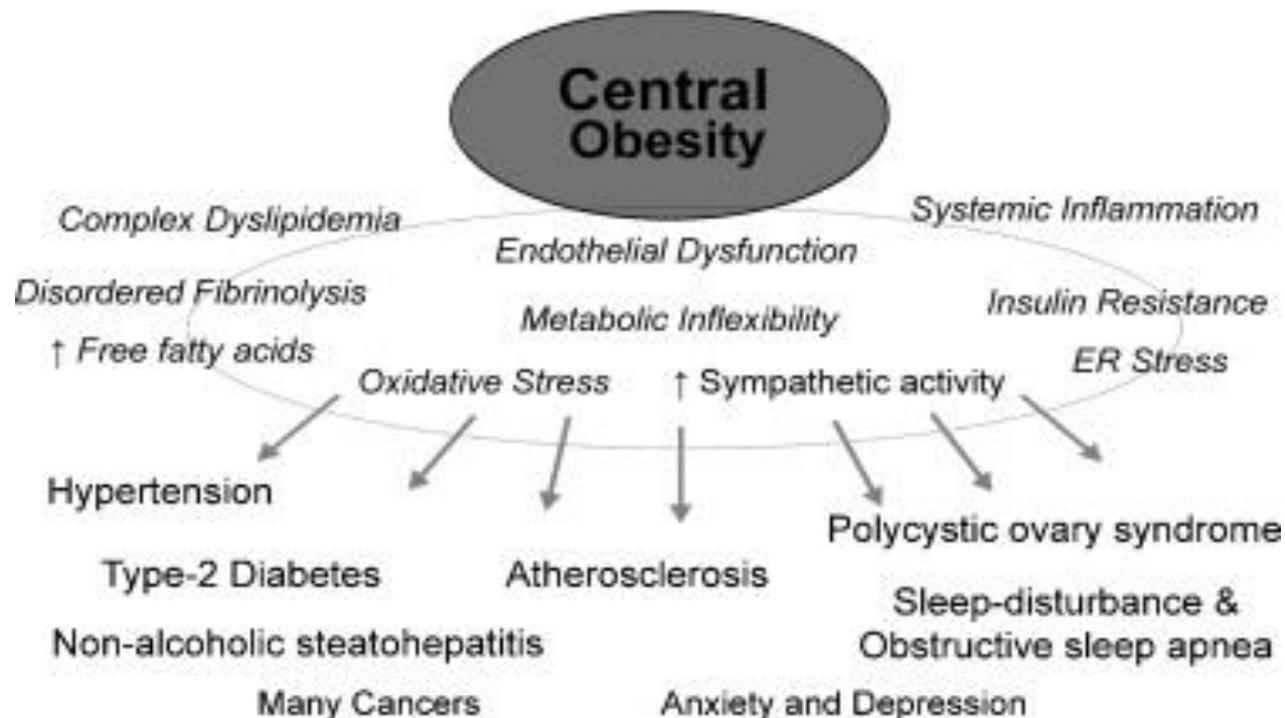


Obesity and Cancer: some of the truth

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The Metabolic Syndrome: A Metabolic and inflammatory cascade



Body Mass Index

- World Health Organization defines

Normal BMI: 18.5–24.9 kg/m²;

Overweight BMI: 25–29.9 kg/m²; and

Obesity BMI: >30 kg/m² (WHO, 2016)

World Health Organization-2016

- Worldwide obesity has nearly tripled since 1975.
- For those ≥ 18 years,
 - 1.9 billion adults (39%) were overweight.
 - 650 million (13%) were obese.
- 41 million children under the age of 5 were overweight or obese.
- 340 million children and adolescents aged 5-19 were overweight or obese.

USA

- $\frac{2}{3}$ over 20 years of age in the USA are overweight with a prevalence of obesity of 35% (Ogden et al., 2012).
- It is predicted to reach 42% by 2030 in people over 18 years (Finkelstein et al., 2012).

Obesity in South Africa

- 70% of females and 39% of males are overweight or obese
- Highest obesity rate in Sub-Saharan Africa
- **28.3% adults are obese**
- Obesity figures doubled in 6 years (compared with 13 years in the US)

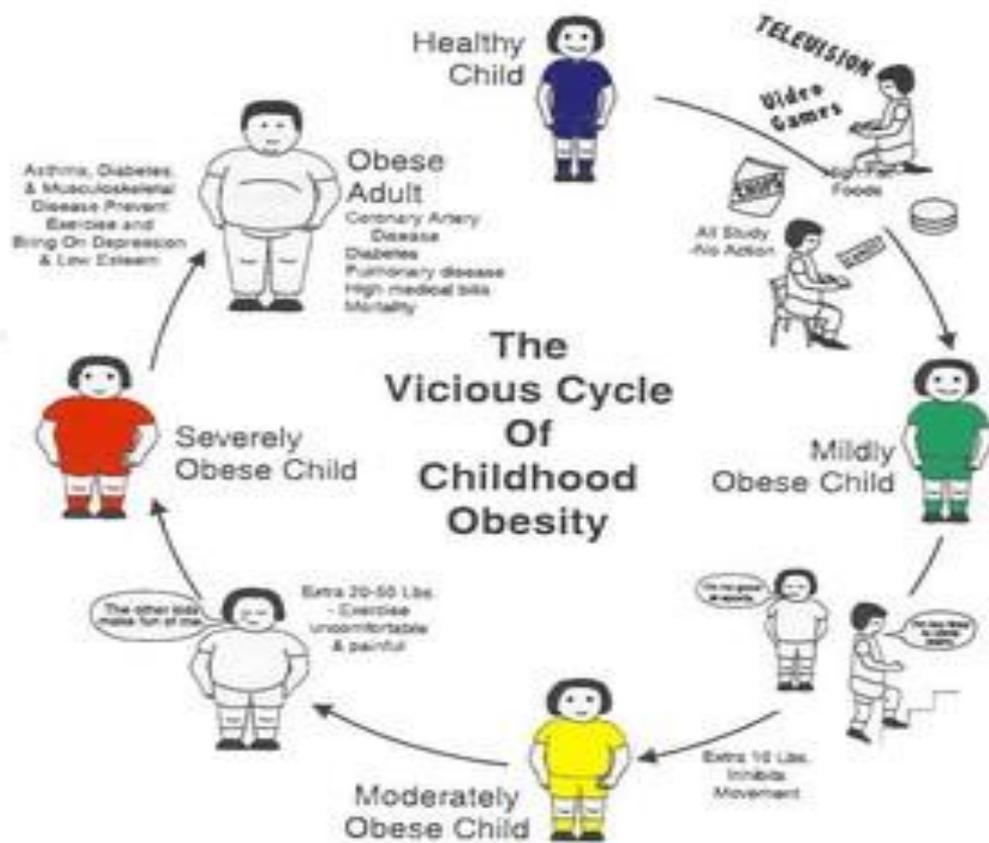
Drivers of Obesity

- The main driver for obesity is an overall rise in caloric intake (Swinburn et al., 2009).
- Increased consumption of high carbohydrate beverages and dietary fat.
- Low levels of physical activity (Cameron et al., 2003)
- Significant but poorly understood role of genetic factors but accounts for less than 5% of obesity (Thorleifsson et al., 2009).

