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Review Article

Obesity-related Cancers: The Coming Epidemic

Abstract

The world is in the grip of an obesity pandemic, with tripling of obesity rates since 1975; it is predicted that one-third of people on Earth will be obese by 2025. The health consequences of obesity are primarily thought to be related to cardiometabolic disorders such as diabetes and cardiovascular diseases. It is less well appreciated that obesity has been related to at least 13 different cancers and in future, (with increasing control over tobacco misuse and infections), obesity will be the main cause of cancers. While this is an area of active research, there are large gaps in the definition of what is an obesity related cancer (ORC) and more importantly, what are the underlying mechanisms. To an extent, this is due to the controversy on what constitutes "unhealthy obesity" which is further related to the causes of obesity. This narrative review examines the causes and measurement of obesity, the types of obesity-related cancers and possible mechanisms. The information has wide implications ranging from prevention, screening, prognosis and therapeutic strategies. Obesity related cancers should be an area of high-priority research. Oncologists can contribute by spreading awareness and instituting management measures for individual patients in their care.

Keywords: *Carbohydrate-insulin model, gut microbiome, hyperinsulinemia, obesity, obesity-related cancers, sarcopenic obesity*

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Introduction

The world of obesity is viewed through the lens of cardiometabolic disorders. It is less well appreciated that obesity confers significant risk of specific type of cancers and that obesity will be the leading cause of cancer in the coming years.

The Obesity Pandemic

The world is facing an obesity pandemic. The World Health Organization estimates that obesity rates across the globe have tripled since 1975, and in 2016, more than 1.9 billion adults were overweight and of these, over 650 million were obese. The Gulf region has been particularly affected by this epidemic, with an estimated 30%–40% of the population being overweight or obese. Based on 2016 data, the CIA World Factbook identifies that Kuwait is the "fattest" country in the Gulf with almost 40% of population being obese; Oman at 27% has the lowest percentage of obese adults in the GCC (ranked 29th globally).

The cardiometabolic risks associated with obesity, such as Type 2 diabetes mellitus (T2DM), hypertension, fatty liver (nonalcoholic fatty liver disease [NAFLD]), hypertension, and coronary artery disease, are well known. It is less well appreciated that obesity increases the risk of several types of cancer.

Obesity-related Cancers

It is estimated that 9% of the cancer burden in North America, Europe, and Middle East in 2013 was obesity related.[1] Mendelian randomization studies have placed the risk of obesity-related cancers (ORCs) even higher.[2] This prevalence is likely to have grown since, especially after control of competing causes of cancer such as smoking and infection. In 2015, tobacco smoking contributed to the largest proportion of cancer cases in the UK, closely followed by overweight/obesity, accounting for 15.1% and 6.3%, respectively.[3] Obesity-related cancers accounted for nearly 43.5% of total direct cancer care expenditures, estimated at $35.9 billion in 2015 in USA alone.[4] The trend in increasing obesity is more marked in Saudi Arabia than in India. This has resulted in a disproportionately higher level of ORCs in Saudi Arabia (4%–9%) as compared to a more modest 0.2%–1.2% in India.[1]

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Increasing childhood obesity is a matter of grave concern as it has shifted the burden of cancer to younger age groups.[5] In addition, being overweight before the age of 40 increases the risks of various ORCs by 15%. The study from Bergen (Norway) showed increased risk of cancers of the endometrium (by 70%), renal cancer in males (by 58%), and colon cancer in male (by 29%).[6]

Defining Obesity

The cause (s) of obesity and the current epidemic is a matter of controversy. The classical energy imbalance ("calorie in, calorie out") model attributes obesity to eating more and moving less ("gluttony and sloth"). This has been challenged by the "carbohydrate-insulin" model which suggests that the components of the Western diet such as highly refined carbohydrates (sugar and fructose) and processed food (including some seed oils and artificial sweeteners) spike insulin levels, which leads to fat storage and continued hunger [Figure 1].[7,8] Some researchers blame the governmental advice in the seventies to cut down on fat and eat more carbohydrates for this epidemic. The field is further clouded by difficulties in defining and quantifying "unhealthy obesity" as it appears that not all obese adults have metabolic complications.

