Pathogenic links between diet, cancer cell metabolism and immune function

Opportunities for clinical application in cancer care and survivorship

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Key learning objectives

1

Epidemiology overview:
Recommended dietary patterns for cancer prevention and why we need them

2

Science overview:
Dietary influence on cancer cell metabolism, oncogenesis and immune function

3

Clinical therapeutic overview:
Dietary approaches during cancer treatment and in survivorship
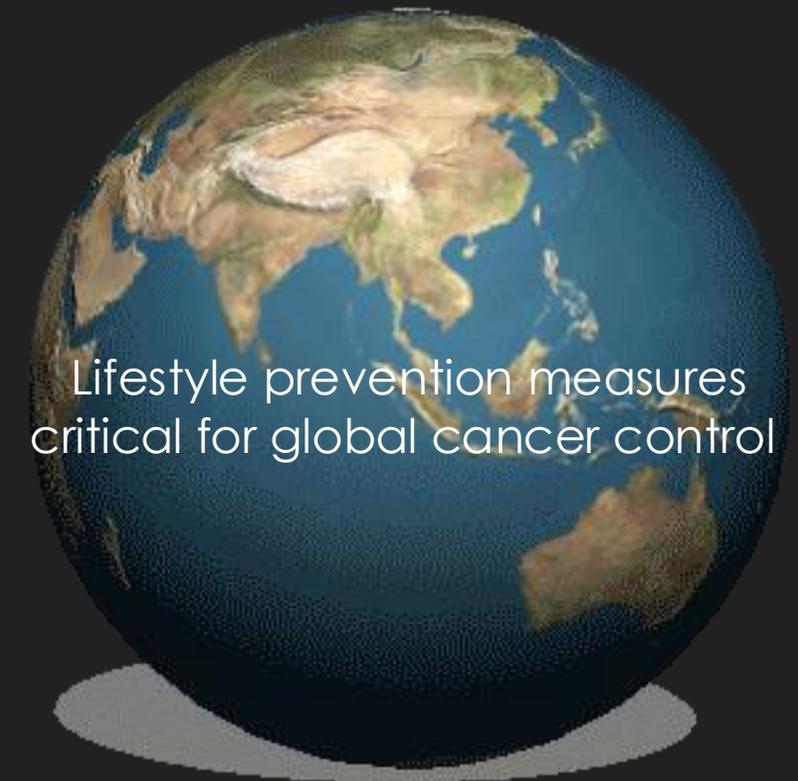
Epidemiology
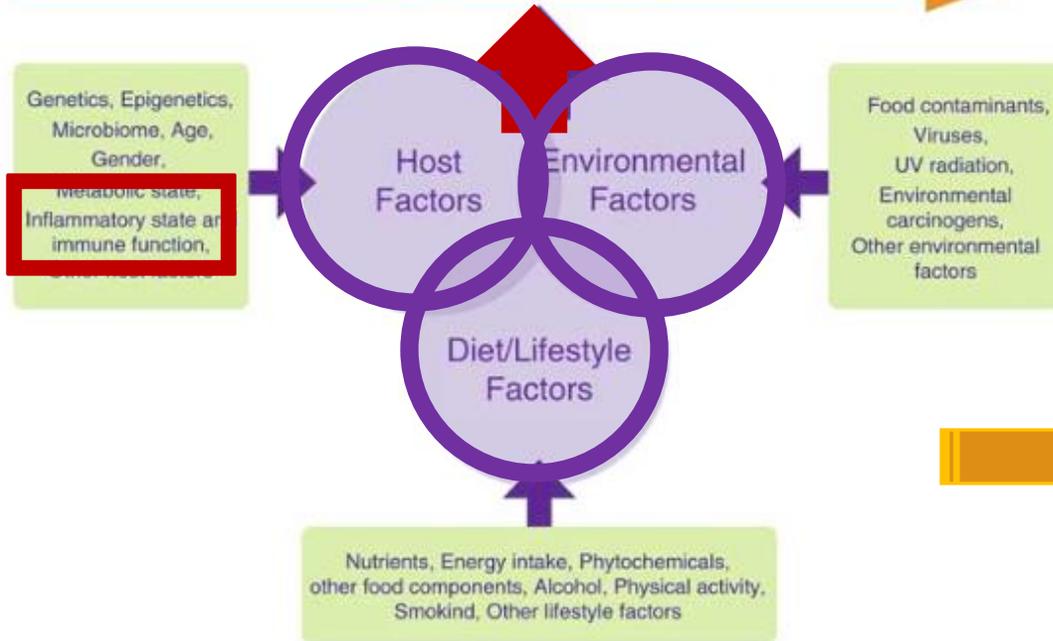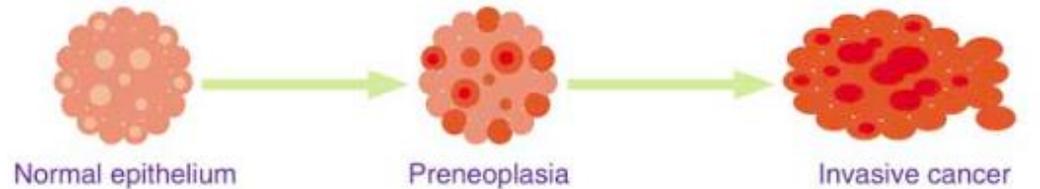
vs
Medical Science
vs
Clinical and
therapeutic applications

Increase in global cancer burden and survivorship

○ Global cancer cases expected to be 35 million by 2050 (77% increase from 2022)

○ 1 in 5 people will develop cancer in their lifetime (1 in 9 men and1 in 12 women will die from it)

○ 2nd leading cause of mortality after CVD (leading cause of premature death in 57 countries) *Bray et al. Cancer 2021*

○ Improved treatments, technologies and screening programs - more long-term survivors-->complications of treatment, second cancers and other chronic diseases
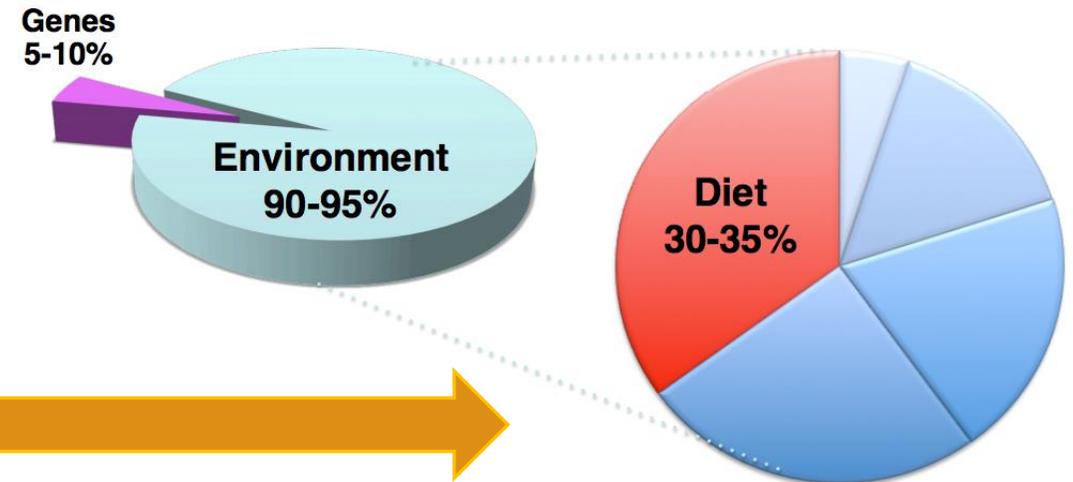
Global cancer statistics 2022

Lifestyle prevention measures critical for global cancer control

Modifiable risk factors for cancer

Diet, nutrition and physical activity, other environmental exposures and host factors interact to affect the cancer process

Normal epithelium → Preneoplasia → Invasive cancer

CANCER PROCESS

Genetics, Epigenetics, Microbiome, Age, Gender, Metabolic state, Inflammatory state and immune function,

Host Factors — Environmental Factors — Diet/Lifestyle Factors

Food contaminants, Viruses, UV radiation, Environmental carcinogens, Other environmental factors

Nutrients, Energy intake, Phytochemicals, other food components, Alcohol, Physical activity, Smoking, Other lifestyle factors