Childhood Obesity

Longitudinal studies show

- 60% of preschool children who are overweight will be overweight at 12 years of age
- Pre-teens who are overweight are more likely to also be overweight adolescents
- Overweight during adolescence is a predictor of overweight in adulthood (Choudhary, 2007)



Childhood Obesity in South Africa

- 14.2% of primary school children are overweight
- Overweight and obesity in young women aged 13-19 years is 30-40%
- Nationally: overweight and obesity are as common as stunting (17% and 19% respectively)
- It is estimated by 2025: 3.91 million school children will be overweight or obese
- 30% of girls in urban areas are overweight (NDoH, 2016)
- Birth to Twenty Study: girls who were obese between the ages of 4-6 years are 42 times more likely to be obese teenagers (Lundeen, 2016)

Predisposition to Obesity in-utero

- Maternal leisure-time physical inactivity (Mudd, 2015)
- Maternal smoking during pregnancy (Rayfield, 2017)
- Excessive gestational weight gain and obesity, gestational diabetes and high birth weight
- Protein content of maternal diet
- Short sleep duration during pregnancy (Lagisz, 2015).
- Children born by caesarean section also seem to be at higher risk of developing obesity in childhood (Kuhle, 2015)

Predisposition to Obesity in Early Infancy

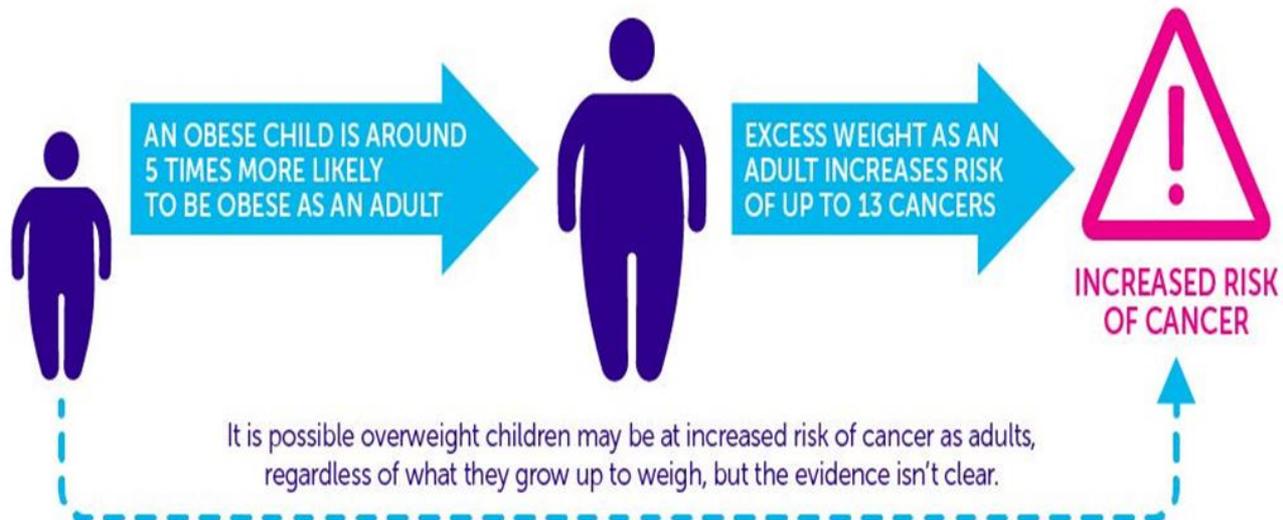
- Sugar-rich foods fed to infants before 4 months of age (Wang, 2016)
- High protein diet in non-breast feed children (Lifshitz, 2015)
- Antibiotic exposure to infants <2 years might be associated with increased risk for childhood overweight or obesity (Miller, 2018)
- Famine exposure during early life may increase the risk of overweight and obesity later in life especially in females (Zhou, 2018)

Other factors contributing to Childhood Obesity

- Availability, accessibility, and affordability of energy-dense foods
- Marketing strategies
- Decreased daily physical activity
- Urbanization (Mei, 2016)
- Shorter sleep duration: poorer cardio-metabolic risk profile in adolescence (Cespedes, 2018)
- Sleep quantity/quality impacts on cardiovascular risk profile, circadian rhythms that influence body weight regulation (Lebourgeois, 2017)
- Short sleep duration and poor sleep quality in children are associated with a significantly increased risk of adolescent obesity (Wu, 2017)

Obesity and Cancer

HOW DOES OBESITY IN CHILDHOOD AFFECT CANCER RISK AS AN ADULT?



LET'S BEAT CANCER SOONER
cruk.org/health

Source: cruk.org/childhoodobesity



Childhood Obesity and Cancer

- Adult weight is not the sole driver of the obesity and cancer link.
- Overweight in AYA has also increases the risk of many cancers.
- With a global trend towards higher rates of childhood obesity and AYA obesity, the reported links with adiposity from earlier birth cohorts portend an even greater burden from obesity and cancer as adults live more of their lives overweight or obese.
- This observation stresses the importance of reversing the current trend of rising obesity rates in children and young adults.

Association between Adolescent Obesity and Adult Cancers

- A study of 2.3 million adolescents ,45 year follow-up period.
- For the first time, possible associations between obesity during adolescence and the risk of developing different types of cancers in adulthood were investigated.
- An association with increased BMI during adolescence and higher risk for leukaemia , Non-Hodgkin lymphoma, pancreatic cancer, gastroesophageal adenocarcinoma colorectal cancer, renal cell carcinoma and acute myeloid leukaemia in adulthood.
- Higher BMI in adolescence was found to be associated with increased cancer risk(Weilrauch-Bluher, 2019)

Childhood Obesity and Cancer

- In 2003-2004, **17.1%** of American children and adolescents aged **2 to 19 years were overweight or obese** (Ogden et al, 2006).
- Excess bodyweight in adolescence carries an increased risk of colon cancer mortality in adulthood
 - men (relative risk [RR], 2.1; 95% confidence interval [CI], 1.1-4.1)
 - women (RR, 2.0; 95% CI, 1.2-3.5) (Bjorge et al, 2008).
- These results underline the necessity of preventing childhood obesity.

Excess body weight in Childhood and Early Adulthood and later Cancer Risk

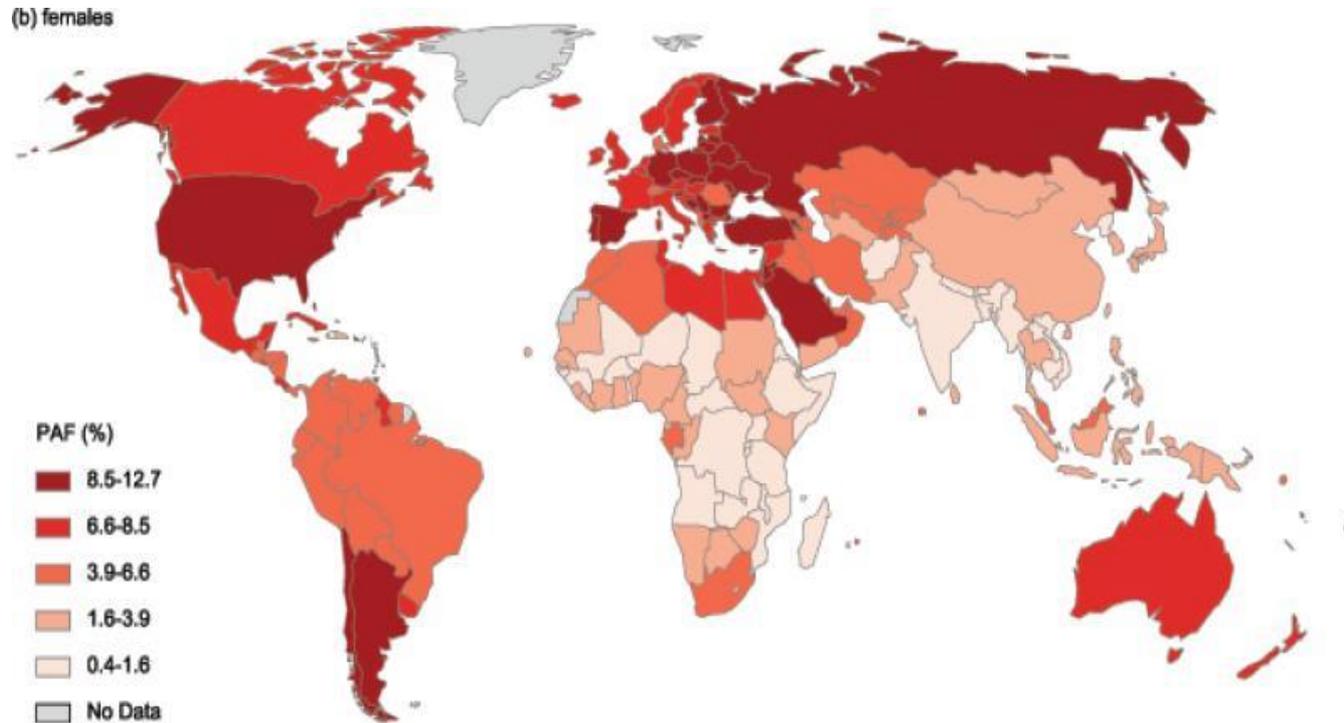
- Overweight or obesity during childhood and early adulthood is associated with an increased risk of **pancreatic cancer** [hazard ratio (HR) 1.67 for overweight and HR 2.58 for obese]
- Additionally, it was associated with higher risk of **younger age** of onset and **reduced survival**.
- In women who were overweight in childhood , there was a 28% higher risk of developing **colon** cancer.
- Excess body weight in both early and later adulthood is also associated with increased risk of **multiple myeloma** (Colditz, 2018)

