Nutrition in cancer care: an oncologist's perspective

Developments in the prevention and treatment of disease with plant-based nutrition

Medical conference- Athens, Greece 2023

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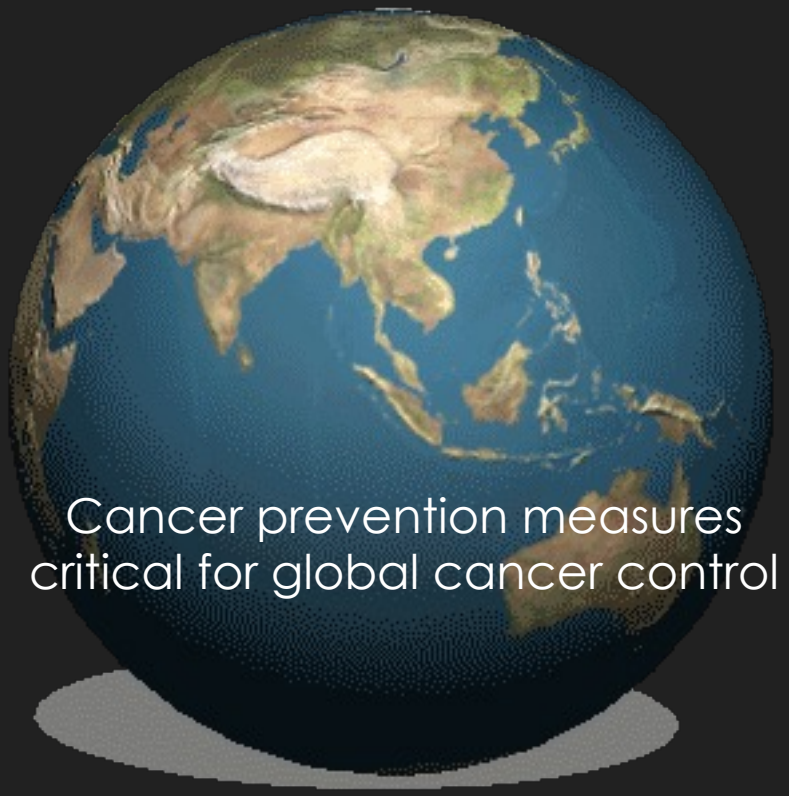
Global cancer burden

- Global cancer burden expected to be 28.4 million by 2040 (47% inc from 2020)
- Larger increase in transitioning countries due to globalization and growing economies
- 2nd leading cause of mortality after CVD (leading cause of premature death in 57 countries) ***Bray et al. Cancer 2021***



Cancer prevention measures critical for global cancer control

Global cancer statistics 2020 ***(Sung et al. CA Cancer J Clin 2021)***

Why does an oncologist care about diet?

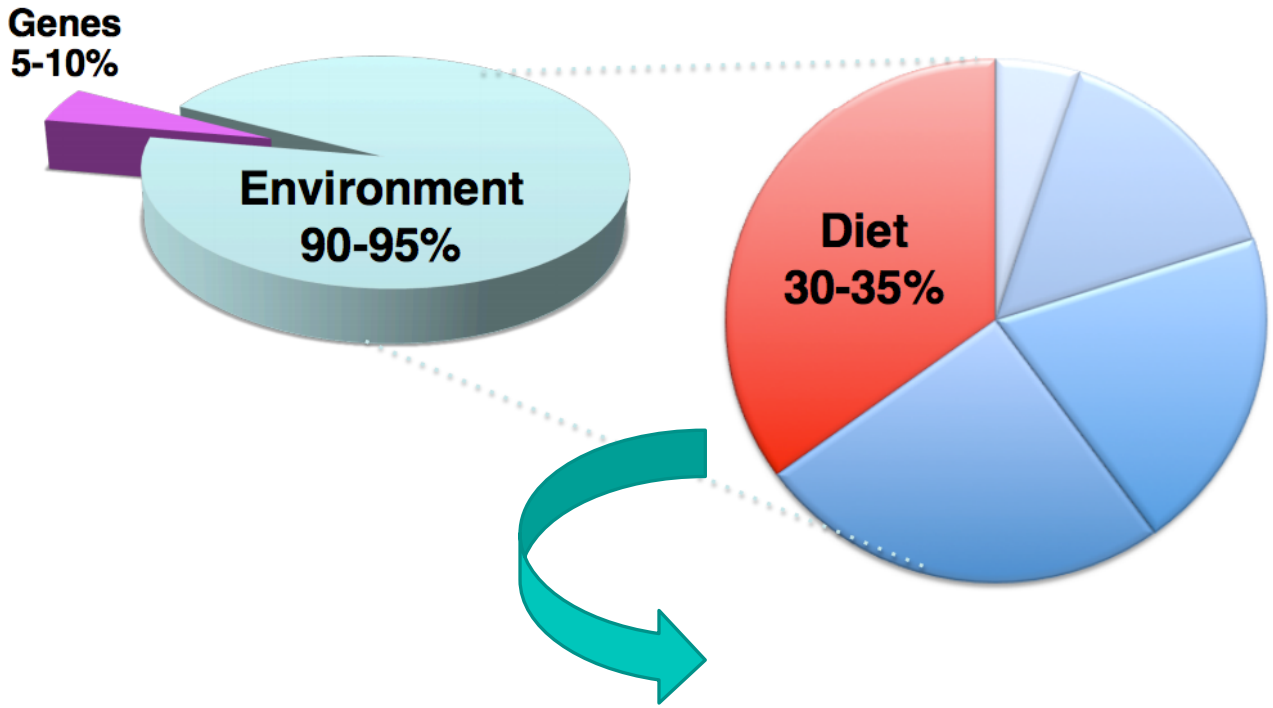
1. Affects on cancer recurrence, treatment tolerance, maximizing well being

2. Reducing the global burden of cancer and other chronic (NCD)

3. Preserving planetary health and reduce suffering of all living beings

Why nutrition and diet?

Examining the Causes of Cancer



Inflammation – Epigenetics – Microbiome-Metabolic-carcinogens/genotoxics

Objectives

1

Review current recommendations from WCRF/AICR for cancer prevention/risk reduction

2

Outline key biological mechanisms linking dietary patterns to carcinogenesis and benefits of PBD (Breast; colon; prostate; lung)

3

Review the dietary patterns used during cancer treatments and how they may affect patient outcomes