©World Cancer Research Fund International dietandcancerreport.org

Examining the Causes of Cancer

Genes 5-10%

Environment 90-95%

Diet 30-35%

Direct effects: food carcinogens; eg.Processed/red meat

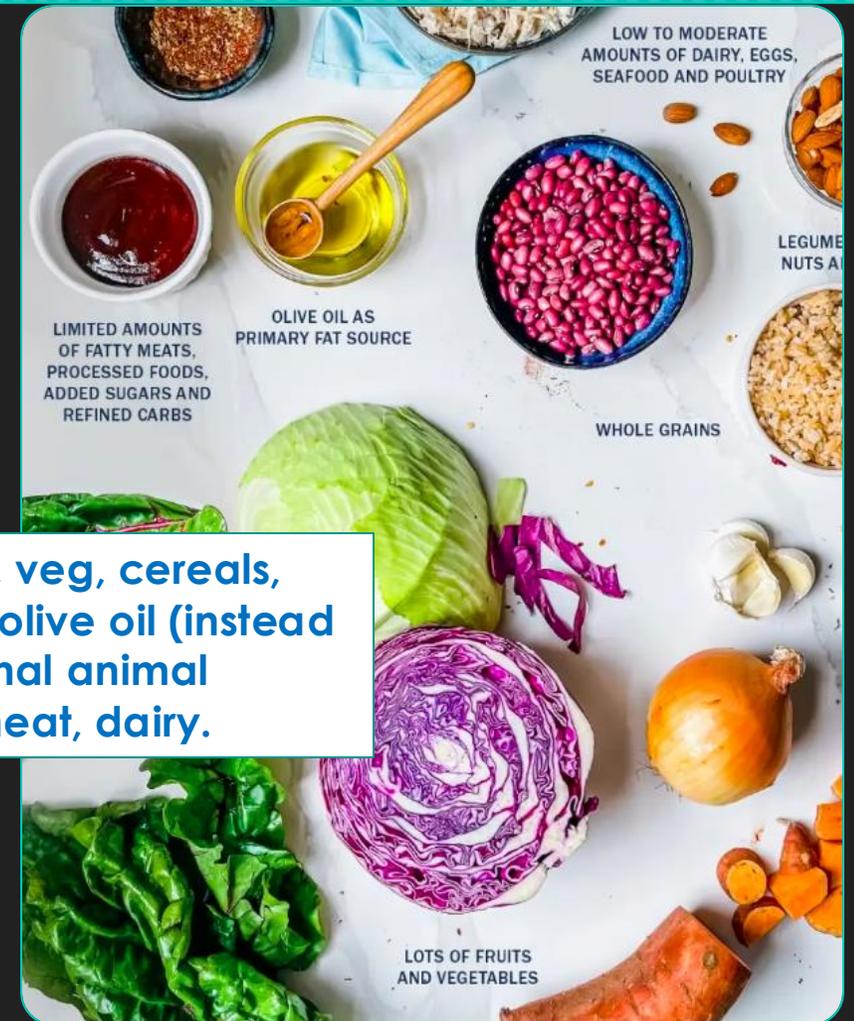**Systemic effects: inflammation; metabolic, microbiome; epigenetic**

Global consistency in dietary recommendations for cancer prevention

World Cancer research fund and AICR 3rd expert report 2018

Cancer Institute Australia

Plant-Based dietary patterns/high quality diets lower cancer risk (and improve survival)

- Emphasize overall dietary patterns (e.g., Mediterranean, plant-based) over individual foods.

- Use dietary scores eg. Healthy eating Index (HEI), Plant based index (PBI), Diet Inflammatory Index (DII) to assess diet quality.

- **Greek EPIC Study**: Higher adherence to Mediterranean diet inked to lower cancer incidence *(Benetou et al. BJC 2008)*.

- **Adventist Health Studies:** Plant-based/vegan diets associated with lower cancer incidence, especially breast and gynecological cancers *(Tantamango et al. Cancer Epidemiol Biomarkers Prev 2013)*.

LOW TO MODERATE AMOUNTS OF DAIRY, EGGS, SEAFOOD AND POULTRY

LEGUME NUTS A

OLIVE OIL AS PRIMARY FAT SOURCE

LIMITED AMOUNTS OF FATTY MEATS, PROCESSED FOODS, ADDED SUGARS AND REFINED CARBS
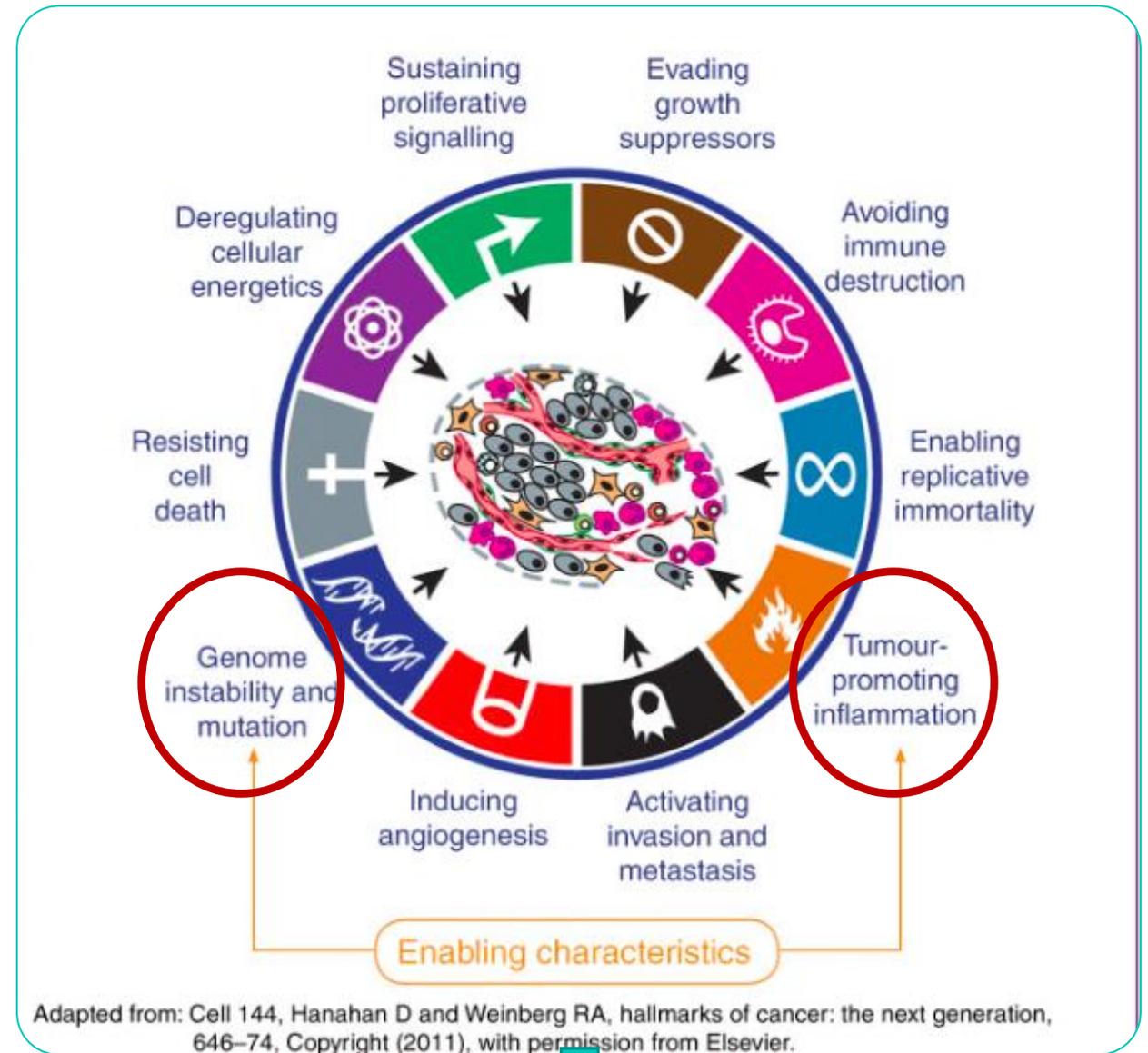
WHOLE GRAINS

LOTS OF FRUITS AND VEGETABLES

Medi diet: Fruit, veg, cereals, legumes, nuts, olive oil (instead of butter) minimal animal products eg. meat, dairy.
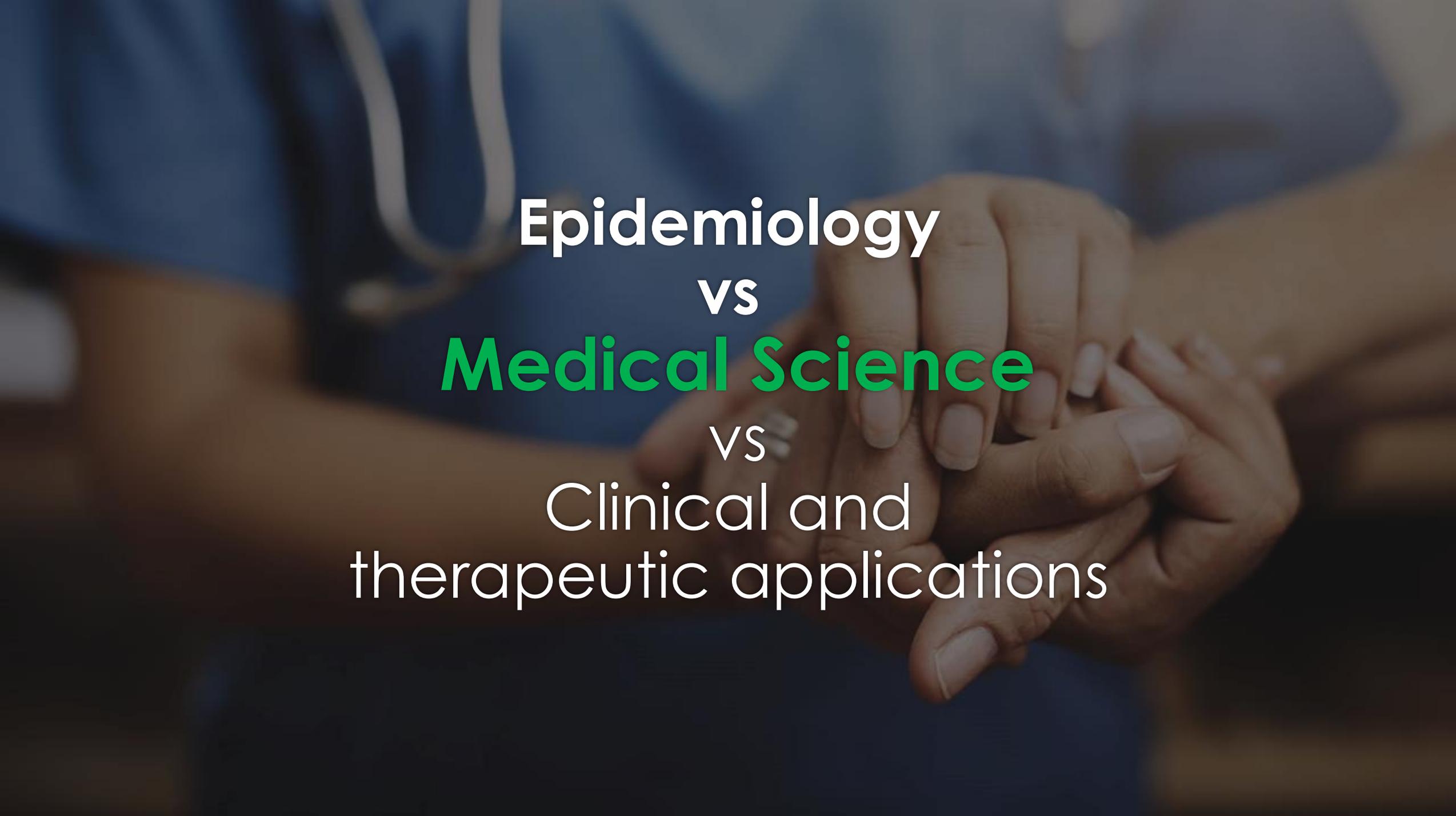
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The hallmarks of cancer