Young Adult Cancer: Influence of the Obesity Pandemic (Berger, 2019)

Cancers traditionally associated with older adults are increasing in younger patients aged 20–40

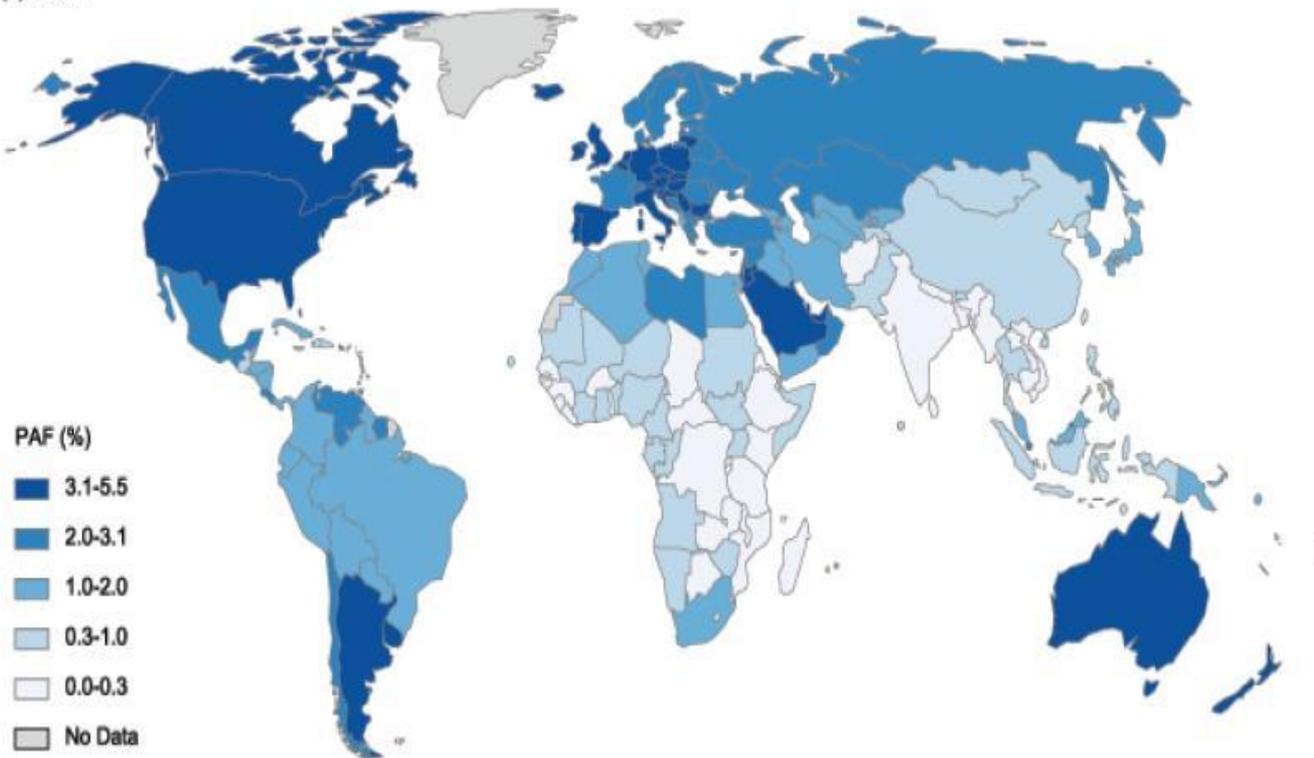
- Breast cancer: 10.5%
- Colorectal cancer: 5.8%
- Kidney cancer: 7.8%
- Endometrial cancer: 7.3%
- Thyroid cancer: 23.9%
- Liver cancer: 2.5%
- Gastric cardia: 6.2%
- Meningioma: 16.8%
- Ovarian cancer: 10.6%

Population attributable fraction of new cancer cases due to excess body mass index in 2012 in females



Population attributable fraction of new cancer cases due to excess body mass index in 2012 in males

(a) males



Global burden of cancer attributable to high body-mass index in 2012: a population-based study (Arnold et al; 2015)

- An estimated **481 000** or 3.6% of all new cancers (or 12.8% of all high-BMI- related cancers) in adults in 2012 were attributable to high BMI.
- **136 000** (1.9%) new cancers in men and **345 000** (5.4%) in women were attributable to high BMI.

Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults (Bashkaran et al; 2014)

- 166 955 BMI-related cancers in 24 million individuals
- BMI was associated with 17 of 22 cancers
- Each 5 kg/m² increase in BMI was linearly associated with cancers

uterus (hazard ratio [HR] 1.62, 99% CI 1.56–1.69; p<0.0001)

gallbladder (1.31, 1.12–1.52; p<0.0001)

kidney (1.25, 1.17–1.33; p<0.0001)

cervix (1.10, 1.03–1.17; p=0.00035)

thyroid (1.09, 1.00–1.19; p=0.0088)

leukaemia (1.09, 1.05–1.13; p ≤0.0001).

Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults (Bashkaran et al; 2014)

- BMI was **positively** associated with
 - liver (1.19, 1.12–1.27)
 - colon (1.10, 1.07–1.13)
 - ovarian (1.09, 1.04–1.14)
 - postmenopausal breast cancers (1.05, 1.03–1.07)
 - overall ($p < 0.0001$)

Estimated that a **1 kg/m²** population-wide increase in BMI would result in **3790** additional annual UK patients developing one of the ten cancers positively associated with BMI.

Lag-time for the development of Cancer

- The precise time lag between development and duration of high BMI and the occurrence of cancer is not well established.
- However, the general perception is that excess bodyweight does not initiate cancer, but rather promotes cancer to clinical presentation over several years.
- It is suggested that a **10-year lag time** of sustained high BMI increased the risk of cancer (Arnold; 2015).

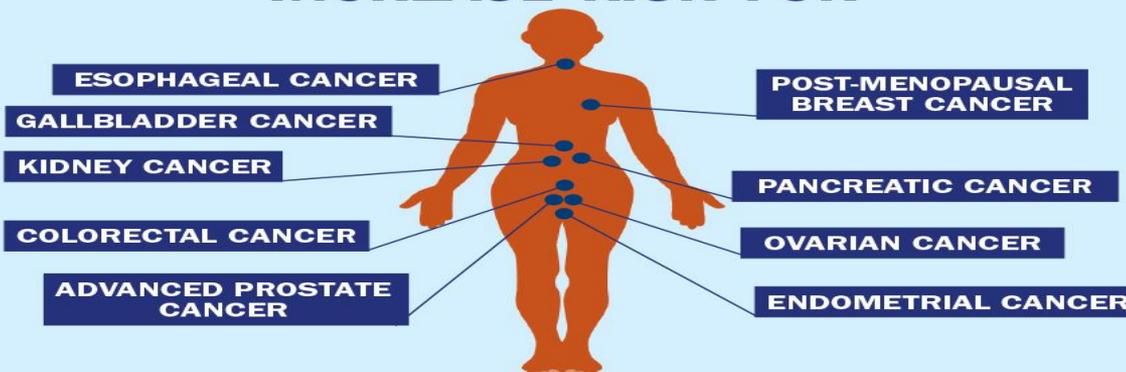
WHAT YOU NEED TO KNOW ABOUT OBESITY AND CANCER



After not smoking,
BEING AT A HEALTHY WEIGHT
Is **THE MOST IMPORTANT THING** you can do
to prevent cancer.