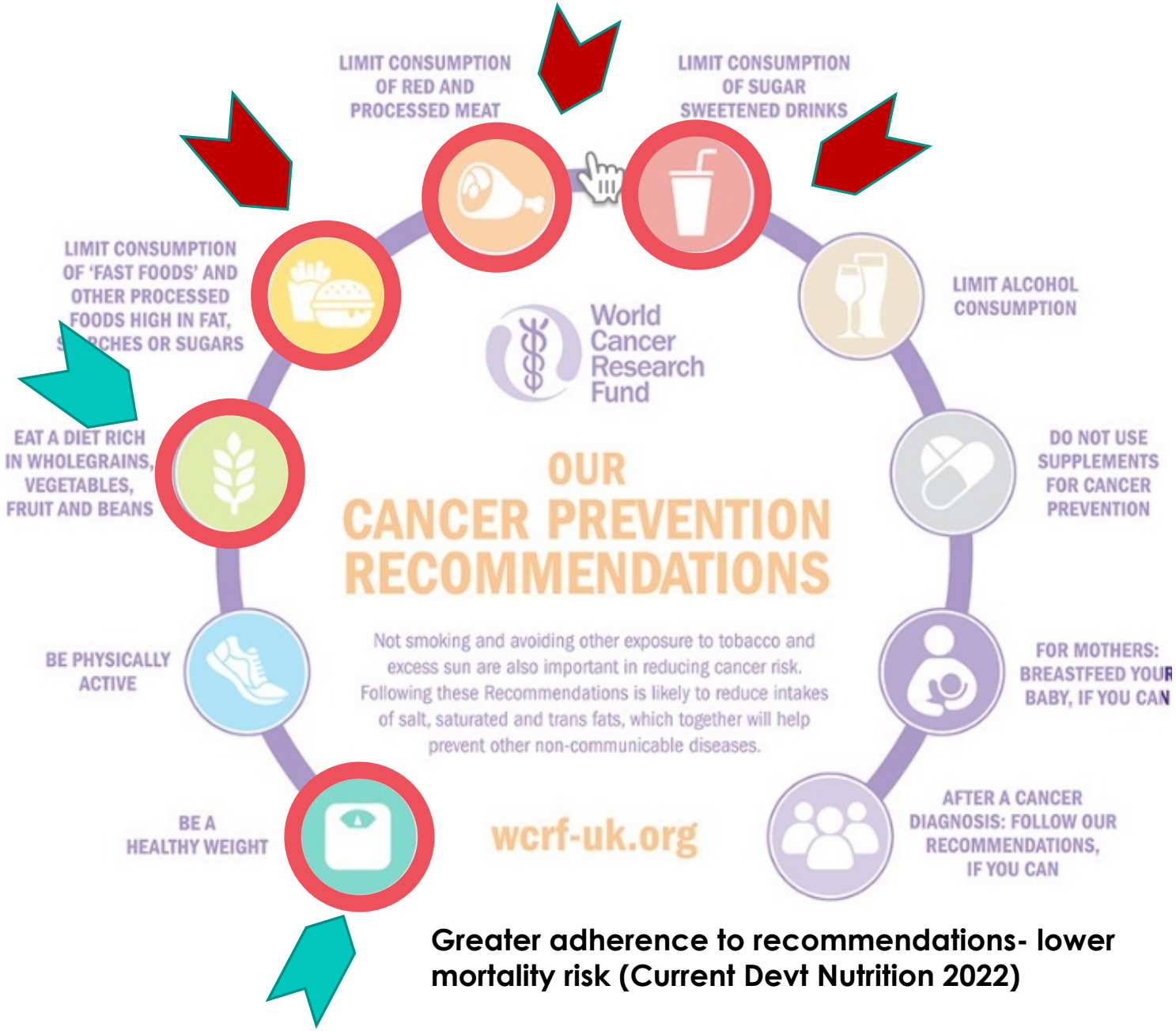
AICR/WCRF 3rd expert report 2018

10 key recommendations to reduce cancer risk

AICR/WCRF 3rd expert report 2018

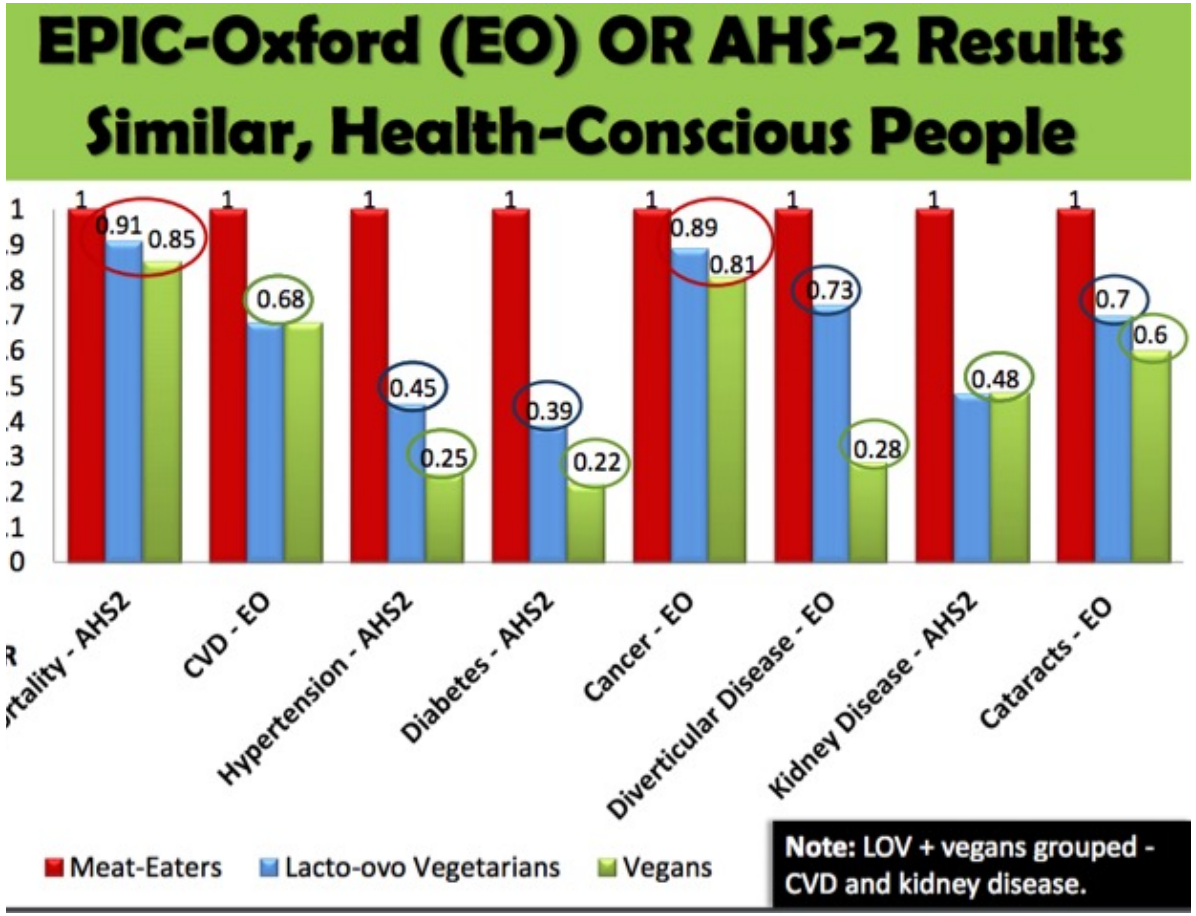
(Dietandcancerreport.org)

10 key recommendations to reduce cancer risk



Greater adherence to recommendations- lower mortality risk (Current Devt Nutrition 2022)

- Largest prospective cohort studies (EPIC-oxford studies and Adventist Health studies)
- Health-conscious populations (diff in dietary patterns)
- Diet impacts Cancer incidence and other chronic diseases



Global cancer map 2016

- Rates for common cancers 6x higher in western countries
- Migration studies (breast, colon, prostate cancer) support this association- immigrants shown to acquire risk of adopted country w/n 1-2 generations
- Environmental/lifestyle/dietary factors play a major role

Key biological mechanisms: diet and cancer

- **Inflammation**- precursor to many chronic diseases processes including cancer
- **Direct DNA damage-** carcinogens eg nitroso-cpds and PAH/HCA in meat (naturally occurring and in cooking)
- **Metabolic dysfunction: Growth factor and hormonal stimulation** eg androgens, estrogens and IGF-1
- **Epigenetic effects**- influences expression of genes including oncogenes "turn genes off or on"
- **Microbiome alterations**- composition of gut microbes influences carcinogenesis, immune system function and inflammation.

Specific components of meat vs WFPB diets on cancer development

1. Carcinogenesis related to meat consumption

Carcinogens eg PCA/HCAs released in cooking process and in preserving process (nitrates/nitrites)

Secondary bile acids- N-nitrosamine cpds produced from carnitine and choline (meat, dairy, eggs)

Endotoxins in meat, Viruses in chicken flesh, bacterial pathogens altering microbiome and causing inflammation

Growth hormones IGF-1 (insulin like growth factor) potent stimulus cancer growth

Red meat derived glycate promotes inflammation (**Neu5GC)**

Saturated fat and **cholesterol**- hormonal effects

Haem iron- oxidation of iron leads to DNA damage via free radicals

Choline- production of TMAO in liver (TMAO assoc with CV disease and higher levels in blood assoc with rectal and prostate cancer)

Bovine sex steroids: androgens and estrogens from milk of pregnant cows- activates cancer cell signaling pathway (mTOR) promoting cell proliferation and growth and inhibits cell death

2. Protective mechanism of PB diets

Fiber (only found in plant cell wall): feed gut microbiome, produce protective SCFAs and remove carcinogens from the colon, bind oestrogens

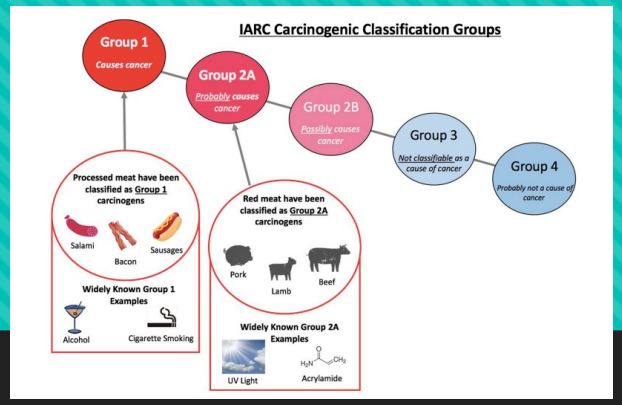
Contain **phytochemicals** with anti-oxidant, anti-inflammatory and anti-angiogenic potential

Promote **lower body weight** (obesity significant RF)

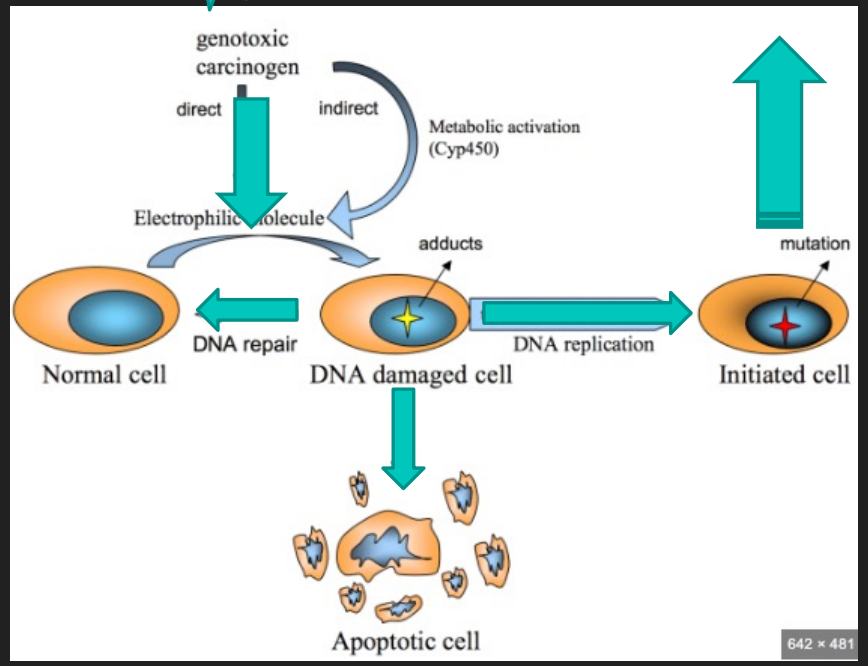
Lower circulating IGF-1 and higher IGF-1BP (growth promoting hormones)