- Loss of genetic control of cell growth and proliferation (a genetic disease mediated by proto-oncogenes and tumour suppressor genes)

- Increased metabolic demands for growth and survival and to adapt to environmental stressors e.g hypoxia and resource deficiency

Adapted from: Cell 144, Hanahan D and Weinberg RA, hallmarks of cancer: the next generation, 646–74, Copyright (2011), with permission from Elsevier.

Metabolic re-programming
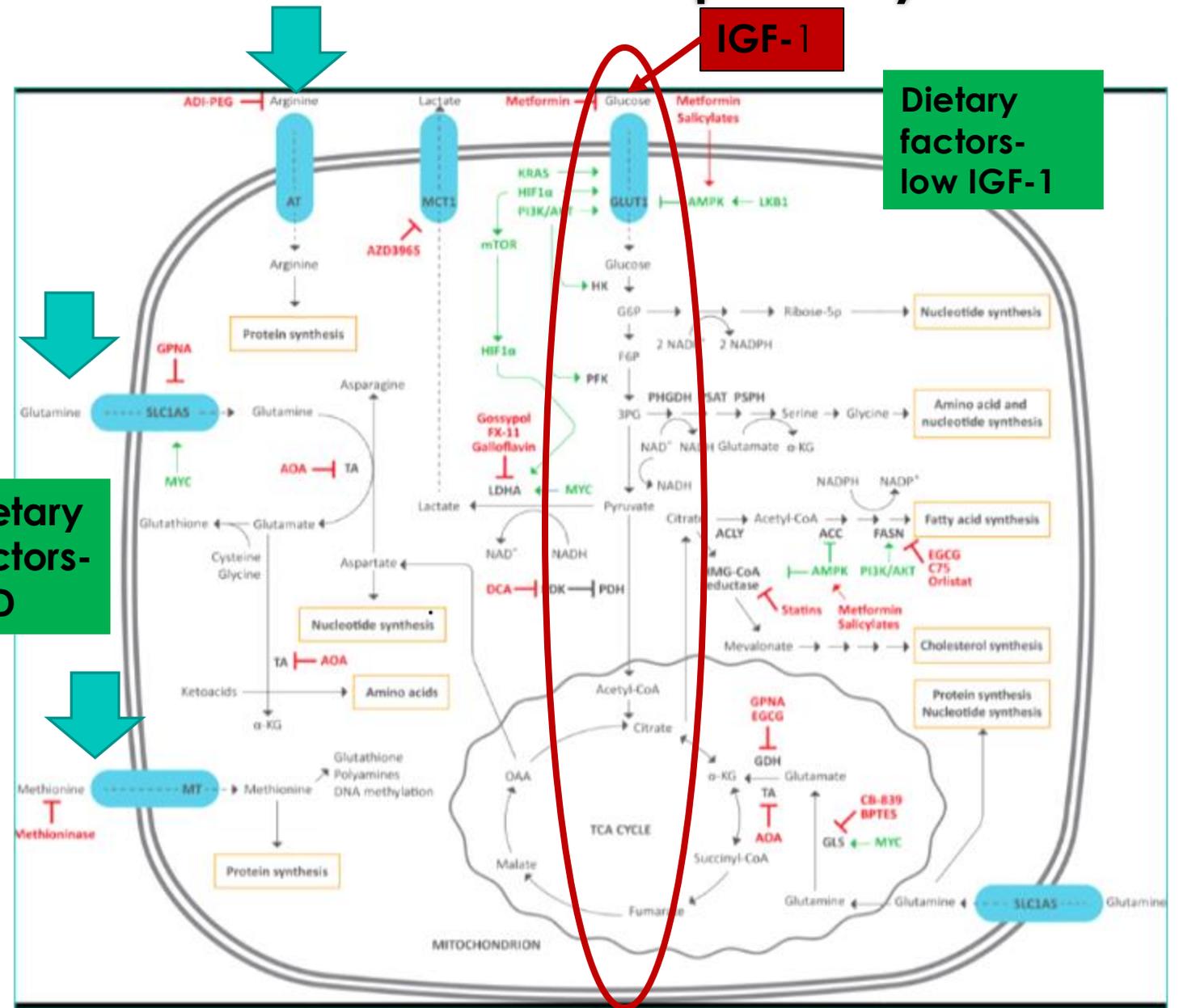
Cancer metabolic pathways

Cancer Metabolism:
Chemical reactions that promote cellular fitness and survival under stressful conditions or allow cells to grow at exponential rate

- Cancer fuels include:
  - Glucose
  - Amino acids
  - Fatty acids and ketone bodies
- Use of "fuels" depends on oncogenic drivers, stage of tumour development and nutrient availability
  - Insulin and IGF-1

High protein diets in adults increase IGF-1, increase cancer; cancer mortality (*Levine et al. Cell metabolism 2014*)

IGF-1

Dietary factors- low IGF-1

Dietary factors- LPD

Metabolic pathways

Pro-survival/proliferative pathways

Dietary factors

Dietary factors

Immune checkpoint pathways

PD-1 receptor

TME

Dietary factors

Debaradinis R.J Fundamentals of cancer metabolism Science advances 2016

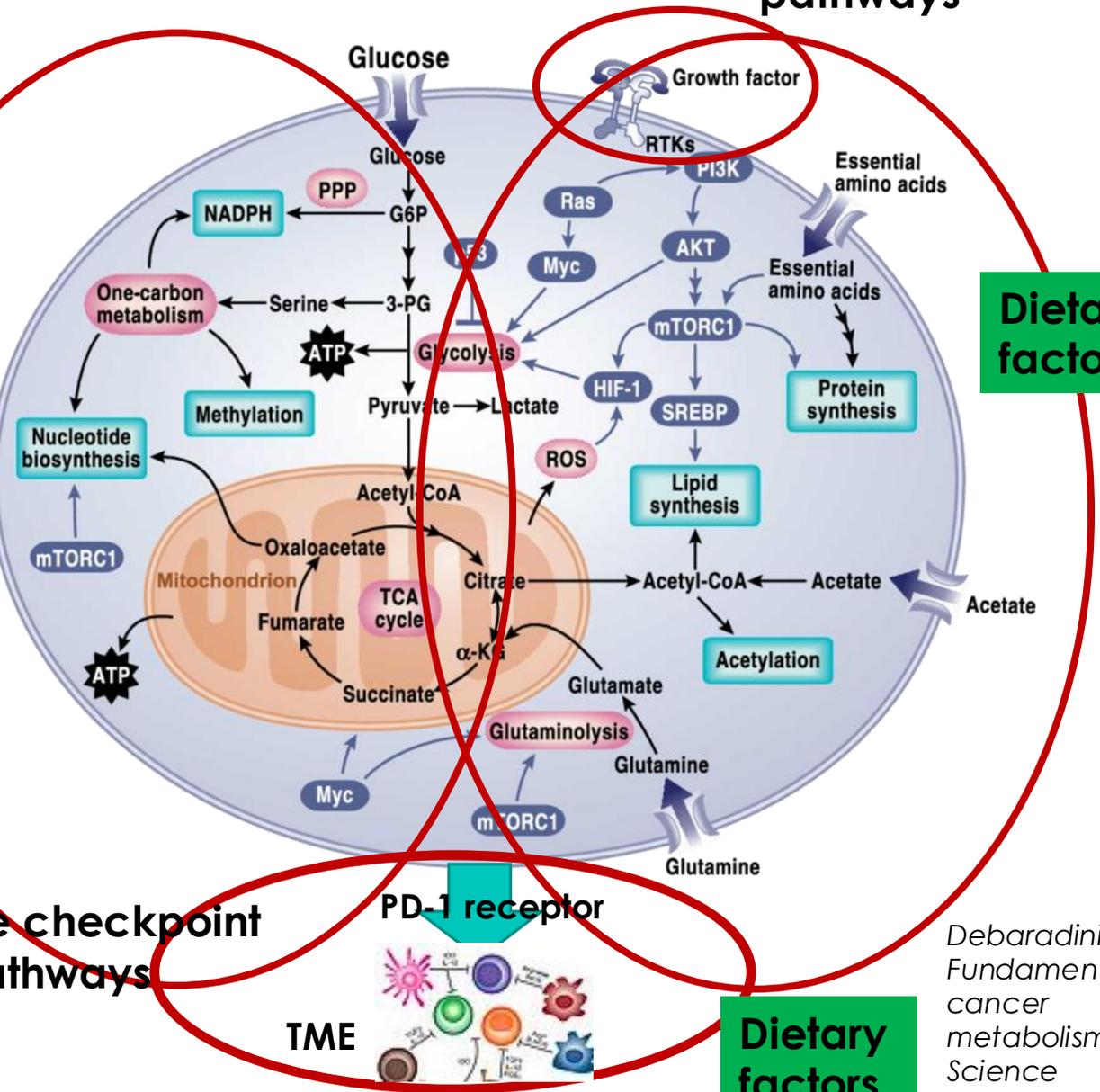**Key proliferative & pro-survival pathways**