Overweight and obesity
INCREASE RISK FOR¹



AICR ESTIMATES THAT **EXCESS BODY FAT** IS A CAUSE OF APPROXIMATELY

122,200

U.S. CANCER CASES EVERY YEAR.²

AND YET...
7 in 10 Americans
are currently
overweight or obese.³



69%

AND ...
Less than half of
all Americans
are even aware of the
obesity-cancer link.⁴



48%

PROTECT YOURSELF!

Move More



Eat Smart



For tips on getting to, and staying at, a healthy weight, visit www.aicr.org

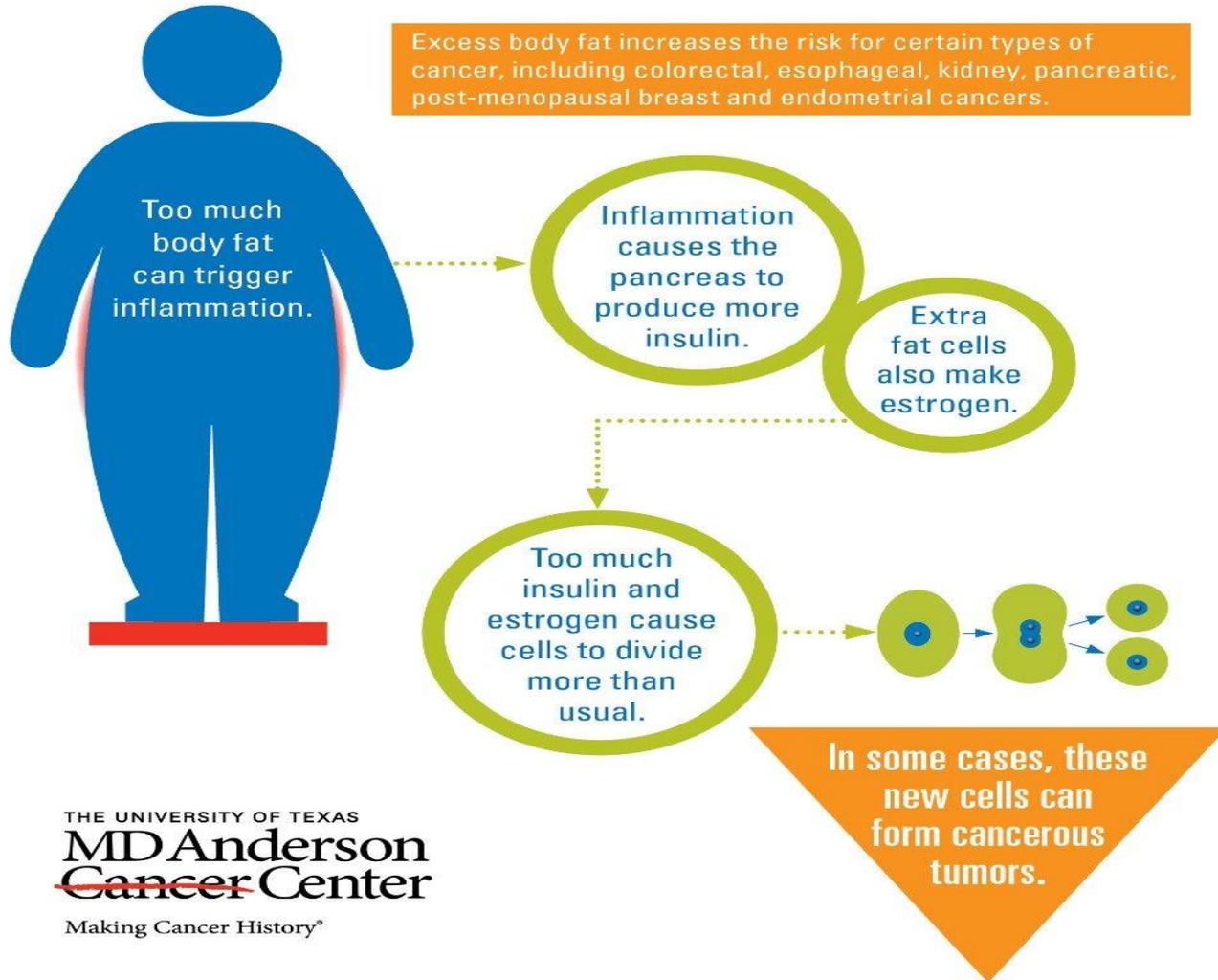
¹ AICR/WCRF Expert Report (2007) and Continuous Update Reports (Ongoing), ² AICR/WCRF Policy Report (2009) and 2014 preventability update, ³ US Center for Disease Control and Prevention: Obesity and Overweight, ⁴ 2013 AICR Cancer Risk Awareness Survey

The evidence is the latest from the Continuous Update Project (CUP), which systematically updates and reviews the research conducted worldwide into cancer risk related to diet, physical activity and body weight. All the evidence gathered is then assessed by a panel of independent scientists who make recommendations for cancer prevention.

Pathophysiology of Obesity and Cancer

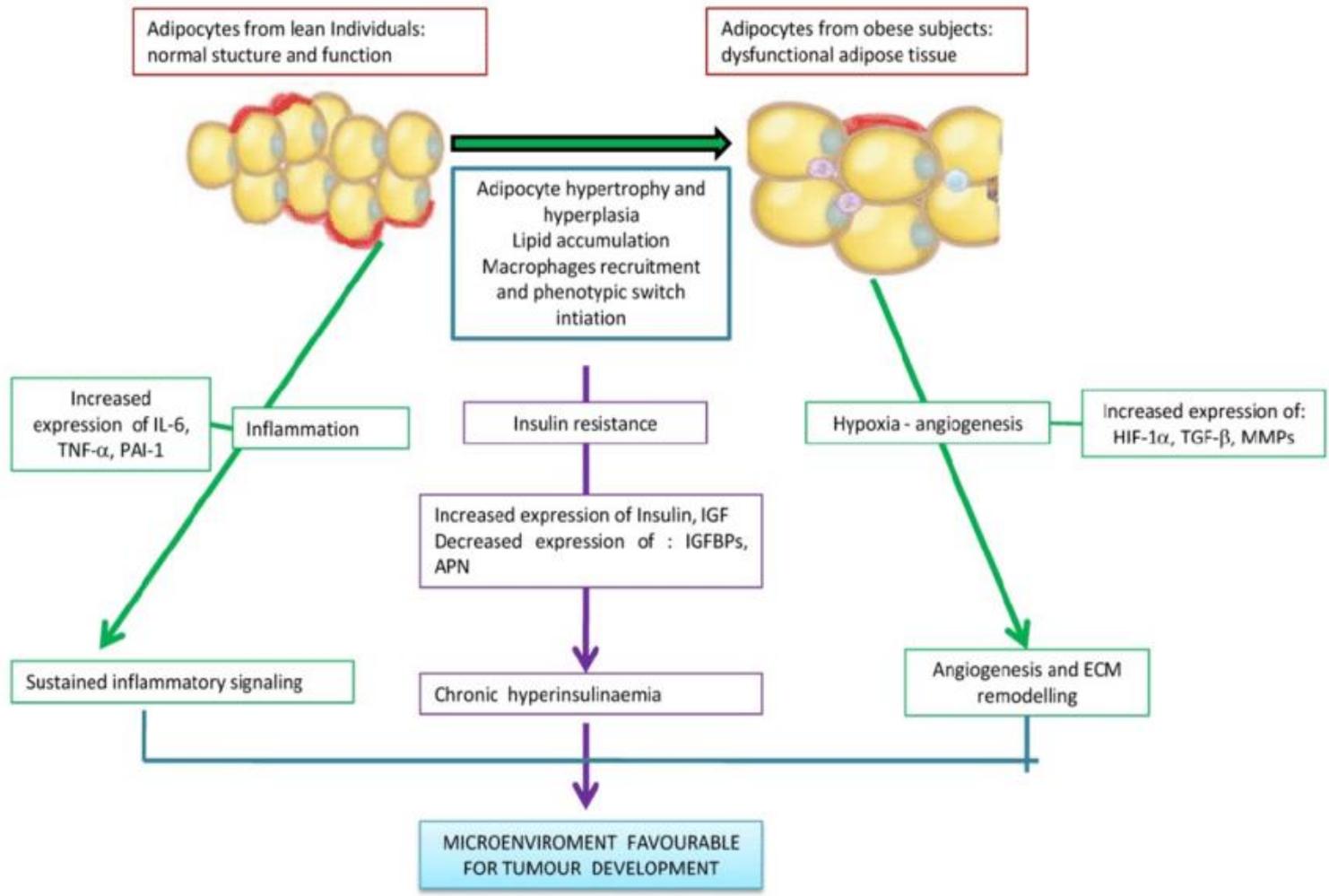
- Obesity is strongly associated with changes in the physiological function of adipose tissue, leading to **insulin resistance**, **chronic inflammation**, and altered secretion of **adipokines**.
- Several of these factors, such as **insulin resistance**, increased levels of **leptin**, **plasminogen activator inhibitor-1**, and endogenous **sex steroids**, decreased levels of **adiponectin**, and **chronic inflammation**, are involved in carcinogenesis and cancer progression.