Absence of carcinogen promoting effects of meat and animal products

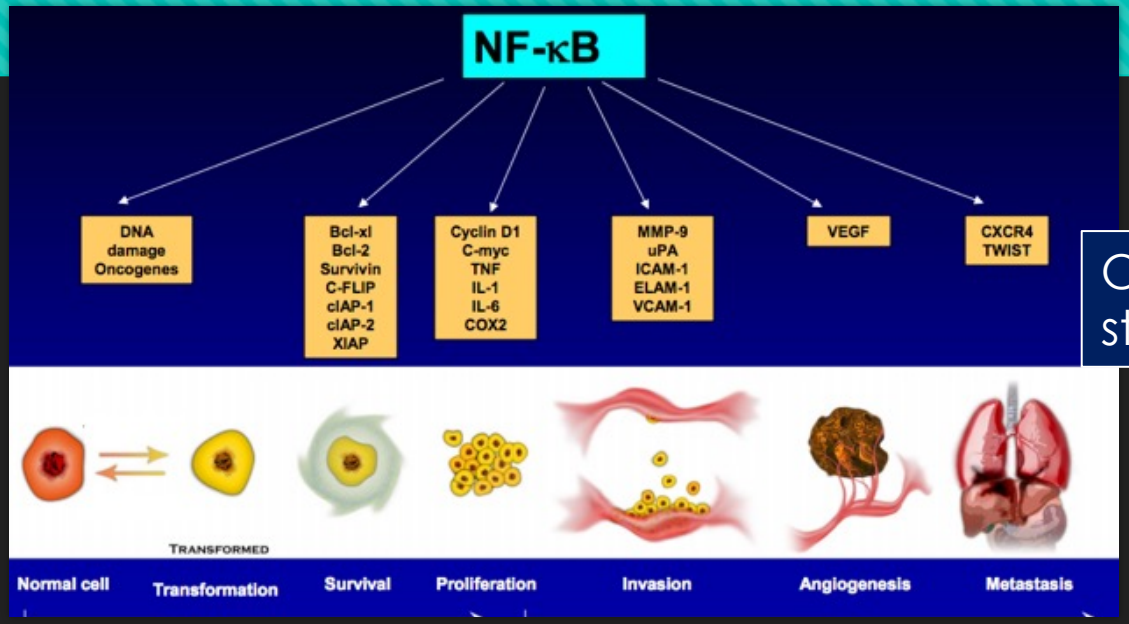
Carcinogens in foods



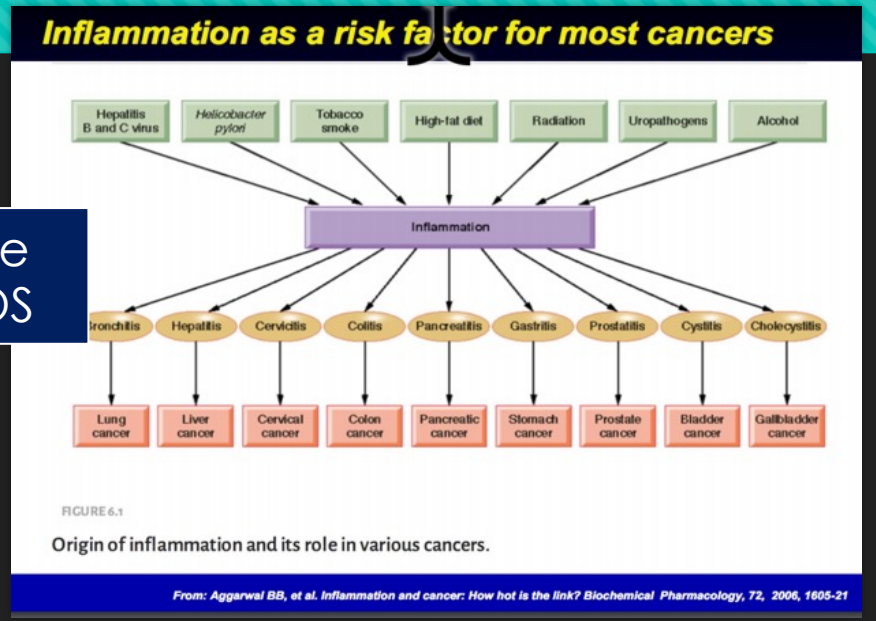
- **World health Organization (WHO)**
  - **Processed meat** carcinogenic (group 1) **Red meat** probably carcinogenic (group 2A) for CRC
  - Meta-analysis over 1000 studies across 8 countries (IARC working group report) **(*Bouvard et al. Lancet Oncology 2015*)**
    - Also stomach, pancreatic and prostate cancers
  - Increase risk pre-menopausal breast ca with most childhood consumption **(*Int J Cancer 2018*)**
  - Wide variety of carcinogenic molecules (NOC, PAHs, HCA, haem iron, Neu5Gc) **(*Jeyakumar etal. J Gastroenterol 2017*)**



Inflammation, diet and cancer



Oxidative stress-ROS

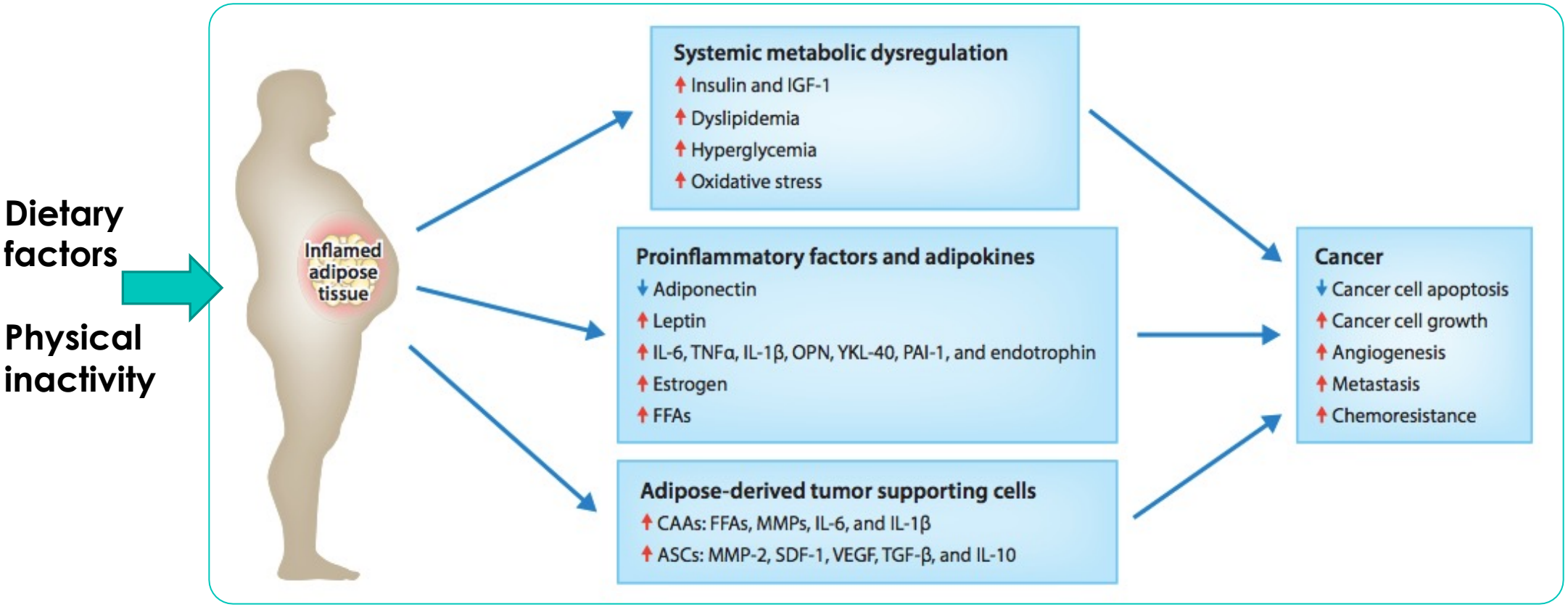


Dietary Inflammatory index (DII): 6 bio-markers
Shivappa et al Public Health Nutr 2014

Saturate fats/red meat
Refined CHOs → MOST Inflammatory

Soy products
Fruit/veg phytochemicals→ LEAST Inflammatory

Inc DII scores independent risk of CRC and breast cancer (meta-analyses) ***Hayati etal.EJCN 2022***