- RAS/RAF/ERK
- PI3K/AKT/mTOR
- STAT/JAK
- Growth factor receptors
  - EGF-R (HER-2/3)
  - VEGF-R, PDGF-R, FGF-R
  - IGF-1R

- Immune Checkpoint pathway
  - Eg.PD-1 (cancer immune escape)
  - Immunotherapy drugs block this escape mechanism

Inflammation: a hallmark of cancer

Chronic inflammation influences cancer risk: Diet factors, smoking, tobacco, viruses, alcohol, autoimmune)

Cancer causes chronic inflammation as it progresses: Inflammatory cells recruited to tumour microenvironment (TME)
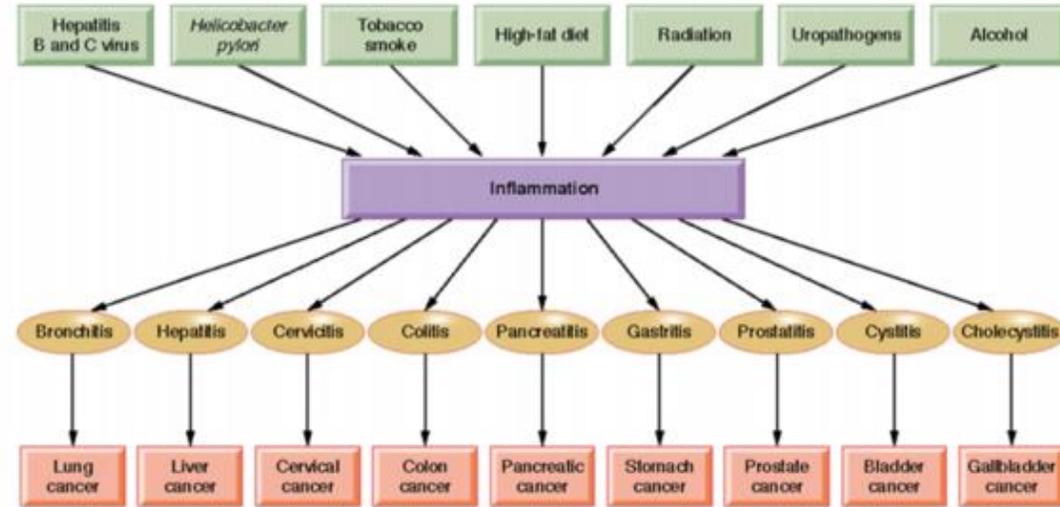

Inflammation as a risk factor for most cancers

FIGURE 6.1
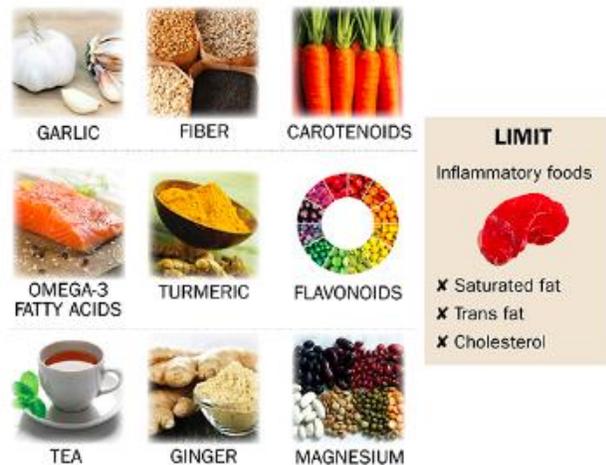
Origin of inflammation and its role in various cancers.

Causality	Tumor initiation	Advanced cancer
DNA damage (Radiation, chemicals) Hereditary Unknown	Inflammation-independent carcinogenesis	**Chronic Inflammation** Recruitment of inflammatory cells Immune evasion Angiogenesis Extracellular matrix remodeling Fibrosis Genomic instability Proliferation Anti-apoptotic pathways Metastatic dissemination
Microbial infections Autoimmunity Chronic inflammation Fibrosis Immune deregulation Inflammation induced by chemicals (tobacco, alcohol, diet, pollution)	Carcinogenesis induced by inflammation Impaired apoptosis Activation of growth promoting oncogenes Inactivation of tumor suppressors	

Diet modulates inflammation

- **Pro-Inflammatory e.g** sialic acid (Neu-5GC) in red meat and obesity state-increase inflammation

- **Anti-inflammatory e.g** in plants eg. Phytochemicals and fiber reduce inflammation

- Key inflammatory mediators (eg. NF-kB) influence all stages of carcinogenesis

- **Dietary Inflammatory Index score (DII):** predicts the inflammatory potential of diet based on 21 nutrients using 6 key inflammatory biomarkers
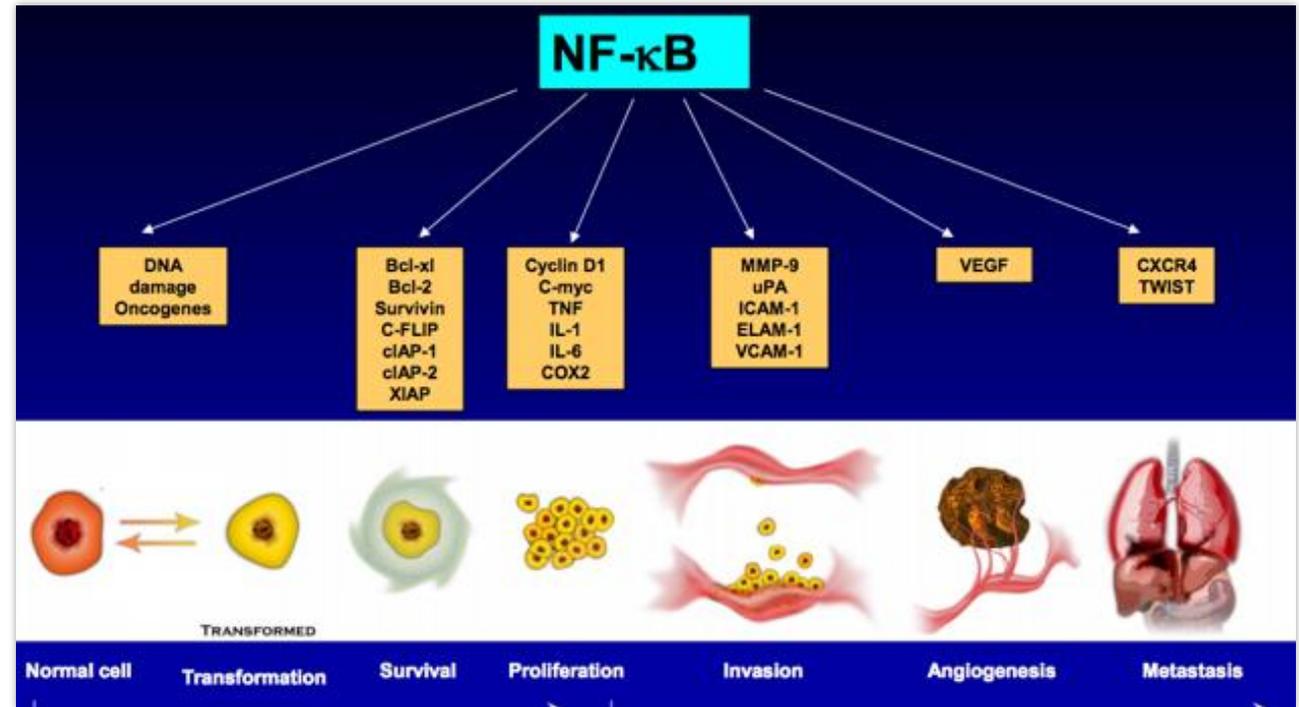

ANTI-INFLAMMATORY FOODS/FOOD COMPOUNDS*

*Based on: Shivappa N et al. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. 2014 Aug;17(8).