The standard method of quantifying obesity is by the body mass index (BMI) (also known as the Quetelet index), which is weight (in kilograms) divided by the height (in meters) squared. Healthy BMI has been defined as a value between 18 and 25; overweight is more than 25, and obese more than 30. Although a convenient method of measurement, this index suffers from serious deficiencies. This index cannot, for instance, distinguish between fat and lean weight. A muscular man will be classified as overweight or worse (for instance, Dwyane Johnson [The Rock] who is 188 cm tall and weighs around 119 kg has a BMI of 33 and is clearly

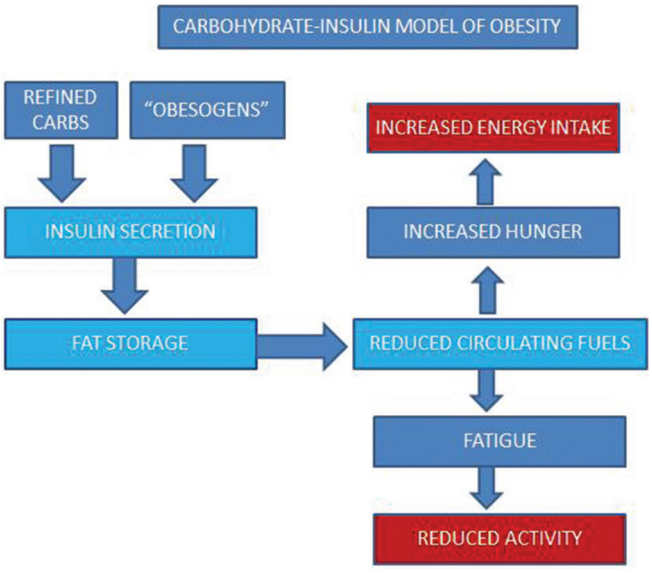

Figure 1: The carbohydrate-insulin model of obesity

obese by this criteria). Again, a proportion of the population who are apparently obese by BMI remain healthy (MHO or metabolically healthy obese);[9,10] this appears to be related to the distribution of body fat. A pear-shaped (gynecoid) body with gluteofemoral distribution of fat (and a low waist–hip ratio (WHR)) is healthier than an apple shape (android) with fat stored in visceral adipose tissue (VAT). This difference in fat distribution between men and women is due to sex hormones, and I believe that this is related to the evolutionary need to leave space in the abdominal cavity in women for the growing fetus.

It has been shown that postmenopausal women with a normal BMI but with higher body fat levels (as measured by the gold standard of dual-energy X-ray absorptiometry or DXA; other methods include hydrostatic weighing; bioelectrical impedance analysis; air displacement plethysmography; and bioimpedance spectroscopy; these can be combined together to generate multicompartment models) are at elevated risk for breast cancer.[11] These are hold the middle ground – "the metabolic obesity in normal weight". On the other end of the spectrum, there are people who are thin but diabetic ("TOFI", thin outside, fat inside) [Figure 2].[12] This variation is partly explained by the idea that fat storage in subcutaneous tissue is essentially safe (to a limit), but when it spills over and stored ectopically (in muscle, and especially in the liver), leads to insulin resistance, hyperinsulinemia (HI), hyperglycemia, and diseases associated with the metabolic syndrome.[13] WHR is one way to measure the ectopic fat stored in VAT and correlates better with metabolic syndrome than BMI;[14] other methods such as relative fat mass (RFM) have been proposed to overcome limitations of BMI.[15] RFM correlates closely with the gold standard DXA scan. However, some studies suggest that ectopic fat stored in liver (as in NAFLD) poses more risk than the fat in other sites.[16] As of now, there is no answer to the pressing question, "Which is the 'real' obesity?." Without a standard method of defining and quantifying "unhealthy obesity," accurately identifying cancers that are distinctly and specifically obesity related will remain imprecise.