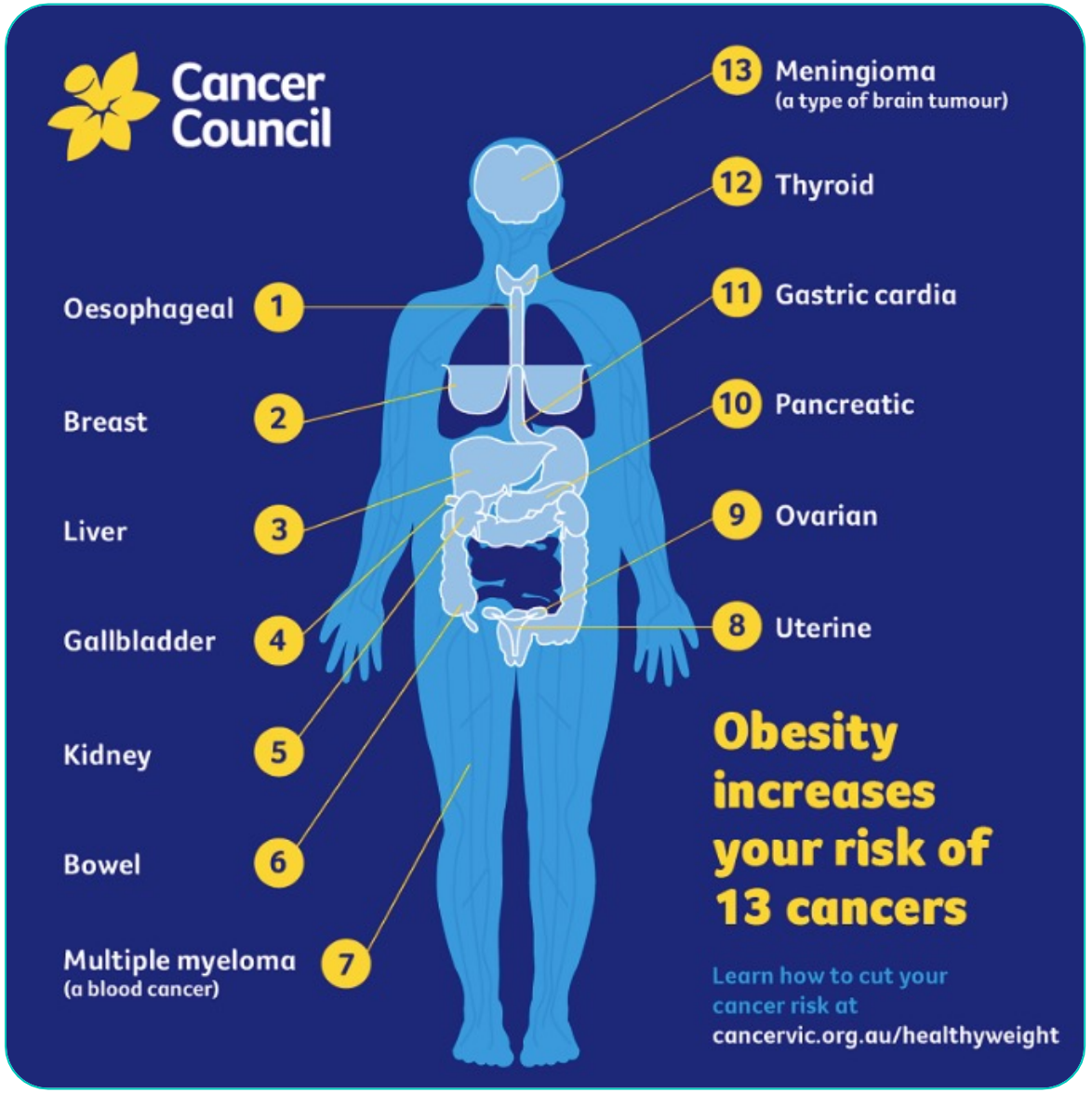


Effect of adipose tissue on carcinogenesis

(Deng et al. Ann Rev Path Mech Dis 2016)

Obesity and cancer risk

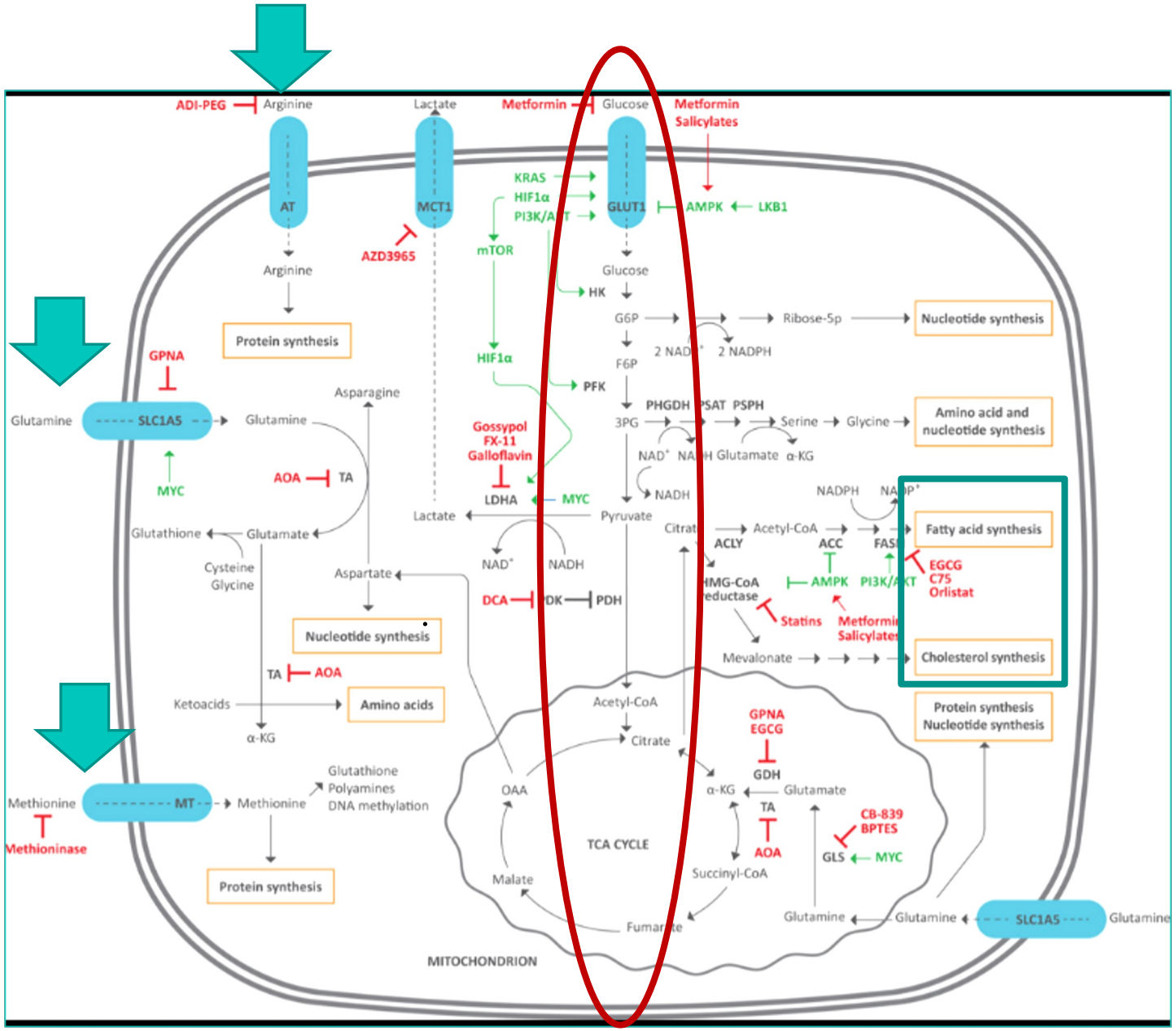
Lauby Secretan et al. Body fatness and cancer IARC working group NEJM 2016

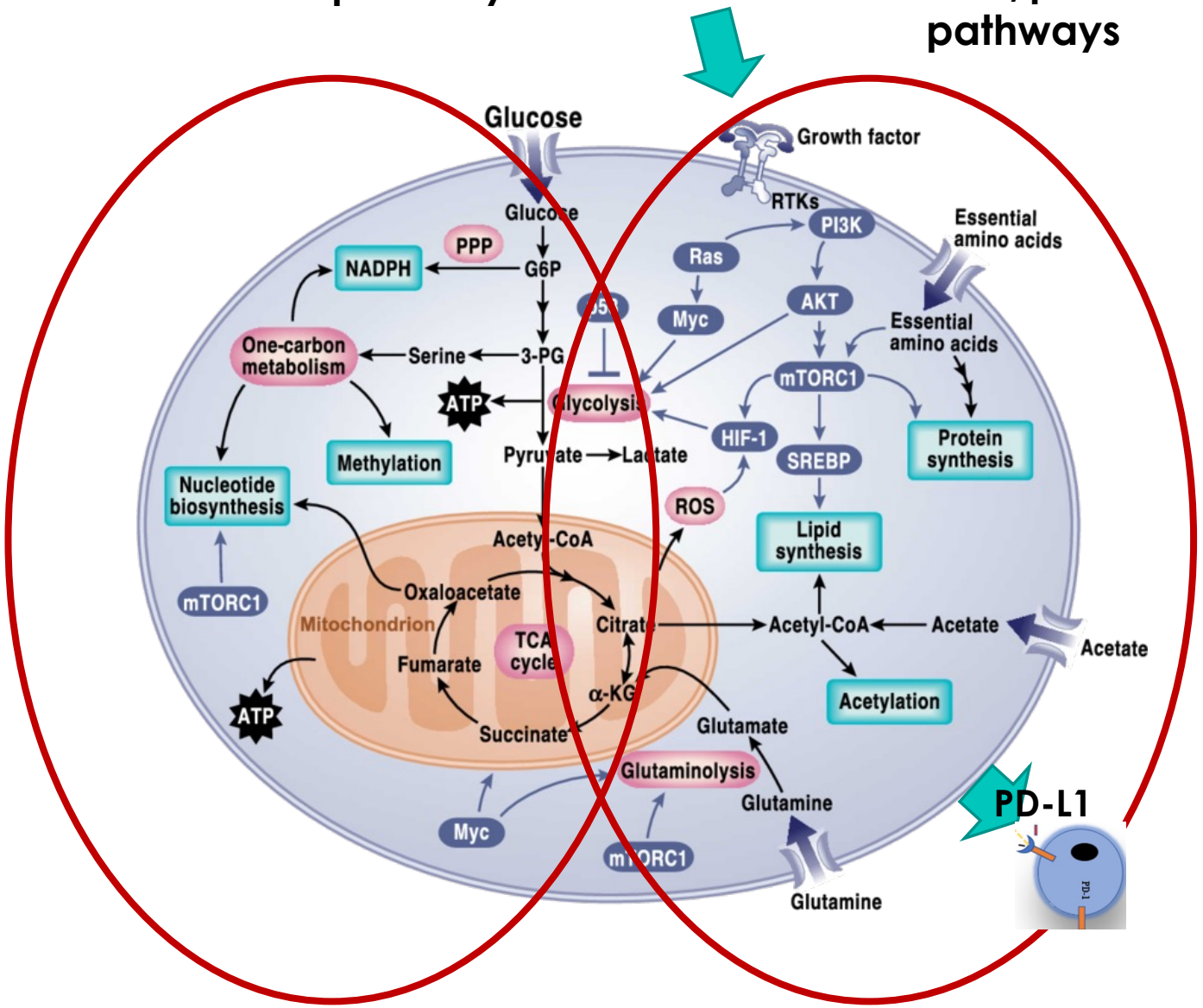


Plant based diets for obesity treatment. Ahmad,S. Frontiers in Nutrition 2022

Key metabolic pathways

- Glucose pathway
- Amino acids
- Lipids
- Cholesterol
- Ketone bodies
- Insulin and IGF-1





Debaradinis R.J Fundamentals of cancer metabolism Science advances 2016

Key proliferative and pro-survival pathways

- PI3K/AKT/mTOR
- RAS/RAF/ERK
- STAT/JAK
- Checkpoint pathway-PD-1 (cancer immune escape)