How excess body fat can cause cancer



Dysfunctional Adipose Tissue

- Adipose tissue: **endocrine** and **metabolic** organ made up of **adipocytes**, **pre-adipocytes**, **fibroblasts**, and **macrophages**
- Produces **adipokines**: **leptin**, **adiponectin**, **plasminogen activator inhibitor**, **vascular endothelial growth factor**, **tumour necrosis factor-alpha**, and **interleukin-6**.
- As adipose tissue expands, adipocytes enlarge and produce chemotactic factors e.g. **monocyte chemoattractant protein**, that attract monocytes/macrophages into adipose tissue .

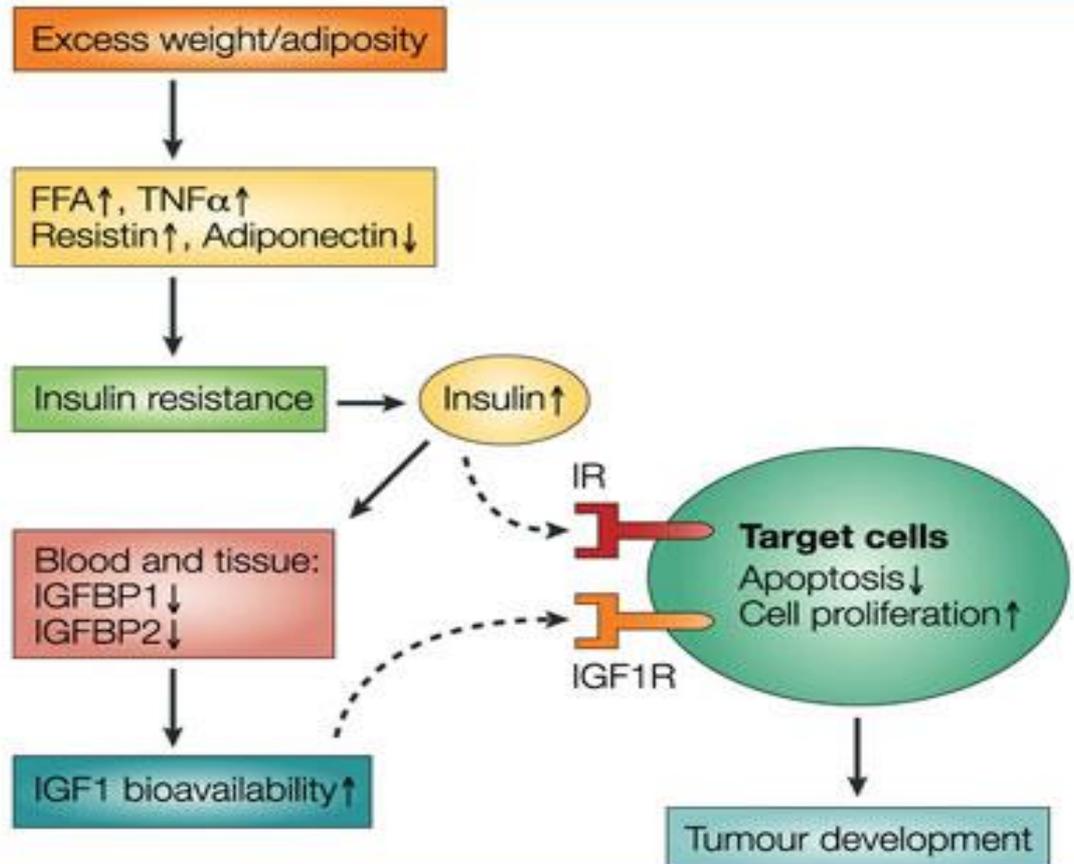


Adipokines

- Several adipose-derived factors - adipokines -
 1. **adiponectin**
 2. **tumour necrosis factor- α**
 3. **interleukin-6** (Fain et al., 2004).
- The expansion of adipose tissue in obesity leads to a rise in the plasma levels of these factors (Vendrell et al., 2004).
- The incidence of several cancers is increased with elevated circulating leptin and IL-6 levels (Wu et al., 2009)
- The risk of colorectal adenomas, which have the potential to develop into carcinomas, have been associated with an increased secretion of TNF- α and IL-6 (Kim et al., 2008).