Dietary Inflammatory index (DII):
Shivappa et al .Public Health Nutr 2014

Fruit/veg/soy products (phytochemicals in foods)
→ **LEAST Inflammatory**

Saturated fats/red meat, simple CHOs
→ **MOST Inflammatory**

**High DII scores independent risk of CRC and breast cancer (meta-analyses)** *Hayati etal.EJCN 2022*
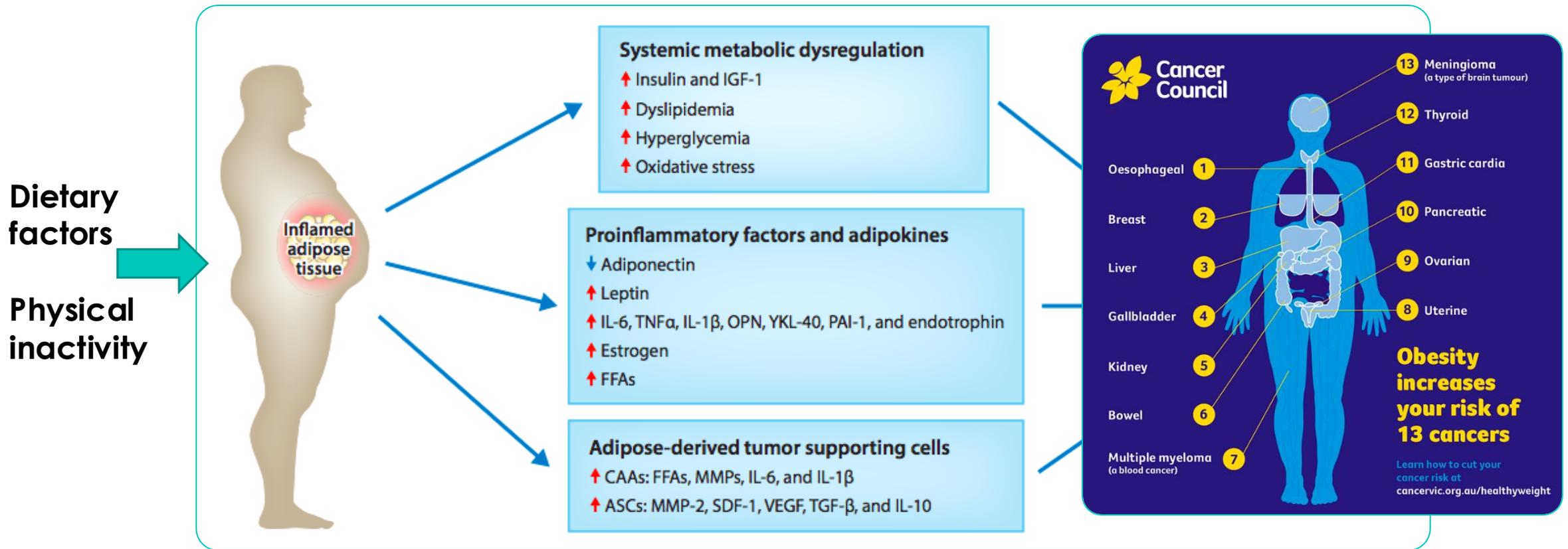
(Deng et al. Ann Rev Path Mech Dis 2016)

Effect of adipose tissue on carcinogenesis- obesity as a chronic inflammatory state

Immune regulation in cancer- avoiding immune attack

- **Immune system** (innate and adaptive) important role in cancer development and progression

- During cancer formation; **TME** characterized by changes in chronic inflammatory and immune cells

  - **Early stages**: NK and CD8+ (cytotoxic) T cells-recognize and eliminate immunogenic cancer cells

  - **Later stages:** characterized by peripheral immune tolerance-escape immune detection (recruit T-regs)and build an immunosuppressive TME

Werb et al. Genes Dev 2018
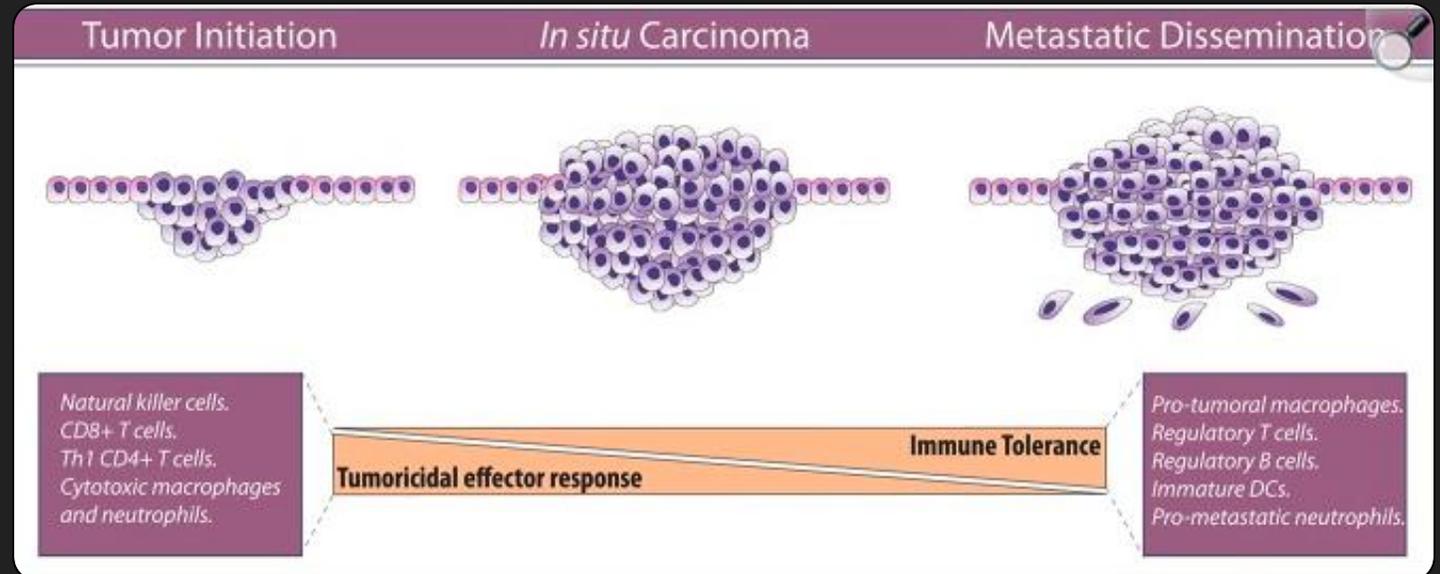
Diet-microbiome-immune system and cancer

- Digest food
- Produce SCFA
- Synthesize vitamins
- Metabolize drugs
- Neutralize toxins
- Maintain gut lining
- ~~une system~~
- ~~on and off~~
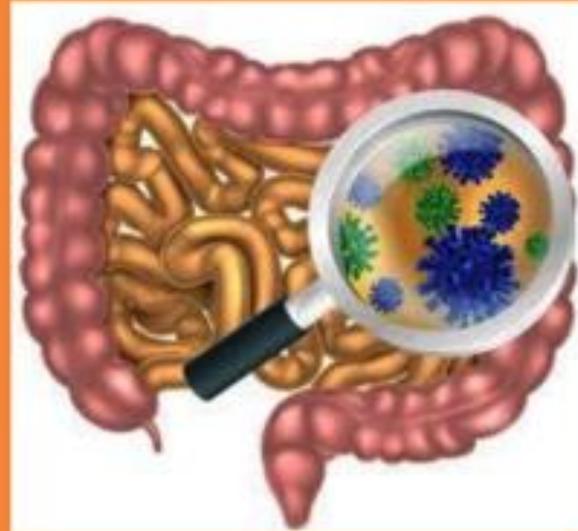
- Obesity
- Diabetes
- Inflammatory Bowel Disease
- **CANCER**
- **ER**
- Eczema
- Allergies
- Asthma
- Depression
- Autoimmune disease

Dysbiosis→
- impaired immune function
- chronic inflammation
- metabolic dysregulation

- No. 1 determinant of healthy microbiome is the number and diversity of plants in diet **(Am Gut Project)**

- Metabolites from fats and meat promote dysbiosis; increase disease risk

- Fiber/polyphenol rich F/V, omega-3s (nuts/seeds) promote eubiosis; reduces disease risk

- Gut microbiome is highly dynamic and responds to dietary changes rapidly *(Nature 2014)* which can affect colonic inflammation and cancer risk *(O'Keefe et al. Nature Comm 2015)*