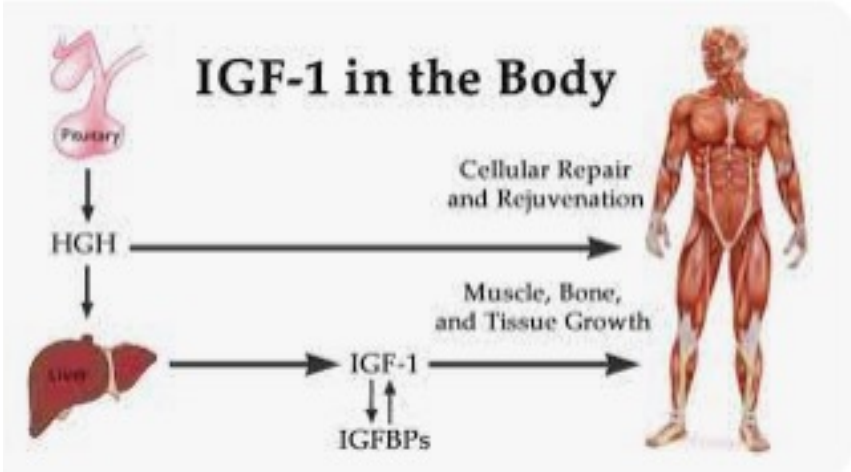
- Growth factor receptors
  - VEGFR
  - PDGFR
  - FGFR
  - EGFR

- IGF-1R

IGF-1 and cancer risk

- GH receptor/IGF-1 deficiencies-low risk age related diseases including cancer, improve longevity
- Protein restriction reduces GHR-IGF1 activity
- High IGF-1 levels linked to various cancers

- 6,381 adults over 50 followed 18y
- Ages 50-65 higher animal protein levels led to
  - 75% inc cancer mortality
  - 4x inc cancer and diabetes mortality
  - 73 fold inc risk diabetes
  - Not seen with plant proteins



NIH Public Access
Author Manuscript
Cell Metab. Author manuscript; available in PMC 2015 March 04.

Published in final edited form as:
Cell Metab. 2014 March 4; 19(3): 407–417. doi:10.1016/j.cmet.2014.02.006.

Low Protein Intake is Associated with a Major Reduction in IGF-1, Cancer, and Overall Mortality in the 65 and Younger but Not Older Population

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Highest intake of polyphenols in diet assoc reduced mortality (Tressera-Rimbau etal. BMC Medicine 2014)

The power of plants

- **Phytochemicals** (bioactive cpds)
  - Anti-inflamm and anit-oxidant (reduce oxidative stress/ROS/DNA damage)
  - 64x anti-oxidant power of animal products
- **Fibre** >30g/d
  - Insulin regulation, carcinogen removal, healthy gut microbiome

frontiers | Frontiers in Public Health

SYSTEMATIC REVIEW
published: 03 June 2022
doi: 10.3389/fpubh.2022.892153

The Relationship Between Plant-Based Diet and Risk of Digestive System Cancers: A Meta-Analysis Based on 3,059,009 Subjects

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Background and Objectives: Diets containing red or processed meat are associated with a growing risk of digestive system cancers. Whether a plant-based diet is protective against cancer needs a high level of statistical evidence.

Methods: We performed a meta-analysis of five English databases, including PubMed, Medline, Embase, Web of Science databases, and Scopus, on October 24, 2021 to identify published papers. Cohort studies or case-control studies that reported a relationship between plant-based diets and cancers of the digestive system were included. Summary effect-size estimates are expressed as Risk ratios (RRs) or Odds ratios (ORs) with 95% confidence intervals and were evaluated using random-effect models. The inconsistency index (I^2) and τ^2 (Tau^2) index were used to quantify the magnitude of heterogeneity derived from the random-effects Mantel-Haenszel model.

Results: The same results were found in cohort (adjusted RR = 0.82, 95% CI: 0.78–0.86, $P < 0.001$, $I^2 = 46.4\%$, $Tau^2 = 0.017$) and case-control (adjusted OR = 0.70, 95% CI: 0.64–0.77, $P < 0.001$, $I^2 = 83.8\%$, $Tau^2 = 0.160$) studies. The overall analysis concluded that plant-based diets played a protective role in the risk of digestive system neoplasms. Subgroup analyses demonstrated that the plant-based diets reduced the risk of cancers, especially pancreatic (adjusted RR = 0.71, 95% CI: 0.59–0.86, $P < 0.001$, $I^2 = 55.1\%$, $Tau^2 = 0.028$), colorectal (adjusted RR = 0.76, 95% CI: 0.69–0.83, $P < 0.001$, $I^2 = 53.4\%$, $Tau^2 = 0.023$), rectal (adjusted RR = 0.84, 95% CI: 0.78–0.91, $P < 0.001$, $I^2 = 1.6\%$, $Tau^2 = 0.005$) and colon (adjusted RR = 0.88, 95% CI: 0.82–0.95, $P < 0.001$, $I^2 = 0.0\%$, $Tau^2 = 0.000$) cancers, in cohort studies. The correlation between vegan and other plant-based diets was compared using Z-tests, and the results showed no difference.

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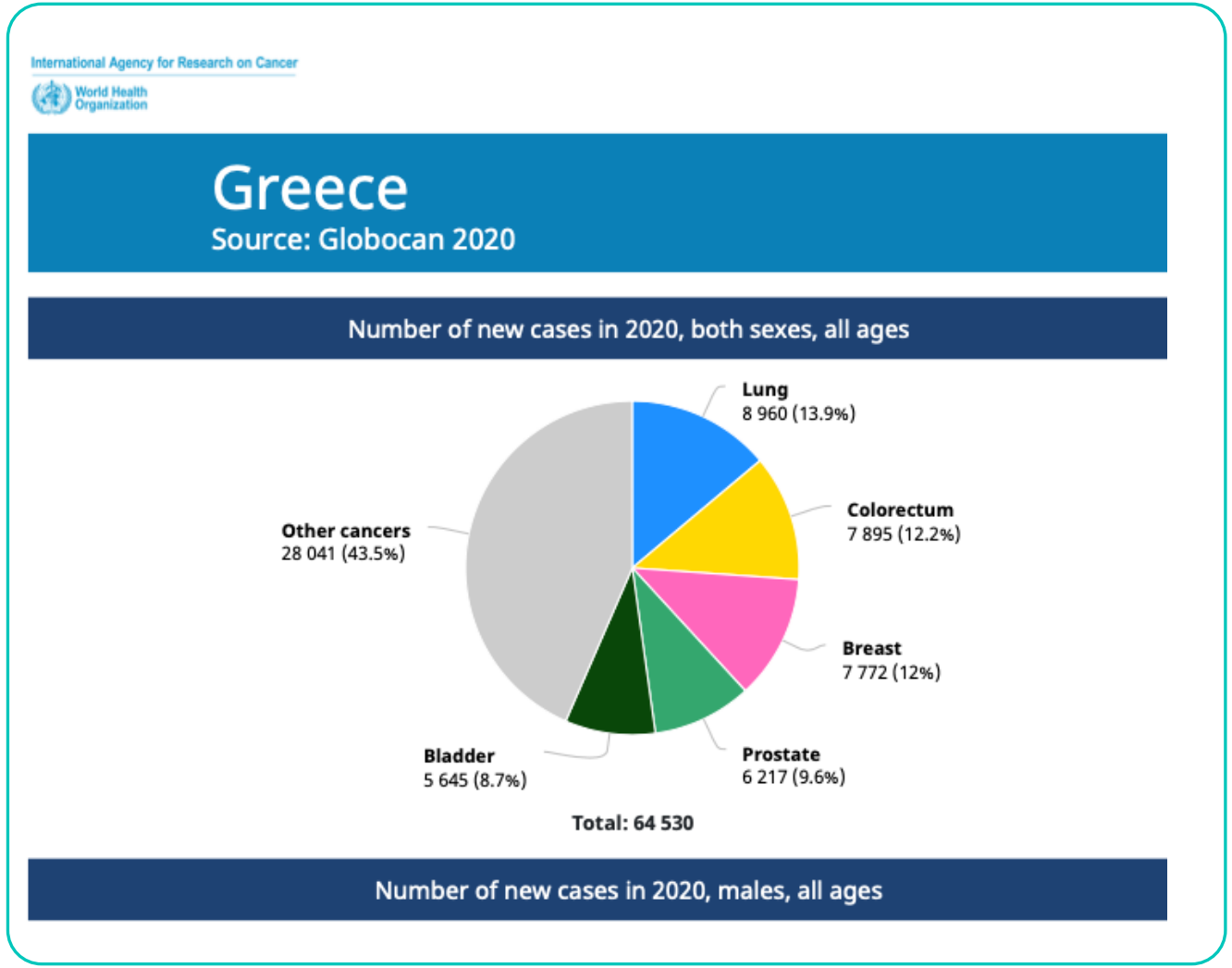
Specialty section:
This article was submitted to Public Health and Nutrition, a section of the journal Frontiers in Public Health