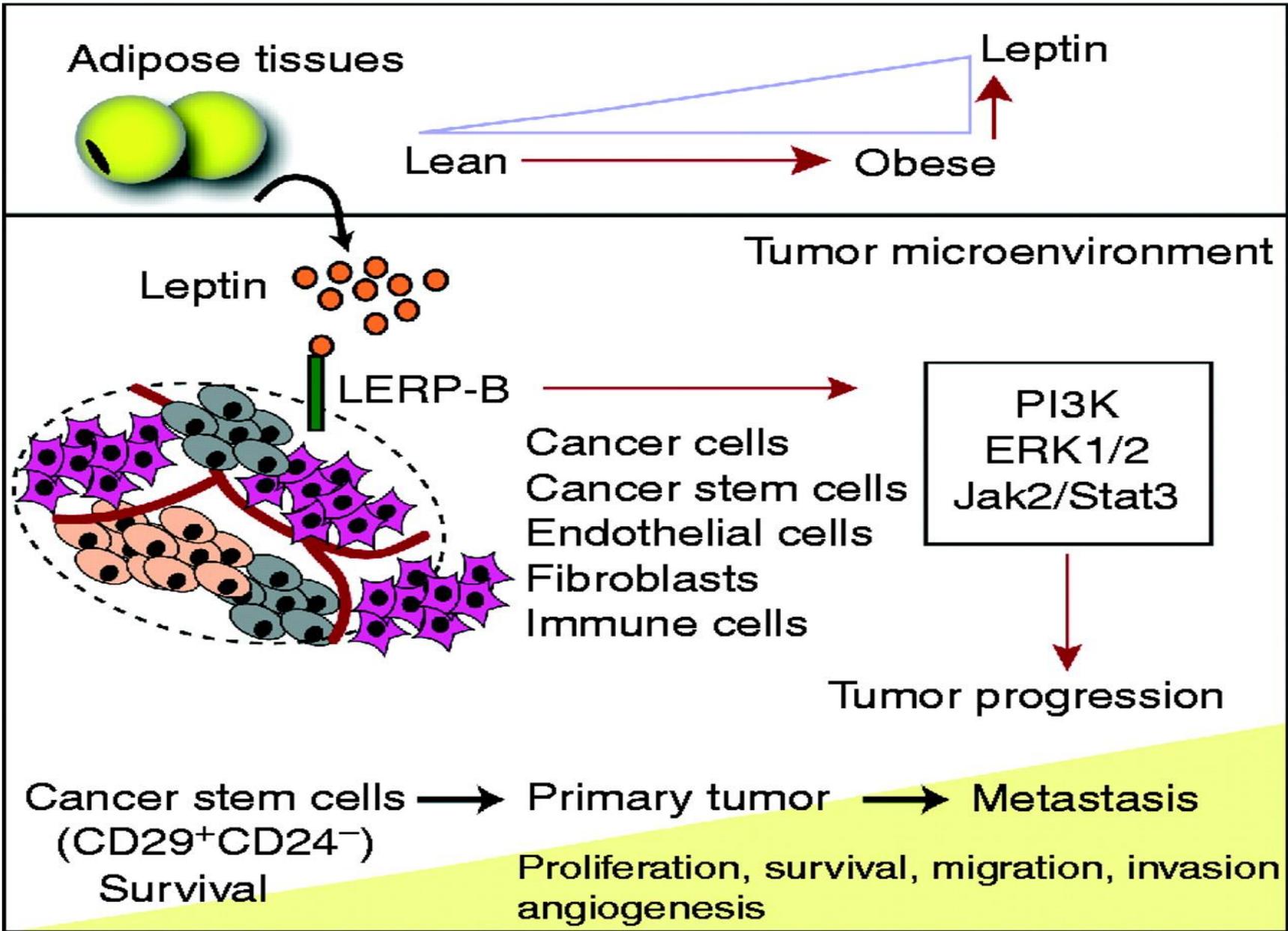
Insulin Resistance

- Adiposites: site of **insulin activity**, promotes triglyceride storage and inhibits lipolysis (Choi et al., 2010).
- Postmenopausal breast cancer is an obesity-associated cancer resulting from insulin resistance (Bhaskaran et al., 2014).
- **Insulin resistance** is a feature of obese individuals, accompanied by a high circulating insulin, a well-established risk factor for cancer (Kim et al., 2004) and which is associated with marked changes in the levels of inflammatory markers (Lee and Lee, 2014).



Leptin

- Leptin regulates food intake and body weight via actions on the CNS and adipocytes to **suppress appetite and promote metabolism** (Halaas et al., 1995).
- It is present at higher levels in obese individuals and positively correlates with an increased proportion of body fat and leptin resistance.
- High leptin levels are associated with an increased risk of **colon cancer** (Stattin et al., 2004) and breast cancer (Han et al., 2005; Wu et al., 2009).
- Postmenopausal women with the highest waist circumference and leptin concentration have the greatest risk of **breast cancer** (Wu et al., 2009).
- An increased leptin receptor expression has been identified in several types of cancers (Attoub et al., 2000; Kim, 2009).



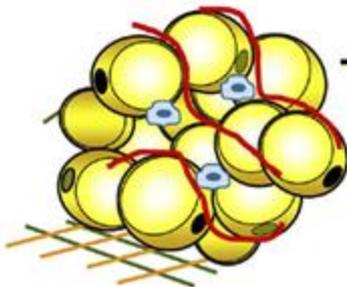
How does Leptin promote carcinogenesis?

- Stimulates **cell proliferation and tumour growth** (Chen et al., 2013) and an increased expression of leptin receptors in several types of cancer (Dieudonne et al., 2002).
- Leptin is a promotor of cyclin D1 (Gonzalez et al., 2006), important for cell cycle progression.
- Leptin also promotes **angiogenesis**, contributing to tumour growth (Gonzalez et al., 2006).
- Leptin also increases aromatase expression leading to enhanced pro-estrogenic pathways, oestradiol production and oestrogen receptor- α signalling (Catalano et al., 2004)
- Postmenopausal breast cancer is strongly associated with obesity (Renehan et al., 2008).
- Postmenopausal women with high waist circumference and leptin concentration have the greatest risk of breast cancer (Wu et al., 2009).

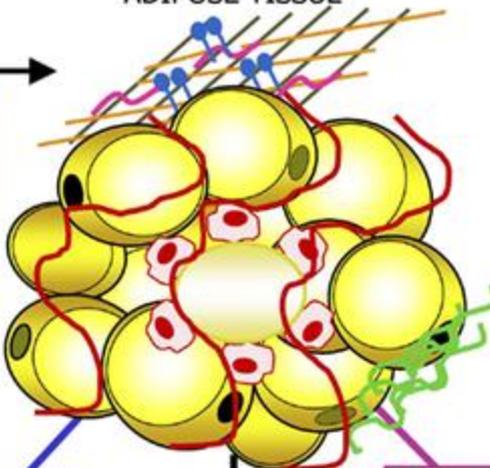
Chronic Inflammation

- **Obesity induces chronic low- grade inflammation**
- Increased number of macrophages in adipose tissue
- Trigger for the chronic inflammatory response of adipose tissue is thought to be hypoxia.
- Proposed: as adipose tissue enlarges, individual cells are further from blood vessels and become poorly oxygenated
- This state of relative hypoxia activates hypoxia-inducible factor, (HIF) a key regulator of oxygen homeostasis.
- The increased expression of IL-6 and leptin, the decreased production of adiponectin, and the HIF-mediated attraction of macrophages into adipose tissue initiates the inflammatory response in adipose tissue (Kruiksdijk, 2009)
which stimulates carcinogenesis

**LEAN individual: NORMAL
STRUCTURE AND FUNCTION**

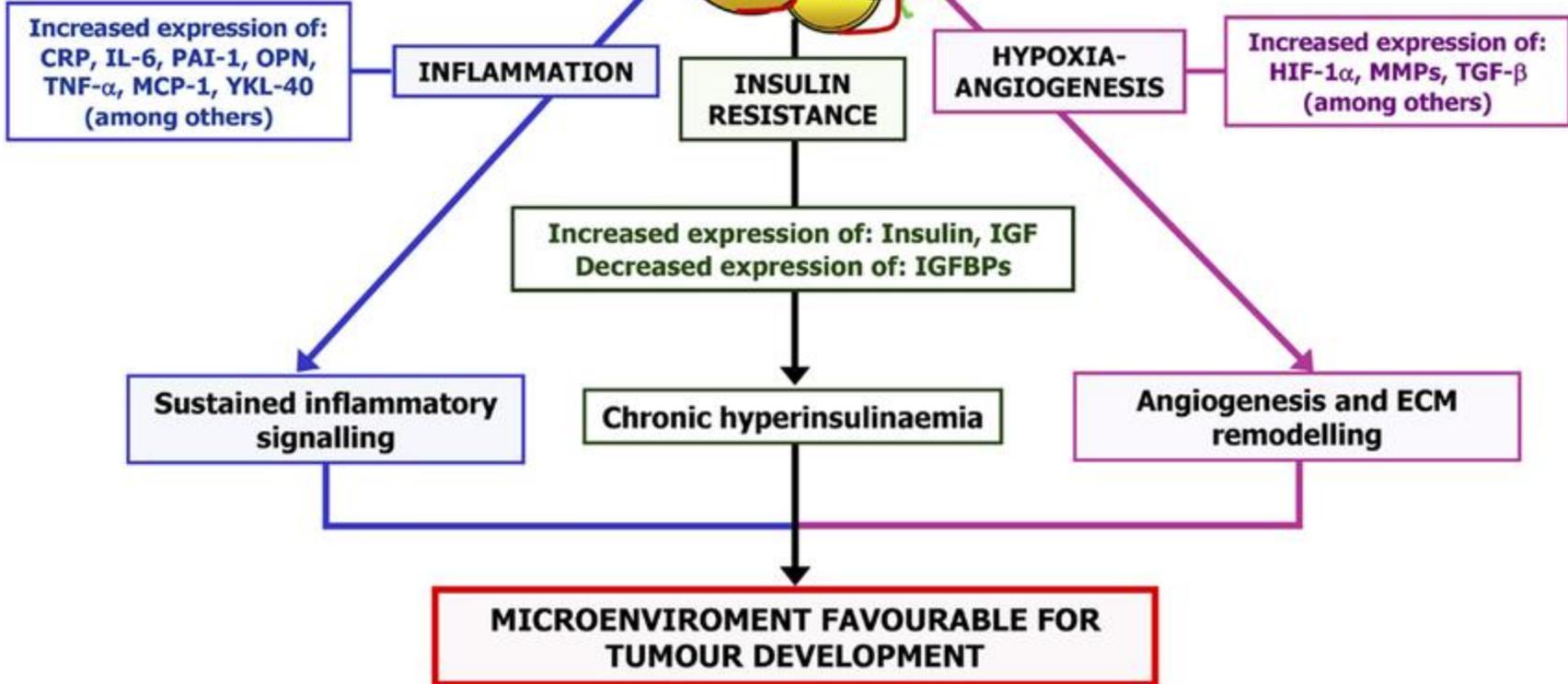


**OBESSE subject: DYSFUNCTIONAL
ADIPOSE TISSUE**



Adipocyte hypertrophy and hyperplasia
Lipid accumulation
Macrophages recruitment & phenotypic switch initiation