Dietary fiber: a key factor linking gut microbiome to immune health
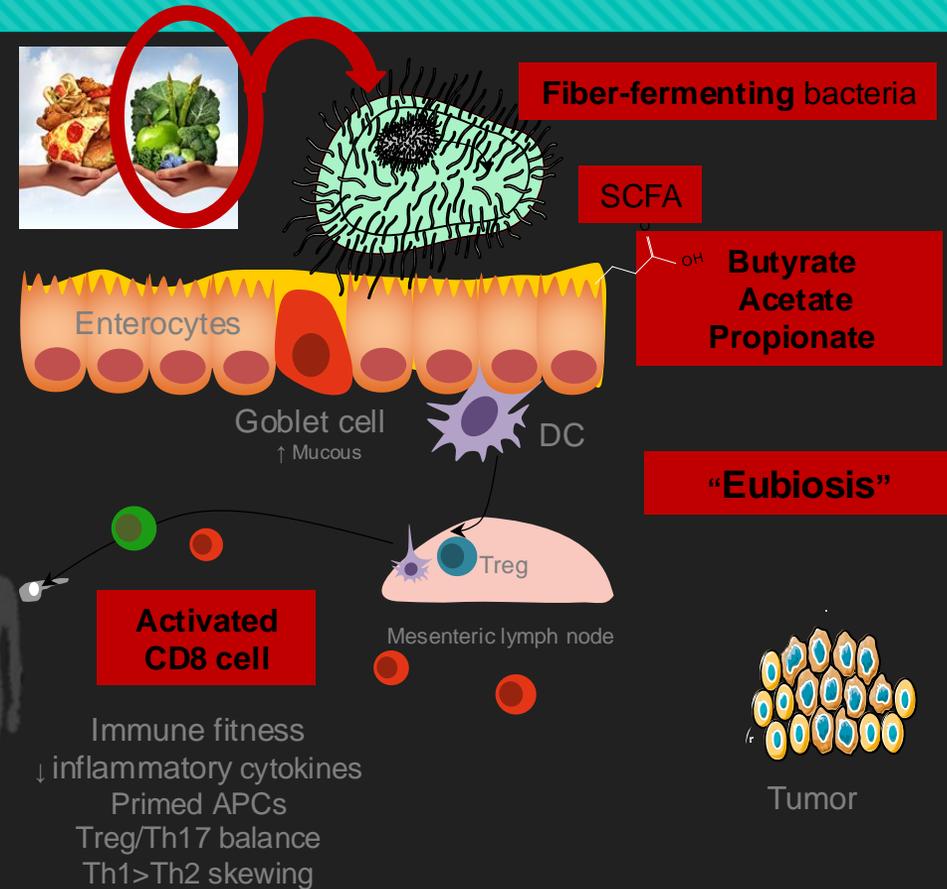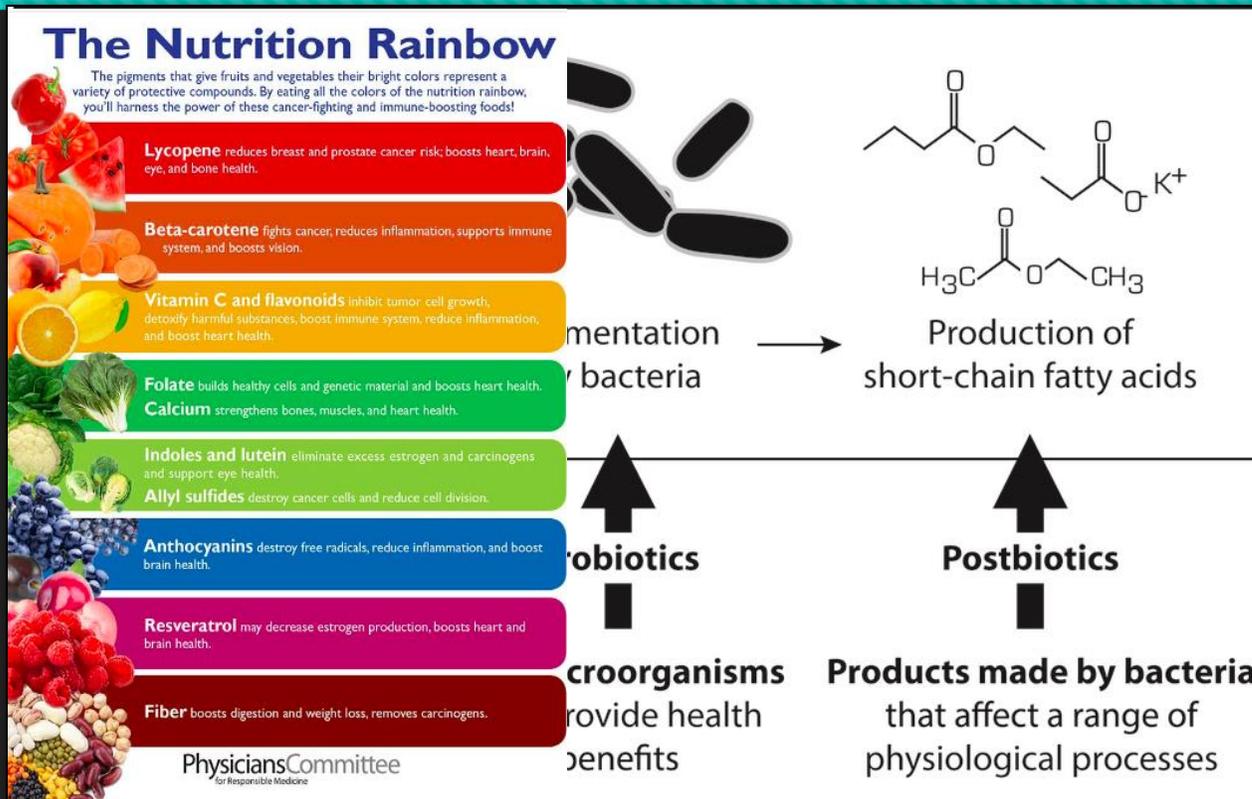
Anti-inflammatory, immune modulating and anti-oxidant effects of plant derived phytonutrients e.g polyphenols also mediated by gut microbiome

Courtesy of J McQuade, *Lancet Oncology 2019*

Epidemiology
vs
Medical Science
vs
Clinical and therapeutic applications

Diet during cancer treatments:

CURRENT

- Focus on healthy diet emphasizing plants and avoid malnutrition
- Studies show improved symptoms and QOL outcomes eg. Breast, lymphoma, prostate ca with more healthful PB diets

EVOLVING..

- Dietary interventions
  - targeting gut microbiome eg high fibre/plant based (immunotherapy)
  - targeting metabolic pathways in specific cancer eg. AML and brain tumours (aa restriction, ketogenic)
- Precision oncology to assist in different cancer types (ie genomics, metabolomics, microbiome)

A schematic for genomics-driven cancer medicine (PRECISION ONCOLOGY).

Liquid biopsy

Gut biota

Circulating DNA, RNA
Exosomes
Immune markers
Bioactives
Others …
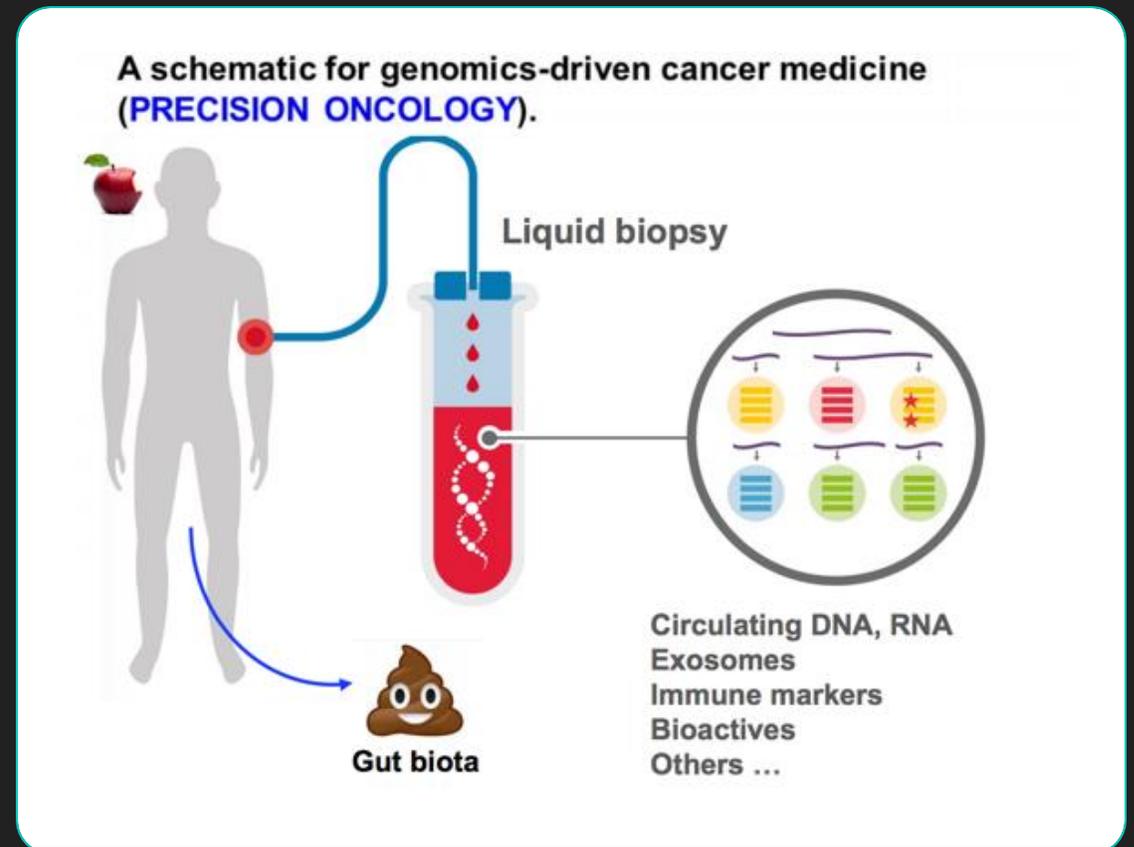
Diet during cancer treatment?