Received: 08 March 2022
Accepted: 09 May 2022
Published: 03 June 2022

Plant based diets and GI cancers

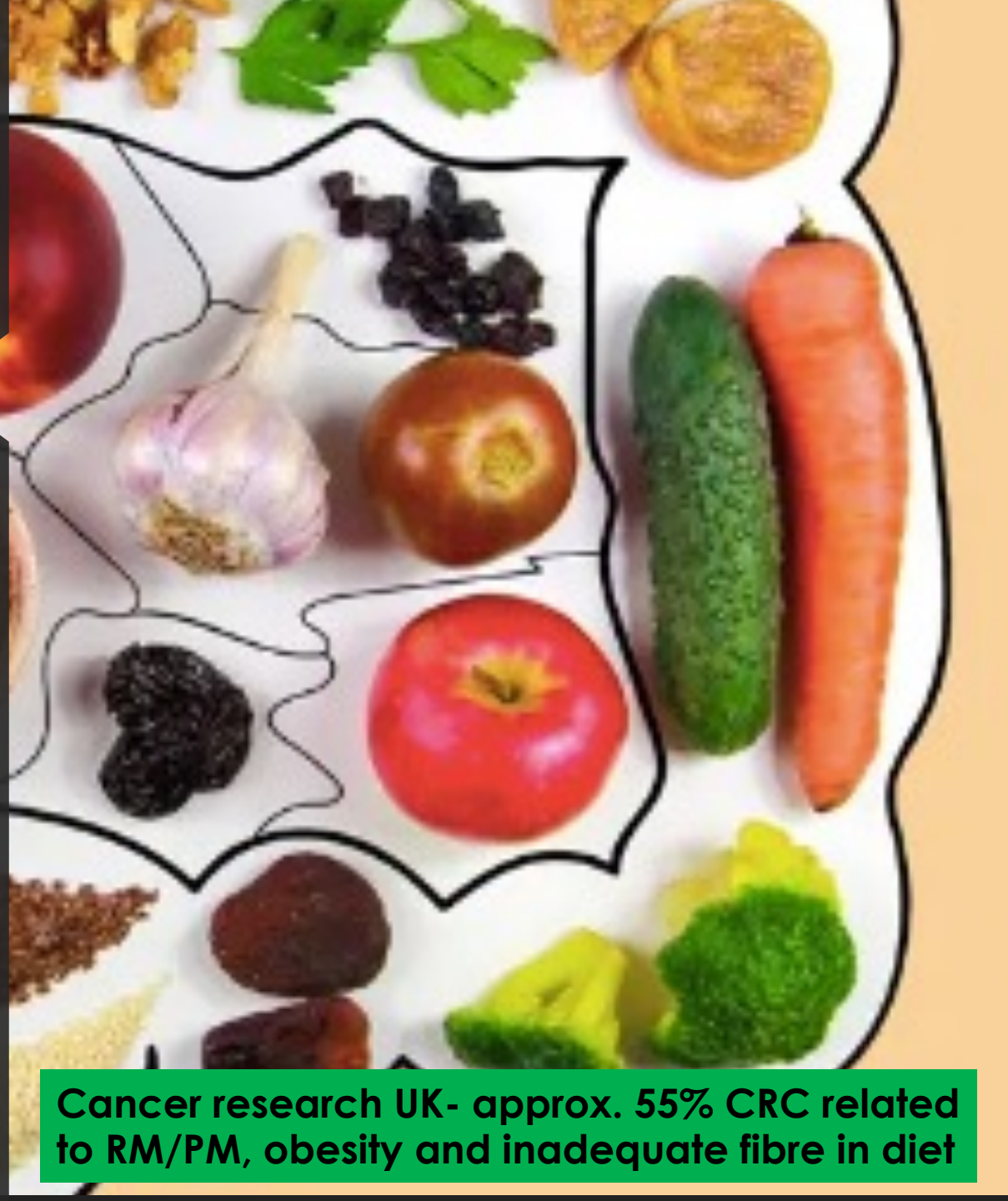
- Included vegan and mostly plant-based diets eg. Mediterranean and DASH/prudent diets
- 34,000 GI tract cancers diagnosed- PB Diets reduced risk of cancers of digestive system (oesophageal, gastric, colo-rectal and biliary)
- PB diets play a protective role in digestive tract cancers irrespective of type (12-29%)

- Dietary factors influencing incidence and recurrence of commonest cancers
  - Colo-rectal
  - Breast
  - Prostate
  - Lung



Colo-rectal cancer

- Globally increase in CRC by 60% by 2030
- 3rd leading cause of cancer diagnoses,4th leading cause cancer death
- **Incidence:**
  - Processed and red meat- inc risk (WHO class I/II carcinogens) processed meats assoc with reduced DFS ***(Zhu; BMJ Open 2013)***
  - Legumes (beans, peas, lentils)-most legumes esp soy bens lowest risk of CRC ***(Medicine 2018; Zhu; Science reports 2015)***
  - *Every 10g fibre inc in diet reduced risk CRC 10% (**Plos 2012**) esp wholegrains* ***(Hullings; AmJ Clin Nutrition 2020)***
- **Recurrence/survival:**
- Nut intake (>2 serves/wk tree) dec CRC recurrence (42%) improved survival (57%) stage III CRC ***(Fedelu; JCO 2018)***
- High Fibre (wholegrains) lower CRC specific mortality ***(Song: JAMA Oncol 2018)***



Cancer research UK- approx. 55% CRC related to RM/PM, obesity and inadequate fibre in diet

Breast cancer

- **Commonest cancer in Greek women (1 in 8; 80% E2+)**
- **Incidence:**
  - Obesity 1.5-2x (inc all cause and BC mortality)
  - Diabetes/hyperinsulinaemia (16%)
  - ETOH (2-3 SD day 14-20%)
  - Saturated fat (20-28%)(***EPIC-oxford JNCI 2014)***
  - Red and PM in early adulthood; swapping out for legumes dec risk ***(Farvid; BMJ 2014)***
  - Dairy milk ***(Fraser; Int J Epidemiol 2020)***
- **EPIC study update (Nutrients 2021;41 studies)**
  - Low consumption fruit/veg higher risk (HR 1.76)
  - Higher intake dietary fibre and leafy veg – lower risk (HR 0.75-0.90)
- MediDiet – higher adherence protective effect PM BC **(*Clinical nutrition Umbrella review 2023)***
- **Recurrence:**
  - Excess body fat and wt gain after diagnosis inc recurrence, 2nd primary and mortality ***(Cochrane database systemic review 2020)***
  - Low fat dietary intervention(<20%) reduced death after BC in PMW (***WINS RCT study-JCO 2017)***

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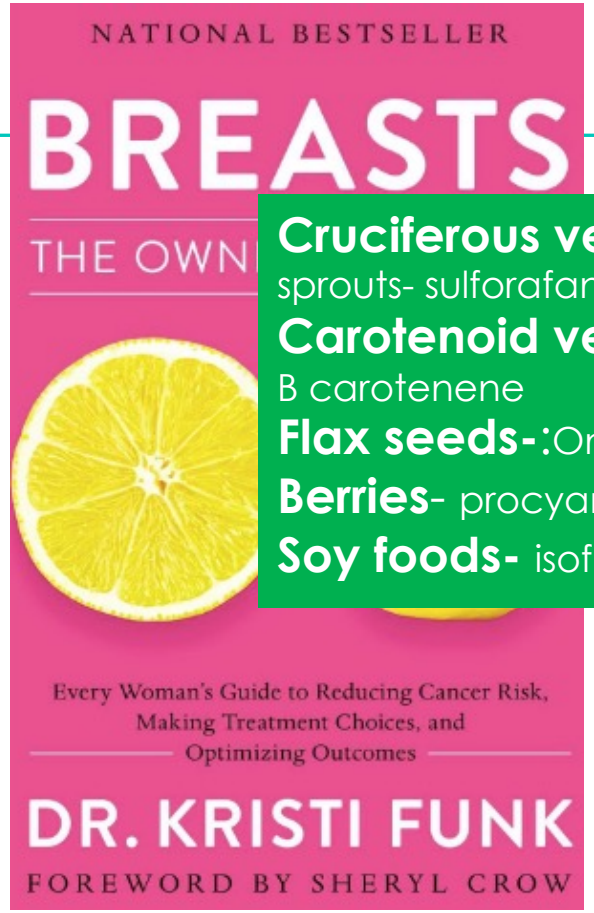
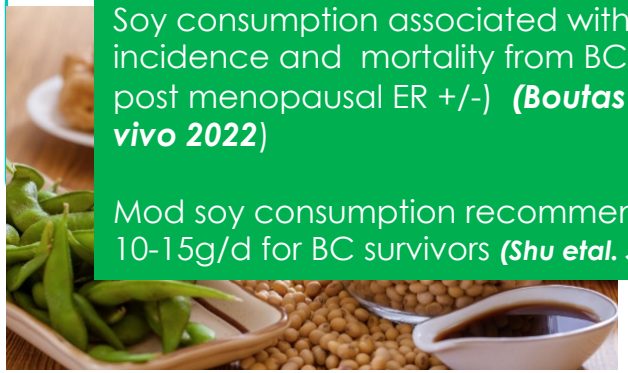
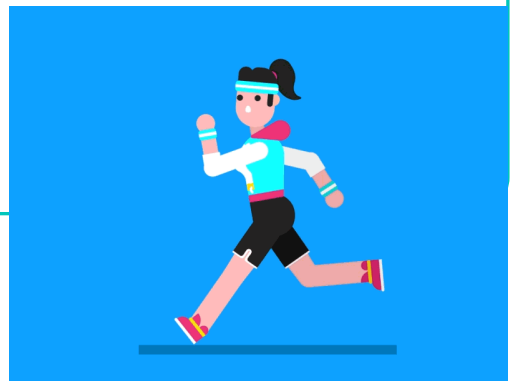


Cruciferous veg: broccoli, kale, sprouts- sulforafanes
Carotenoid veg: carrots, pumpkin: B carotenene
Flax seeds-: Omega-3s
Berries- procyanidins
Soy foods- isoflavones



Soy consumption associated with reduced incidence and mortality from BC (pre and post menopausal ER +/-) ***(Boutas et al. In vivo 2022***)

Mod soy consumption recommended 10-15g/d for BC survivors ***(Shu etal. JAMA 2009)***



Prostate cancer

2nd leading cause of cancer in Greek men (5th cause of ca related death world-wide GLOBOCAN 2018)