- Adipocyte
- M1 Macrophage
- M2 Macrophage
- Fibrotic depots
- Fibronectin
- Collagen
- Laminin
- Proteoglycan
- Capillaries

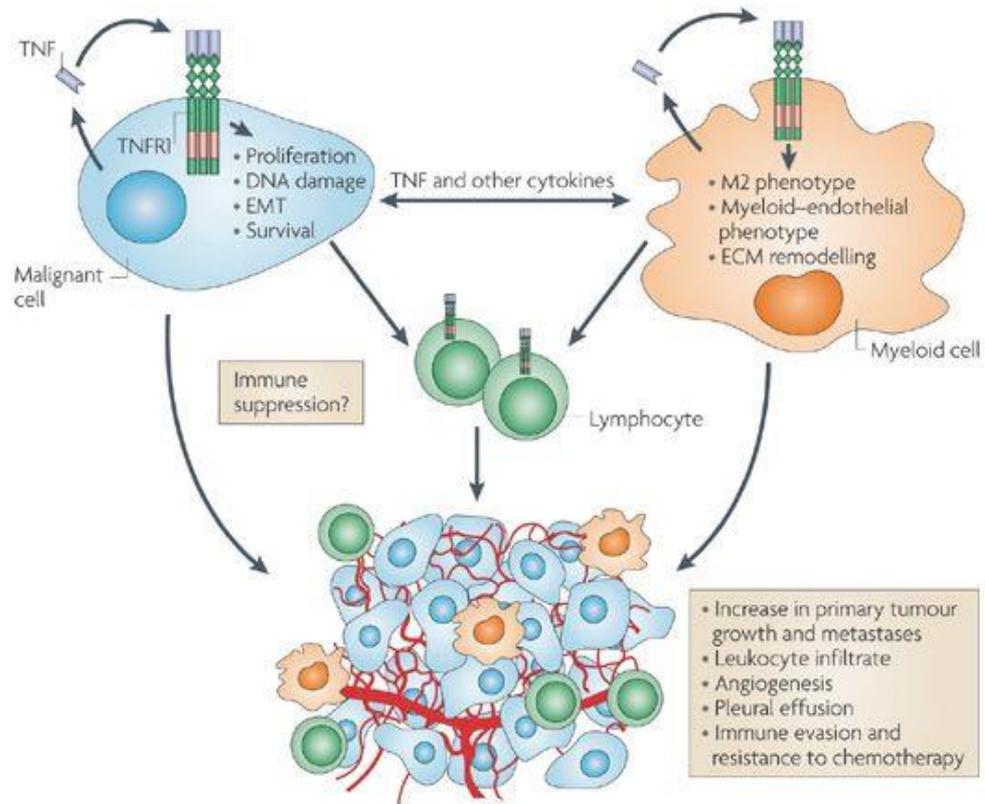


Ceruloplasmin

- A recently identified adipokine is ceruloplasmin which is **highly concentrated in adipose tissue from obese individuals** (Arner et al., 2014).
- It is estimated that adipose tissue secretion accounts for almost one quarter of the circulating level of this protein.
- As ceruloplasmin is involved in **angiogenesis**, its increased presence in obese subjects is thought to promote the development of several cancers.

Tumour Necrosis Factor α

- Is up-regulated with an increase in BMI (Kim et al., 2008)
- TNF plays important roles in diverse cellular events such as cell survival, proliferation, differentiation, and death.
- As a pro-inflammatory cytokine, TNF is secreted by inflammatory cells, which may be involved in inflammation-associated carcinogenesis.
- Correlation between circulating TNF- α levels and the prevalence of colorectal adenomata (Kim et al., 2008).
- TNF stimulates proliferation, survival, migration, and angiogenesis in most cancer cells



Interleukin-6

- Strong association between inflammation and cancer is reflected by the high **IL-6 levels in the tumour micro-environment, promotes tumorigenesis by up-regulating apoptosis, survival, proliferation, angiogenesis, invasiveness and metastasis of cancer cells.**
- Plasma levels of IL-6 in the systemic circulation of morbidly obese patients are significantly greater than control healthy volunteer subjects (Vendrell et al., 2004).

Inositol-requiring Enzyme (IRE)

- A recently described enzyme is IRE is an endoplasmic reticular enzyme which activates the Unfolded Protein Response, a coordinated reaction to stress which can lead to macromolecular degradation and apoptosis.
- Adipose macrophages activate IRE which induces a shift to a more highly pro-inflammatory state (Bujisic et al; 2017) which contributes to carcinogenesis.

Th17 T-Helper cells

- Th1 and Th2 helper T cells are involved in the inflammatory status
- The discovery of Th17 cells as a subtype of CD4+ effector T cells which contribute to the development of inflammation and hyperglycaemia (Ip et al., 2016).
- **Th17 cells represent a crucial link between inflammatory status, type-2 diabetes, elevated BMI values, and carcinogenesis (De Simone et al., 2013).**

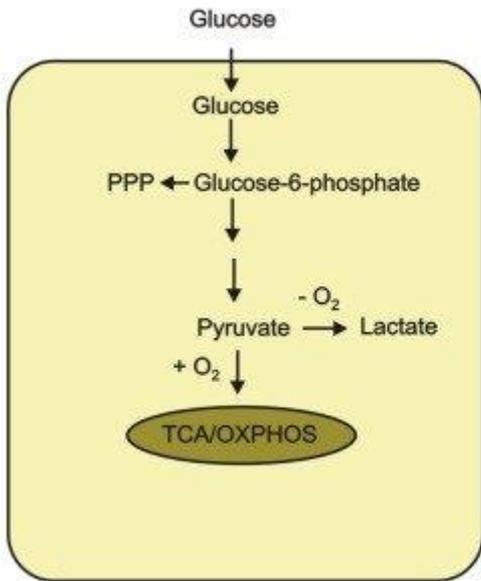
Obesity and Diabetes Responsible for Rising Global Cancer Burden

- "While obesity has been associated with cancer for some time, the link between diabetes and cancer has only been established recently"
- In men, liver cancer is the most common cancer caused by diabetes and high BMI, accounting for 126 700 cases, and colorectal cancer is second, accounting for 63 200 cases.
- In women, 147 400 breast cancer cases constituted 29.7% of all cancers attributable to diabetes and high BMI.
- Endometrial cancer is second, accounting for 121 700 new cancer cases or 24.5 per cent of all diabetes and high BMI related cancers

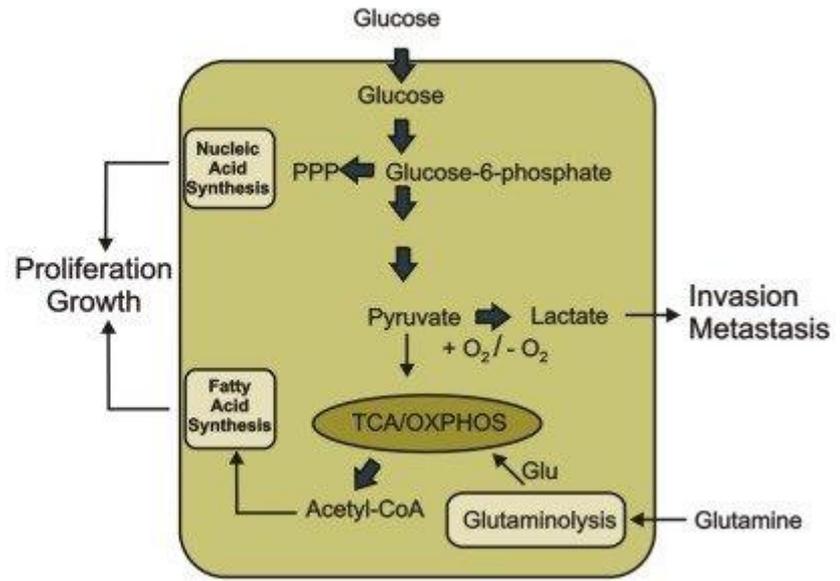
Glucose Metabolism

- A chronically high blood glucose: hyperinsulinemia, insulin resistance, and enhanced bioactivity of the IGF axis which increases the risk of cancer.
- Insulin also influences cancer development by altering sex hormone metabolism.
- High dietary GI and GL is significantly associated with increased risk of colon and bladder cancer (Sieri et al; 2017)