- targets deregulated metabolic pathways w/t affecting healthy cells

- Doesn't contribute to excess weight loss

- Optimizes immune function

- Addresses cancer related nutritional def and malnutrition driven cancer complications

- NO benefit from western diets

- Chronic caloric restricted, Int fasting and KD most studied

- Low protein diets eg methionine restriction-may enhance immunotherapy

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)	Excessive weight loss
	Improved insulin sensitivity and glucose tolerance	Risk of cachexia
	Decreased leptin levels	Risk of malnutrition
	Promotes autophagy	
	Decreased angiogenesis	
Intermittent fasting	Associated with improved chemotherapy-associated side effects	Excessive weight loss
	Improved insulin sensitivity and glucose tolerance	Risk of cachexia
	Decreased growth factors (i.e. IGF-1 and Ras/MAPK)	Risk of malnutrition
	Decrease anabolic metabolism (termed differential stress resistance)	
	Increased AMPK	
Ketogenic diet	Increased ketosis	Weight loss
	Decreased inflammation and growth factors (i.e. IGF-1)	Hypoglycemia, nausea, vomiting, and lethargy
	Inhibition of tumorigenesis	
	Utilization of Warburg effect	Increase in serum cholesterol
	Selective increased oxidative stress in cancer cells	Progressive bone loss

Gray et al. SAGE Open Medicine 2020

Optimizing diet during Immunotherapy

- Diet directly impacts cancer treatment response and outcomes to immunotherapy through a dietary fiber-gut microbiome mechanism *(Spencer et al. Science 2021; Simpson et al. Nature Med 2022)*

- Adherence to Mediterranean style diet associated with improved response rates and PFS *(JAMA Oncology 2023)*

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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Study Protocol | Open access | Published: 04 December 2024

Diet and Immune Effects Trial (DIET)- a randomized, double-blinded dietary intervention study in patients with melanoma receiving immunotherapy

Rachel M. Farias, Yan Jiang, Erma J. Levy, Cindy Hwang, Jian Wang, Elizabeth M. Burton, Lorenzo Cohen, Nadim Ajami, Jennifer A. Wargo, Carrie R. Daniel & Jennifer L. McQuade

BMC Cancer **24**, Article number: 1493 (2024) | Cite this article

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

The value of plant-based diets for Cancer Survivors

- 44 million people living with cancer (diagnosed last 5 years (*Global cancer observatory; IARC 2020*)
- 5 yr survival rates improved significantly for breast, prostate and CRC cancers
- Cancer survivors face a number of health challenges eg. cardio-metabolic diseases (CVD, DM, osteoporosis, Dementia)

- WCRF/AICR-survivors should follow the same recommendations as for prevention
- Higher quality diet – reduced all cause and cancer specific mortality *(Park et al. Eur J Nutrition 2023*

Diet and Breast cancer survivors

- Weight gain after diagnosis increases recurrence and mortality *(Cochrane Review 2020)*. Smoking and inactivity are additional recurrence predictors.

- High fiber, soy, low saturated fat improve survival in PM breast cancer *(Willett Nutr Cancer 2011)*.

- **CVD is leading cause of death after breast ca -> Alzheimer's dementia** *(SEER database 2000-2015)*

Cancer treatments: E2 blockers chemo, anti-HER-2, radiotherapy	⟷	Shared risks: menopause, obesity, DM, physical inactivity
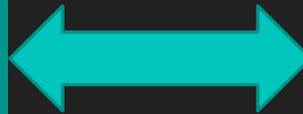
BC Survivors-17% higher risk of second primary cancers *(Molina et al. Gynecol Oncol 2015).*

Healthy dietary patterns associated with reduced all cause and non breast cancer mortality *(NHS ; Nutrients 2022)*

Many well-established dietary patterns to reduce and manage cardiometabolic risk eg. PB, DASH, MEDi etc.

Diet and Prostate Cancer Survivors

- **Androgen Deprivation Therapy (ADT)**: Used for advanced prostate cancer; lowers testosterone but increases cardiovascular risk-> leading cause of mortality *(BJU Int 2016)*

- **Mediterranean Diet and higher HEI**: Linked to reduced all-cause mortality *(Castro-Espin; Nutrients 2022; De Maso et al. Nutrients 2021)* and improved survival *(Karavasiloglou et al. PLOS one 2019)*

- **Plant-Based Diet**: Early prostate cancer (surveillance): Higher adherence lowers fatal prostate cancer risk 19% *(Loeb et al. Am J Clinical Nutrition 2022)* and reduces prostate cancer progression 47% *(Liu et al. JAMA Network 2024)*
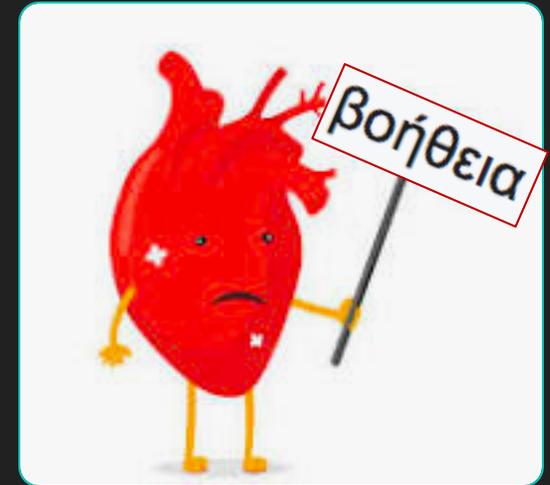
Diet for Colo-rectal cancer survivors

- **High fiber** (whole grain) reduces CRC-specific mortality *(Song et al., JAMA Oncol 2018)*.

- **Nut intake** (>2 servings/week) lowers CRC recurrence and boosts survival in stage III CRC *(Fedelu et al., JCO 2018)*.

- **Processed meat** consumption negatively affects survival post-CRC treatment *(BMJ Open 2012)*

- **Adhering to WCRF/AICR guidelines and the Mediterranean diet** improves survival after stage III CRC *(Song et al. 2021; Castro-Espin, Nutrients 2022)*.

- **Plant-based diets (vegan, Mediterranean) protect against almost all digestive cancers, especially colon and pancreatic** *(Zhao, Frontiers in Public Health 2022)*.

Interest in dietary and Lifestyle Interventions for Cancer Survivors

- Rising demand for personalized nutrition advice for survivors and high dietary inadequacy evident in studies (e.g., breast cancer).

- A 2019 qualitative study involving 45 oncologists; 74 patients:
  - Most patients inquired about lifestyle factors (diet) and all clinicians acknowledged their importance.
  - 40% of patients and 78% of clinicians believe post-diagnostic outcomes influenced by diet, physical activity, smoking, obesity, and alcohol.
  - 77% of patients and 85% are willing to change their dietary and physical habits to enhance cancer outcomes.
  - Barriers include fatigue and time for patients, and resource limitations, time constraints, and lack of information for clinicians.
  - **Patients expect their doctors to be knowledgeable in this area!**

Patient and clinician views and interest in integrating diet, physical activity and other lifestyle measures into standard cancer care

Introduction

The World Health Organisation (WHO) reports that up to 40% of cancers are potentially preventable by addressing diet, physical activity and other lifestyle measures. As survivors of cancer are becoming a more populous demographic, interest in the role of supportive therapies following definitive treatment is growing accordingly.[1] Increasing research evidence for lifestyle intervention shows significant scope to improve overall quality of life by reducing the risks of cancer recurrence and cancer-specific mortality.[2, 3] Benefits are also observed in overall survival on lifestyle measures in standard cancer care to improve outcomes and to promote health preservation for people living with and beyond cancer.

Recent studies have investigated health behaviour programs for patients with cancer and other chronic conditions, alongside strategies to increase their efficacy.[9-12] They affirm the ethical and scientific merit to tailoring programs according to users' preferences and circumstances.

This paper is a comparative analysis of findings from two corresponding Cabrini Integrative Cancer Care (CICC) surveys targeting cancer patients and clinicians at Cabrini Hospital in Melbourne, Australia. The surveys were designed to gauge interest, existing knowledge about cancer-related lifestyle factors and areas requiring further education. This analysis aims to provide valuable feedback to educators, department heads and hospital administrators for the development of a tailored integrative cancer wellness program to advance the standard of care for cancer patients.

Methods

Selection procedure

A total of 45 medical, surgical and radiation

Summary:
Take home points

- Extensive research shows that plant-based diets reduce cancer risk AND cancer survivors benefit from PB diets to improve cardiometabolic risk and survival

- Cancer involves genetic, metabolic, and immune factors, precision oncology may customize dietary strategies

- High-fibre, nutrient-rich PB in cancer patients can positively impact response to immunotherapy

- Next time patients ask about diet, recommend prioritizing plant-based foods for cancer prevention and care.

Imagine the path forward in cancer care..

Improve cancer survival and QOL:
- Screening (early detection)
- Improving treatments
- Precision oncology

Reduce cancer burden; prevention:
- Lifestyle (diet/PA/Risky behaviors)
- Screening (pre-cancer)

Survivorship: reduce cancer recurrence, cardiometabolic diseases– diet/lifestyle to improve health-span

Nutritional education/implementation/resources before and after a cancer diagnosis

Healthier and more productive individuals and communities

Healthier economies- re-direct resources to other areas

Healthier environment - resources for food supply and compassion for animals

Σας ευχαριστώ

Resources:
(Information and practical steps for a plant forward diet)

- Physicians committee for responsible Medicine (pcrm.org)
- Doctors for nutrition (doctorsfornutrition.org)
- NutritionFacts.org (Dr Michael Gregor)
- Pinklotus.com (breast ca: Dr Kristi Funk)
- Angiogenesis Foundation

- ACLM and ASLM (American College Lifestyle medicine Australasian Society Lifestyle Medicine)
- AICR/WCRF websites

Contact:
Dr Despina Handolias (Melbourne Oncology Group Australia)
IG: @veganoncologist E: d.handolias@gmail.com

The Nutrition Rainbow

The pigments that give fruits and vegetables their bright colors represent a variety of protective compounds. By eating all the colors of the nutrition rainbow, you'll harness the power of these cancer-fighting and immune-boosting foods!