- Metabolic syndrome eg obesity, saturated fat inc risk ***(BMC Medicine 2015)***
- Dairy: >2.5 serves vs <0.5 serve (32% inc PHS) (28% inc AHS-2) ***(Chan, Am J Clin Nutr 2001; Orlich, Am J Clin Nut 2022;)***
- Soy (Isoflavones) and tomato (lycopene)
  - AHS 27,900: 4 servings tomato c.f zero 28% red risk (***Fraser, Cancer causes control 2022)***
  - Soy products; intake assoc with red risk of advanced PC ***(Applegate; Nutrients 2018)***
- ***ASCO GU 2023-*** CaPSURE study (T1-T3a)PC
  - Highest plant consumption 52% lower risk of progression (median 7.4 years)
  - 53% lower risk of recurrence highest vs lowest intake of PB foods

PBD index- improved functional and QOL outcomes incl sexual function, bladder and
bowel function
(Loeb et al. JCO 2023)

Lung cancer

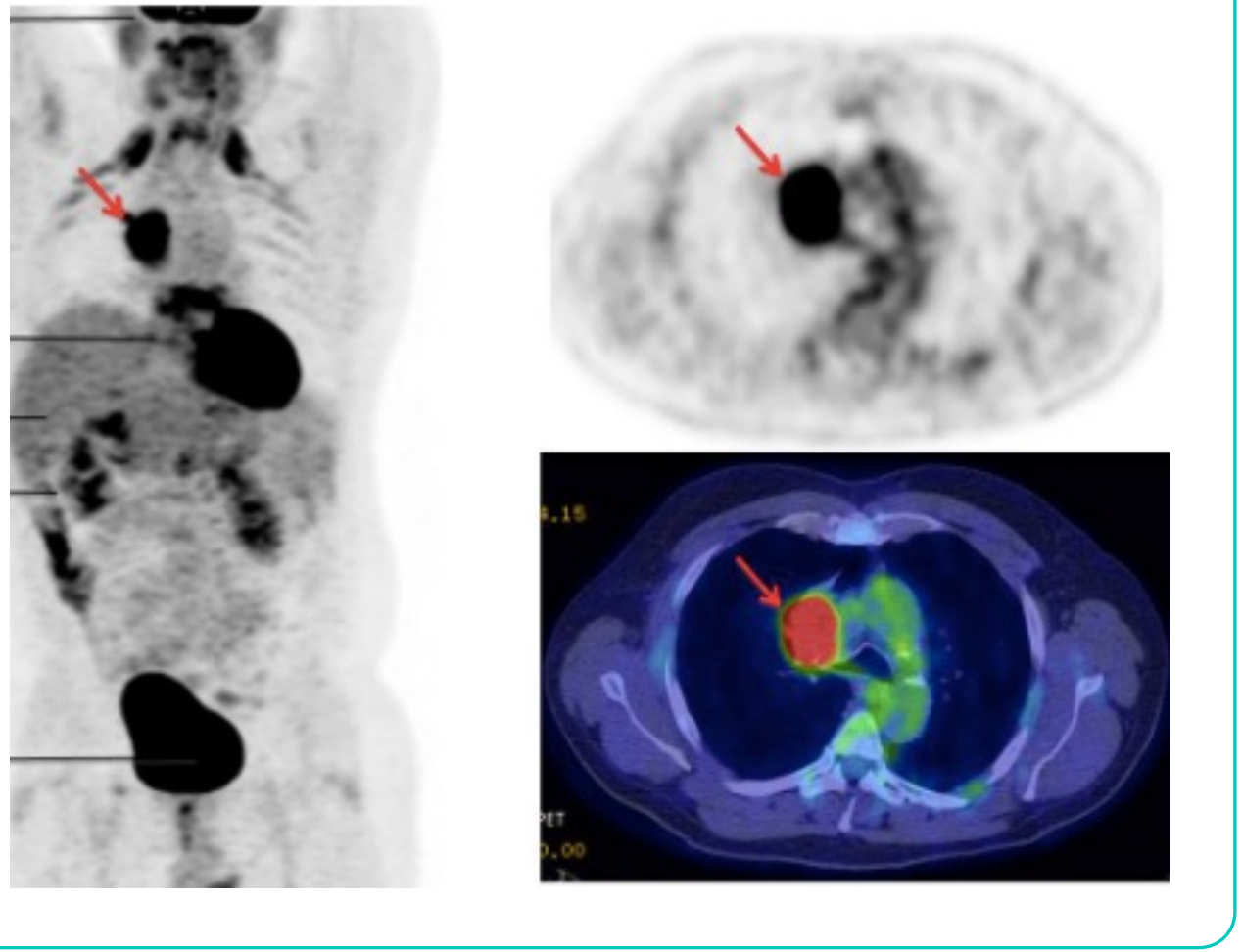
- Leading cancer diagnosis in Greek men
- No. 1 cause of cancer mortality

- PB dietary patterns (healthy) may reduce lung cancer mortality

  (***Plant-based dietary patterns and lung cancer mortality: a perspective cohort study. Food and function. Zhao et al. 2023)***

- Improved pre-op nutrition
  - Following induction chemo/RT in surgical patients
    - Reduces severity of post op complications factors incl Vit A/C/E selenium and zinc to strengthen antioxidant barrier
    - omega 3 and protein suppl (improves QOL, functional status)

  (***Diet as a factor supporting lung cancer treatment- a systematic review Nutrients 2023***)



What is the ideal diet during cancer treatment?

Diet during cancer treatment?

- targets deregulated metabolic pathways w/t affecting healthy cells
- Doesn't contribute to excess wt loss
- Optimizes cellular and immune function
- Addresses cancer related nutritional def and its complications

- NO benefit from western diets

- Chronic caloric restricted diets most studied
- Fasting Mimicking diet (FMD) around time of treatment may improve toxicity

Comparison of dietary interventions.

Dietary intervention	Benefits	Limitations
Western diet	None	Low nutritional density Associated with prostate, breast, and colorectal cancer Associated with chronic diseases
Caloric Restriction	Reduction in oxidative stress, inflammation, and growth factors (i.e. IGF-1 and Ras/MAPK) Improved insulin sensitivity and glucose tolerance Decreased leptin levels Promotes autophagy Decreased angiogenesis	Excessive weight loss Risk of cachexia Risk of malnutrition
Intermittent fasting	Associated with improved chemotherapy-associated side effects Improved insulin sensitivity and glucose tolerance Decreased growth factors (i.e. IGF-1 and Ras/MAPK) Decrease anabolic metabolism (termed differential stress resistance) Increased AMPK	Excessive weight loss Risk of cachexia Risk of malnutrition
Ketogenic diet	Increased ketosis Decreased inflammation and growth factors (i.e. IGF-1) Inhibition of tumorigenesis Utilization of Warburg effect Selective increased oxidative stress in cancer cells	Weight loss Hypoglycemia, nausea, vomiting, and lethargy Increase in serum cholesterol Progressive bone loss

Gray et al. SAGE Open Medicine 2020

THE HUMAN MICROBIOME

100 trillion microbes

3% human body mass

1-10X microbes : human cells

10-100X microbial : human genes

largest # microbes – GI tract

- Obesity
- Diabetes
- Inflammatory Bowel Disease
- **CANCER**
- Eczema
- Allergies
- Asthma
- Depression
- Autoimmune disease

The Gut Microbiome

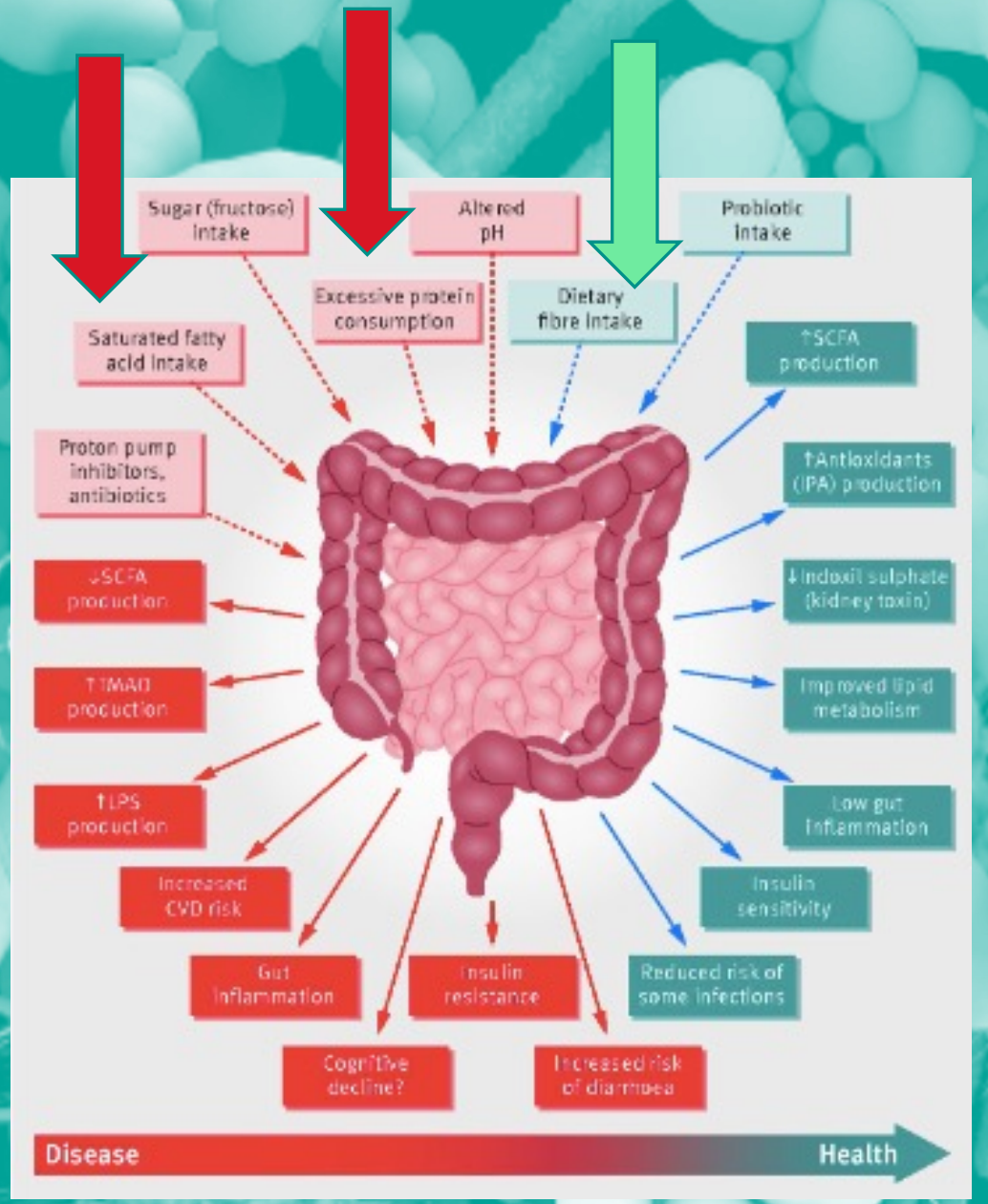
- Digest food
- Produce SCFA
- Synthesize vitamins
- Metabolize drugs
- Neutralize toxins
- Maintain gut lining
- Train immune system
- Turn genes on and off

