efficacy

Alfarouk, KO, et al. (2015). Resistance to cancer chemotherapy: failure in drug response from ADME to P-gp. *Cancer cell international*, *15*(1), 71.
Wojtkowiak, JW et al. (2011). Drug resistance & cellular adaptation to tumor acidic pH microenvironment. *Molecular pharma*, *8*(6), 2032-2038.



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# ….but Reduces Efficacy of Other Chemotherapy Drugs

- Most chemotherapy agents are either alkaline or acidic
- The acidic microenvironment enhances the uptake and cytotoxicity of acidic chemotherapeutic drugs
- Alkalising therapy reduces the efficacy of these acidic chemotherapeutics by reducing their uptake and cytotoxicity
- Thus it is important to know and understand a patient's chemotherapy regime when considering alkalising supplements

Alfarouk, KO, et al. (2015). Resistance to cancer chemotherapy: failure in drug response from ADME to P-gp. *Cancer cell international*, *15*(1), 71.
Wojtkowiak, JW et al. (2011). Drug resistance & cellular adaptation to tumor acidic pH microenvironment. *Molecular pharma*, *8*(6), 2032-2038.



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# Which Chemotherapeutic Agents are Alkaline and Which are Alkaline

| Drugs | pKa | Ionization behavior |
|---|---|---|
| Daunorubicin | 8.3 | Weak base |
| Doxorubicin | 8.3 | Weak base |
| Mitoxantrone | 8.3 | Weak base |
| Paclitaxel | Zwitterion | |
| 5-Fluorouracil | 7.76* | Weak acid |
| Cyclophosphamide | 6.0 | Weak acid |
| Chlorambucil | 5.8 | Weak acid |
| Cisplatin | 5.06 | Weak acid |

Alfarouk, K. O., Stock, C. M., Taylor, S., Walsh, M., Muddathir, A. K., Verduzco, D., ... & Reshkin, S. J. (2015). Resistance to cancer chemotherapy: failure in drug response from ADME to P-gp. *Cancer cell international*, *15*(1), 71.



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# Section 4: Clinical Strategies



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## Summary: What the Evidence Shows

- ✓That tumours cause acidity in their micro-environment, and that this promotes cancer growth and metastases
- ✓That acidogenic diets are associated with an increased cancer risk while alkaline diets are associated with a reduced cancer risk
- ✓That diet-induced acidosis is a potential upstream and indirect trigger in a multifactorial cascade of molecular events associated with carcinogenesis
- ✓That alkalising buffer therapy raises extracellular tumour pH and reduces or delays cancer invasion and metastases in experimental models



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## What the Evidence Does NOT Show

- X That an acidogenic diet directly causes cancer, in isolation from other factors
- X That eating an alkaline diet alone can cure cancer
- X That drinking alkaline water can cure cancer
- X That taking large doses of alkalising substances such as sodium bicarbonate can cure cancer
- X That drinking large quantities of alkalising vegetable juices can cure cancer

Robey, I. F. (2012). Examining the relationship between diet-induced acidosis and cancer. *Nutrition & metabolism*, *9*(1), 72
Fenton, T. R., & Huang, T. (2016). Systematic review of the association between dietary acid load, alkaline water and cancer. *BMJ open*, *6*(6).



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## Assessing Acid-Base Balance

- Assessing the acid-base status of patients can be done easily in clinic, especially if your patients have recent blood tests
- There are three main assessment methods:
  1. **Urinary analysis**
  2. **Serum bicarbonate analysis**
  3. **Serum anion gap analysis**
- These can be used together or singularly
- Each assessment method reflects slightly different aspects of acid-base balance in the body, but acidic results in any one of these tests indicates Chronic Metabolic Acidosis



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# How Severe is Their Acidosis?