Lycopene reduces breast and prostate cancer risk; boosts heart, brain, eye, and bone health.

Beta-carotene fights cancer; reduces inflammation, supports immune system, and boosts vision.

Vitamin C and flavonoids inhibit tumor cell growth, detoxify harmful substances, boost immune system, reduce inflammation, and boost heart health.

Folate builds healthy cells and genetic material and boosts heart health.
Calcium strengthens bones, muscles, and heart health.

Indoles and lutein eliminate excess estrogen and carcinogens and support eye health.
Allyl sulfides destroy cancer cells and reduce cell division.

Anthocyanins destroy free radicals, reduce inflammation, and boost brain health.

Resveratrol may decrease estrogen production, boosts heart and brain health.

Fiber boosts digestion and weight loss, removes carcinogens.

PhysiciansCommittee
for Responsible Medicine

Summary of anti-cancer effects of plant based diets

- **Metabolic effects**:
  - WFPB diet promotes lower body weight/less T2DM

- **Healthier Sources**
  - Protein (and omega-3s)
  - Micro-nutrients eg. Vitamin C/D zinc etc for immune function

- **Fibre** >30g/d
  - Microbiome health, Insulin regulation, carcinogen removal

- **Phytochemicals** (bioactive cpds eg. polyphenols)
  - Anti-inflammatory, anit-oxidant (reduce oxidative stress/DNA damage), immune effects
  - 64x anti-oxidant power of animal products

Impact on protein intake, and cancer risk

- Protein intake influences growth hormones (e.g., IGF, IGF-1).
- High IGF-1 levels associate with increased cancer risk.
- Study of 6,381 adults; low protein intake, reduced IGF-1 levels
  - higher protein intake: 4x inc cancer risk; 75% rise in cancer mortality
  - 73x inc in diabetes risk
- No similar risks observed with plant proteins.
- 8-week whole food PB diet trial in metastatic breast cancer:
  - Reduced IGF-1 levels regardless of CHO intake.
  - Enhanced QOL and improved metabolic biomarkers (insulin, IGF-1, cholesterol).

    (Harris et al., Cancer and Metabolism, 2024)

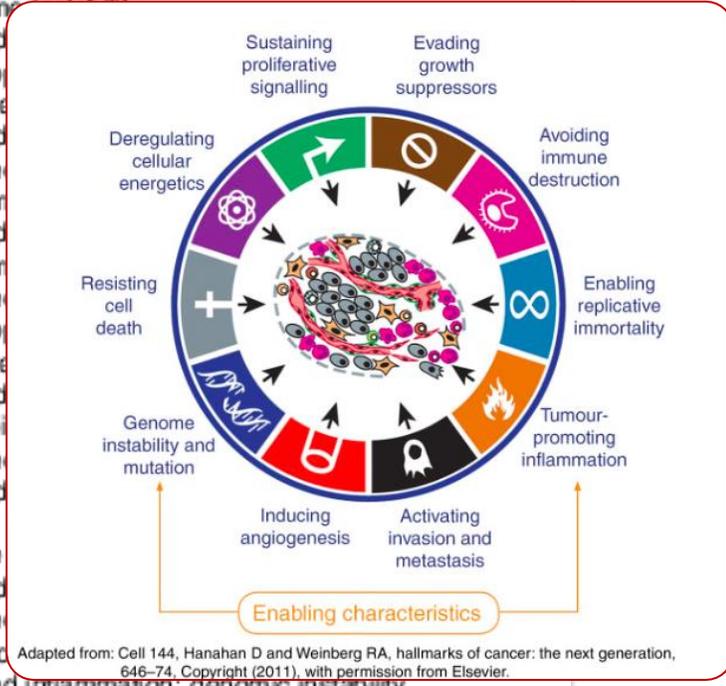
IGF-1 in the Body
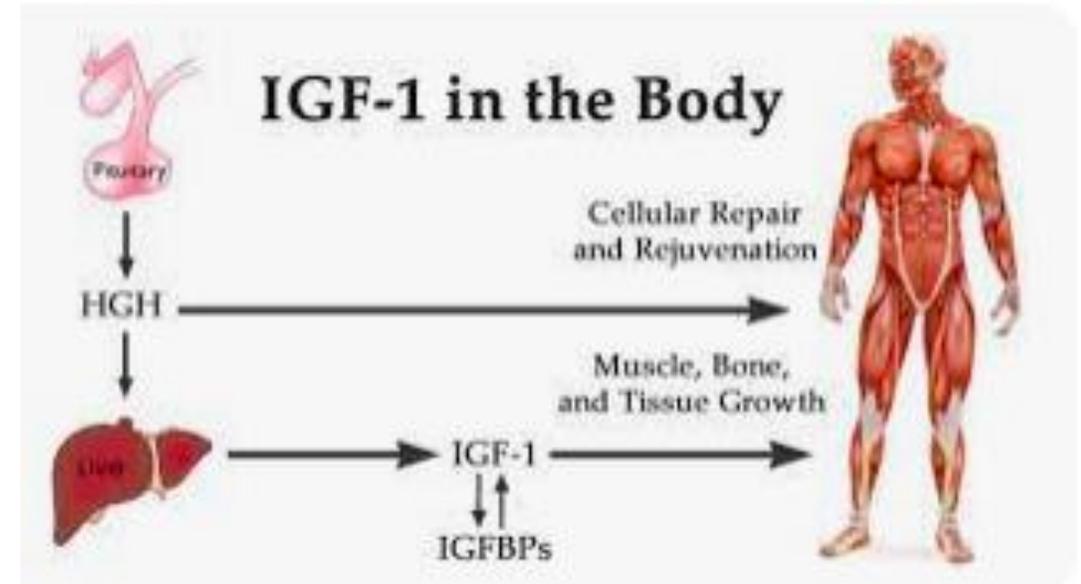
Published in final edited form as:
Cell Metab. 2014 March 4; 19(3): 407–417. doi:10.1016/j.cmet.2014.02.006.

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

Morgan E. Levine[a,1], Jorge A. Suarez[a,b,1], Sebastian Brandhorst[a,b], Priya Balasubramanian[a,b], Chia-Wei Cheng[a,b], Federica Madia[a,h], Luigi Fontana[c,d,e], Mario G. Mirisola[a,b,i], Jaime Guevara-Aguirre[j], Junxiang Wan[a,b], Giuseppe Passarino[f], Brian K. Kennedy[g], Pinchas Cohen[a,b], Eileen M. Crimmins[a], and Valter D. Longo[a,b,2]

[a]Davis School of Gerontology, University of Southern California, Los Angeles, CA 90033, USA

Exposure	Systemic impact	Cell function	Hallmarks possibly affected
Greater body fatness	Hyperinsulinaemia	mTOR/PI3K/AKT, MAPK	Reduced apoptosis; increased proliferation; genome instability
	Increased oestradiol	MAPK/ERK/PI3K	Increased proliferation in ER-positive tissues; genome instability
	Inflammation	STAT3/NF-κB	Reduced ... macro...
		WNT, P53	Cellular e...
Greater height	Higher IGF-I	mTOR/PI3K/AKT, MAPK	Reduced ...
Greater physical activity	Reduction in insulin	mTOR/PI3K/AKT, MAPK	Increased ... genom...
	Reduction in oestradiol and testosterone	MAPK/ERK/PI3K	Reduced ... genom...
	Reduced inflammation (long term); improved immune function	STAT3/NF-κB	Increase... macro...
		WNT, P53	Cellular e...
Greater intake of red and processed meat	Elevated exposure to nitrites; endogenous N-nitroso compound formation	DNA adduct formation → mutations in p53, KRAS	Reduced ... instabi...
		Oxidative stress, inflammation	Increase...
Greater intake of dairy foods	Higher IGF-I	mTOR/PI3K/AKT, MAPK	Reduced ...
Lower vegetables and fruit intake	Folate deficiency	DNA uracil misincorporation	Genome ...
	Low dietary fibre intake	Low butyrate	Reduced ...
	Low levels of carotenoids, vitamins A, C, E	Oxidative stress, inflammation	Increase... apopt...
Greater alcohol intake	Elevated acetaldehyde	Oxidative stress, lipid peroxidation	Increased inflammation; genomic instability
	Increased oestradiol	MAPK/ERK/PI3K	Increased proliferation in ER-positive tissues
	Inflammation	STAT3/NF-κB	Reduced apoptosis; increased cell division; altered macrophage function
	Folate deficiency; interference with 1-carbon metabolism	DNA uracil misincorporation	Genome instability

Adapted from: Cell 144, Hanahan D and Weinberg RA, hallmarks of cancer: the next generation, 646–74, Copyright (2011), with permission from Elsevier.

Specific components of western diets 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
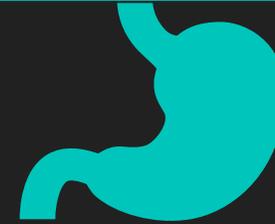
2. Protective mechanism of PB diets

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