Diet-microbiome interactions and cancer

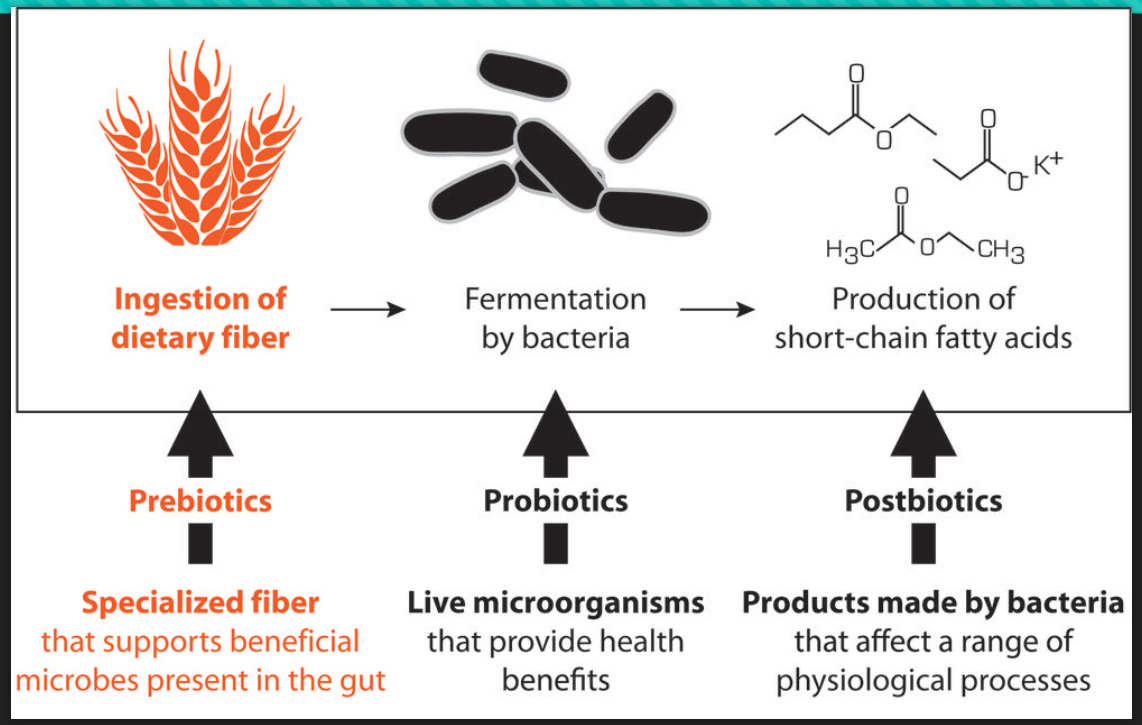
- Dietary factors- key role in the "health" of the microbiota
  - Rapidly and reproducibly alters gut microbiome (***Nature 2014)***
  - No. 1 determinant of healthy, diverse and functional gut = no and diversity of plants in diet (American Gut Project)
  - Dietary metabolites -healthful or harmful

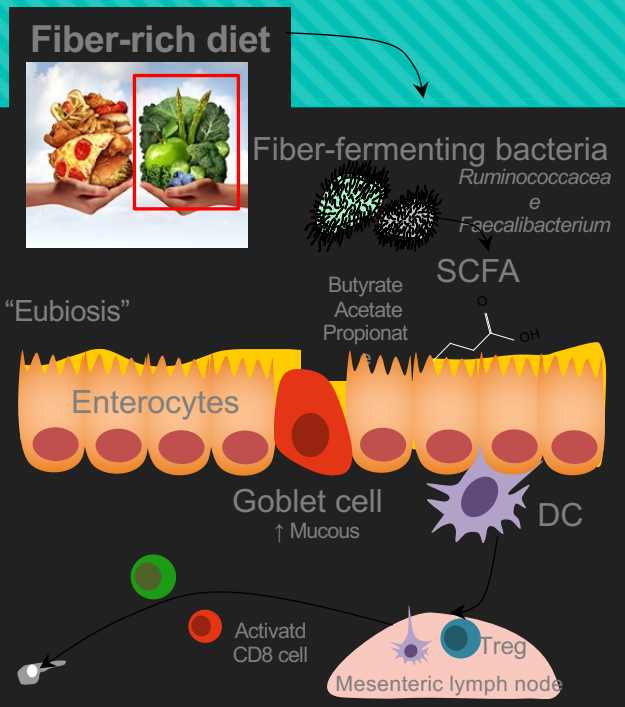
- Dietary swap has dramatic influence on colon cancer risk (American vs African diet) 2 week swap
  - Americans on African diet reduced colon inflammation and biomarkers of cancer risk and vice versa

(O'Keefe eta. Nature Comm 2015)

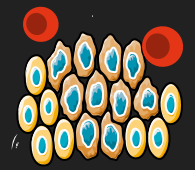


Dietary fiber, SCFAs, and immunity





Immune fitness
↓ inflammatory cytokines
Primed APCs
Treg/Th17 balance
Th1>Th2 skewing



Tumor

Courtesy of J McQuade, *Lancet Oncology 2019*

- Dietary intake directly impacts cancer treatment response to immunotherapy through a dietary fiber-gut microbiome mechanism ***(Spencer; Science 2021)***
- Adherence to Mediterranean style diet associated with improved response rates and PFS ***(JAMA Oncology 2023)***
- *Dietary drivers for associations bn cancer immunotherapy outcomes and gut microbiome* ***(Nature Med 2022)***

Association of a Mediterranean Diet With Outcomes for Patients Treated With Immune Checkpoint Blockade for Advanced Melanoma

Laura A Bolte et al. JAMA Oncol. 2023.

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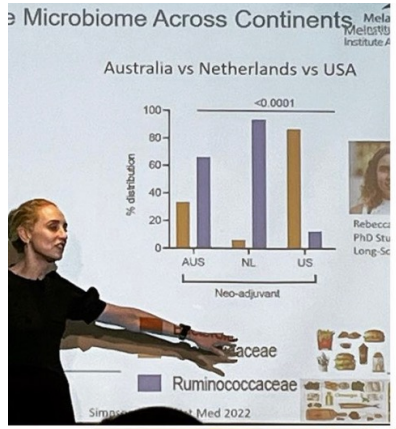
Abstract

Importance: Immune checkpoint blockade (ICB) has improved the survival of patients with advanced



Diet-driven microbial ecology underpins associations between cancer immunotherapy outcomes and the gut microbiome

Rebecca C Simpson et al. Nat Med. 2022 Nov.

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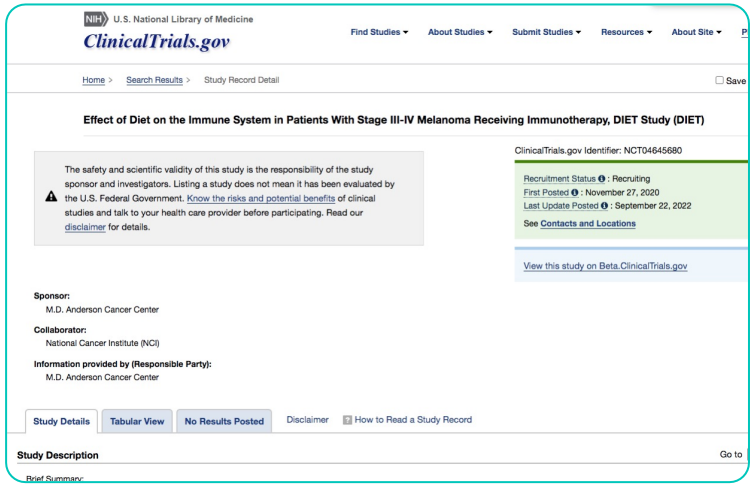

Potential role for diets high in plants/fibre to improve response to cancer therapies

Summary take home points

Prevention and treatment of cancer and the PB Diet

- Extensive research supports healthy eating patterns centered around WPB foods to reduce cancer risk and cancer recurrence (WCRF/IACR recommendations)
- Treating the cancer patient with dietary interventions needs to be tailored-but immune function optimization (high fibre plant-based diet) is a key strategy
- Improved survival (screening and treatment) means we also need to focus on reducing risk of recurrence and reducing other chronic diseases-PB diet is a key strategy

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Recommended Resources

- Physicians committee for responsible Medicine (pcrm.org)
- Doctors for nutrition (doctorsfornutrition.org)
- NutritionFacts.org (Dr Michael Gregor)
- pinklotus.com (breast cancer surgeon Dr Kristi Funk)

- Am Institute cancer Research/World cancer Research Fund (AICR/WCRF)
- ACLM and ASLM (American College Lifestyle medicine and Australasian Society Lifestyle Medicine)
- EAT-Lancet report – Commission on food, planet and health

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