| Level of acidity | Assessment Method | Result |
|---|---|---|
| OPTIMAL | Urinary pH<br>Serum bicarbonate<br>Serum anion gap | 6.8 - 7.2<br>26 - 27 mmol/L<br>9 - 10 mEq/L |
| MILD CMMA | Urinary pH<br>Serum bicarbonate<br>Serum anion gap | 6.5 - 6.7<br>24 - 25 mmol/L<br>11 - 12 mEq/L |
| MODERATE CMMA | Urinary pH<br>Serum bicarbonate<br>Serum anion gap | 6.0 - 6.4<br>23 - 24 mmol/L<br>13 - 14 mEq/L |
| SEVERE CMMA | Urinary pH<br>Serum bicarbonate<br>Serum anion gap | <5.0 - 5.9<br><23 mmol/L<br>>15 mEq/L |



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# Alkaline Diet Recommendations for Chemo-Prevention

- Enjoy a wide variety of fresh fruit and vegetables
- Eat 1-2 serves of fruit per day
- Include 2 or more serves of vegetables with every meal
- Enjoy moderate amounts of eggs and dairy products
- Limit red meat consumption to <2 serves per week
- Limit poultry consumption to <2 serves per week
- Limit salt intake
- Avoid refined grains, processed meats, and soft drinks

Mentella, M. C., Scaldaferri, F., Ricci, C., et al. (2019). Cancer and Mediterranean Diet: A Review. *Nutrients*, *11*(9), 2059.



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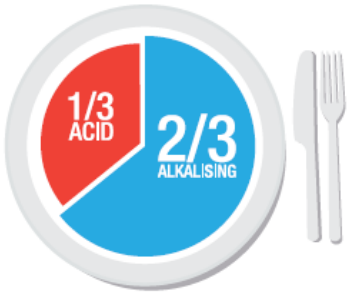
# Balance is the Key to pH Balance

- An acidic food is not a bad choice – many acidic foods are otherwise very healthy, and adequate protein is especially important in cancer sufferers, to reduce the risk of cachexia
- It's all about balance: a greater portion of the total diet should be made up of alkalising vegetables and fruits in order to maintain dietary balance




Arends, J., Bachmann, P., Baracos, V., et al. (2017). ESPEN guidelines on nutrition in cancer patients. *Clinical nutrition*, *36*(1), 11-48.



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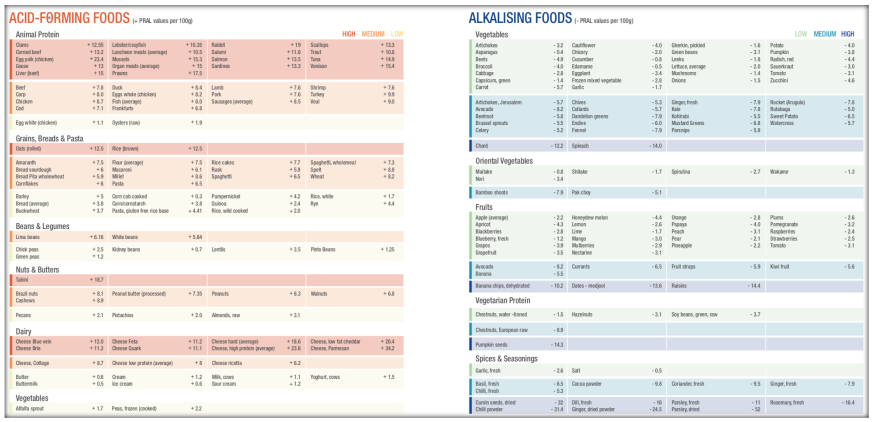
# Educate Patients About Dietary PRAL Values & How to Balance Dietary pH



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# Mineral Citrates Preferable for Alkalisation

- Mineral citrates have been proven to help support healthy pH balance, without disturbing normal digestive processes
- In the digestive tract, citrate dissociates quickly and easily from associated minerals, allowing the free mineral ions and the citrate molecules to be rapidly absorbed into the blood stream
- Once absorbed citrate molecules consume acidic hydrogen ions (H+)
- These are then converted to water and carbon dioxide for easy excretion