Normal cell



Cancer cell

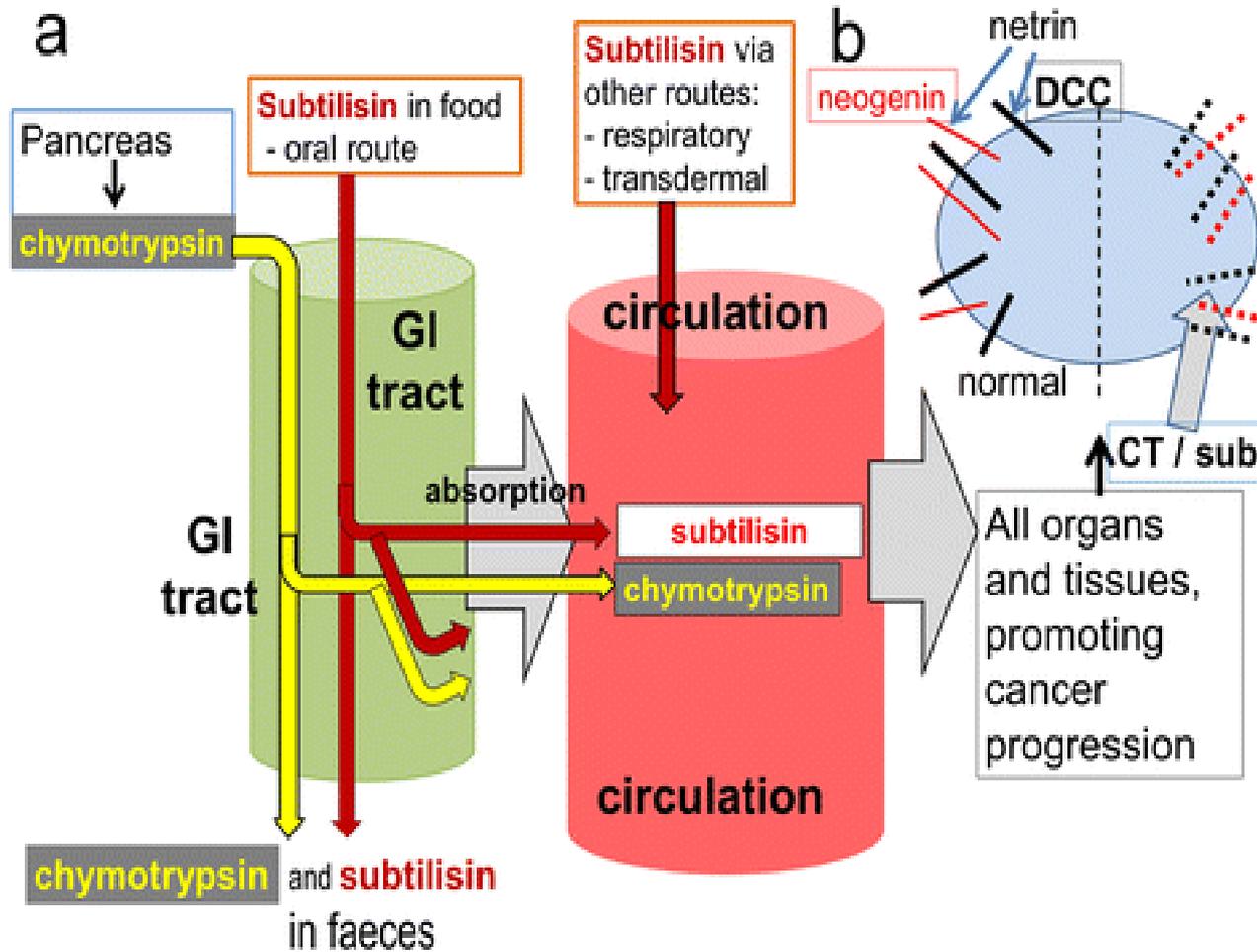


Kynurenine Pathway

- The consumption of the amino acid tryptophan is a critical factor in progressive cancer.
- Many cancers upregulate a liver enzyme, tryptophan dioxygenase, to drive tryptophan consumption.
- The primary product of this process, kynurenine, is an endogenous ligand for the aryl hydrocarbon receptor, which mediates invasive tumour growth.
- Elevated tryptophan consumption helps tumours to overcome immune barriers to cancer progression (Opitz, 2017).

Subtilisin

- Several species of *Bacillus* secrete subtilisin, and colonise the intestine and can survive digestion (Hong et al., 2008).
- Subtilisin is a protease used in the preparation of animal feedstuffs and probiotics administered as alternatives to antibiotics to increase meat production in farm animals (Kampf, 2012).
- Subtilisin entering the food chain, esp. with processing of red meat.
- Epidemiological data : dietary processed red meat is more carcinogenic than fresh produce.
- A significantly higher risk of several forms of human cancer is associated with regular meat consumption (Mourouti et al., 2015)



Obesity and Cancer Surgery

- Association between BMI and an **increased incidence complications**, such as wound dehiscence and infection
-
- Breast cancer: obese patients had nearly 3 times the odds of developing lymphedema.
- **Detrimental effects of obesity on wound healing: decreased vascularity in adipose tissue, increased wound tension, and increased tissue pressure.**
- Delays in the chemotherapy and radiation.
- Prostate cancer: prolonged surgical time and blood loss was in obese patients and increased risk of positive margins after prostatectomy, recurrence and poor outcomes.

Obesity and Radiation

- Radiation therapy: targeted ionizing radiation.
- Prostate cancer: external-beam radiation therapy has inferior outcomes in obese patients
- **Proposed mechanisms: technical issues of delivering radiation therapy to obese patients, e.g. daily set up and an increased likelihood of shifts in tumour.**
- Obese patients with cervical cancer: increased treatment-related toxicities
- Breast cancer: large breast size and high BMI (>25 kg/m²) associated with an increased risk of acute dermatitis after whole-breast radiation therapy.

Obesity and Chemotherapy

- Doses are calculated using the body surface area.
- Up to 40% of obese patients receive **decreased dosing**.
- Use ideal body weight or an arbitrary cap for BSA to calculate treatment dose, because of concerns about **toxicity**.
- Reductions in the dose are associated with disease recurrence and mortality, contributes to reduced survival
- Despite recommendations, variations in chemotherapy dosing suggest substantial uncertainty among physicians about selecting optimal chemotherapy doses for overweight and obese cancer patients.

Overall Dietary Considerations

- Plant-based foodstuffs are considered to be protective against cancer (Orlich et al., 2015).
- Review of 156 studies: cancer risk in people consuming low amounts of fruits and vegetables was approximately double that of individuals with a high intake(Block et al., 1992).
- Family of Bowman- Birk protease inhibitors (BBIs)(found in vegetables and fruit): protect against many cancers.
- Many BBIs are efficient inhibitors of cancer cell growth: preventative and curative properties against cancer (Aggarwal et al, 2006).
- BBIs inhibit serine protease-induced tumour suppressors (Stone et al, 2017) could be a key element in anti-cancer activity.

Policy Strategies

Policy strategies to curb overweight and obesity

- Reduce caloric intake
- Increase physical activity,
- Increase taxes on calorically dense and nutritionally sparse foods
- Subsidise healthier foods, especially in economically disadvantaged groups
- Agricultural policy changes
- Urban planning: encourage walking and physical activity.
- Research strategies that identify population-wide or community-based interventions and policies that effectively reduce overweight and obesity should be encouraged and supported.



OB_S_Y
is a cause of cancer