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# Mineral Citrates Superior to Bicarbonates for Alkalisation

**Citrates**
- No influence on gastric pH
- Excellent absorption of minerals

**Bicarbonates**
- Neutralisation of gastric acid
- $CO_2$ formation in stomach causes discomfort




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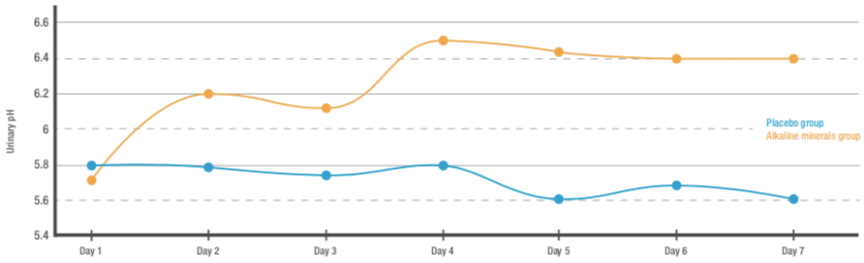
# Alkalising Mineral Citrates Proven to Support Acid-Base Balance

- 25 healthy subjects who took 1 serve of **Alkalising Mineral Citrates** every morning for 1 week, and then measured their urinary pH
- Results showed that supplementation with **Alkalising Mineral Citrates** was associated with a significant increase in urinary pH

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# Dosing of Alkalising Mineral Citrates Based on Severity of Acidosis

| Level of acidity | Assessment Method | Result | Alkalising mineral supplement dose recommended |
|---|---|---|---|
| OPTIMAL | Urinary pH<br>Serum bicarbonate<br>Serum anion gap | 6.8 - 7.2<br>26 - 27 mmol/L<br>9 - 10 mEq/L | Optimal level may be maintained with diet |
| MILD CMMA | Urinary pH<br>Serum bicarbonate<br>Serum anion gap | 6.5 - 6.7<br>24 - 25 mmol/L<br>11 - 12 mEq/L | Delivering 25-50 mEq daily of alkalisation |
| MODERATE CMMA | Urinary pH<br>Serum bicarbonate<br>Serum anion gap | 6.0 - 6.4<br>23 - 24 mmol/L<br>13 - 14 mEq/L | Delivering 50-100 mEq daily of alkalisation |
| SEVERE CMMA | Urinary pH<br>Serum bicarbonate<br>Serum anion gap | <5.0 - 5.9<br><23 mmol/L<br>>15 mEq/L | Delivering 100+ mEq daily of alkalisation |

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# Safety Considerations When Prescribing Alkalising Minerals

- Caution is advised when prescribing alkalising minerals to patients with serious heart, pulmonary or kidney disease, and patients who are on medication for these conditions
- Caution is advised when prescribing alkalising minerals alongside chemotherapeutic drugs, particularly acidic chemotherapeutics – always consult with the patient's oncologist when prescribing any supplements
- High doses of sodium bicarbonate can cause gastrointestinal upset, precipitate SIBO, and may trigger metabolic alkalosis

Pizzorno, J., Frassetto, L. A., & Katzinger, J. (2010). Diet-induced acidosis: is it real and clinically relevant?. *British journal of nutrition*, *103*(8), 1185-1194.
Wojtkowiak, J. W., Verduzco, D., Schramm, K. J., & Gillies, R. J. (2011). Drug resistance and cellular adaptation to tumor acidic pH microenvironment. *Molecular pharmaceutics*, *8*(6), 2032-2038.
Robey, I. F., Lopez, A. M., & Roe, D. J. (2015). Safety and tolerability of long-term sodium bicarbonate consumption in cancer care. *Journal of Integrative Oncology*, *4*(1), 1-8.



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# THANKS FOR LISTENING



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