Nevertheless, the International Agency for Research on Cancer has come up with a list of 13 cancers associated with obesity[17] (as defined by BMI) [Table 1] including common ones such as those of colon and breast. Since then, other associations have been reported,[6,18] including new possibilities such as of the prostate,[19] neuroendocrine tumors,[20] and of the urinary bladder.[21] Theoretically, cancers with similar etiology should have similar mutation spectra,[22] but since cancers are rarely caused by a single factor, defining a homogenous population of ORCs and generating a universal "molecular signature" that could identify a cancer as a member of ORC remains difficult. Overexpression of genes such as the fatty acid synthase (FASN)[23] and fat mass and obesity-associated (FTO)[24,25] have been identified in ORCs.

Association versus Causation and Hill's Criteria

Bradford Hill's criteria is one attempt to demonstrate causality,[26] and as per this criteria, obesity is a plausible cause of cancer [Table 2]. Way back in 2014, a BMJ editorial titled "Obesity: a certain and avoidable cause of cancer" acknowledged that "obesity is an important cause of unnecessary suffering and death from many forms of cancer."[27] Unfortunately, the exact molecular mechanism (s) and pathways are yet to be worked out.[28]

Mechanisms of Cancer Causation

The association of some cancers with obesity can be better understood than the others [Table 3]. The weight loss drug lorcaserin was recently recalled by the FDA for slight excess of cancers in the study arm. However, for the vast majority, the links are less well understood.[29] Suggested possibilities are as follows.

Table 1: Obesity related cancer as per International Agency for Research on Cancer

Cancer
Colon cancer
Breast cancer
Thyroid cancer
Liver cancer
Endometrial cancer
Esophageal cancer
Renal cancer
Gall bladder cancer
Pancreatic cancer
Ovarian cancer
Gastric cardia cancer
Multiple myeloma
Meningioma

Table 2: Postulated mechanisms of obesity related cancers

Cancer	Postulated mechanism
Breast cancer (postmenopausal)	Estrogen produced by adipose tissue
Endometrial cancer	High estrogen levels
Gastro-esophageal cancer	Increased gastro-esophageal reflux due to high visceral fat
Gall bladder cancer	Cholesterol gall stones
Liver cancer	Fatty liver, NAFLD

NAFLD – Nonalcoholic fatty liver disease

Hyperinsulinemia

High insulin levels precede metabolic syndrome by at least a decade. The modern man has relatively high insulin levels partly in response to highly refined carbohydrate and processed food diet and partly due to the tendency to snack between meals.[30] Insulin is both anabolic (leading to fat storage) and proliferative (stimulating at least two pathways known to be involved in carcinogenesis – the PI3K/AKT/mTOR pathway and the MAPK pathway).[31] Single-nucleotide polymorphisms (SNPs) in the insulin receptor gene have been associated with ORCs.[32] A Japanese study showed that HI was independently associated with higher cancer risk irrespective of BMI.[33] Foods high in glycemic index have been implicated in some types of ORCs.[34] Other hormones released by adipose tissue such as leptin[35] and adiponectin have also been implicated.[36] Overexpression of gastric leptin has been linked to stomach cancer.[37] Newer candidates incriminated include adipose fatty acid-binding protein (A-FBP) in breast cancer.[38]

Chronic inflammation

Chronic inflammation and antigenic stimuli, whether due to autoimmune disorders or infection, are linked to cancer. About 10%–15% of cancers are due to infections. Chronic infections by viruses and bacteria are associated with lymphomas and cancers of the gastrointestinal tract; autoimmune disorders of thyroid and gastrointestinal tract (celiac disease, ulcerative colitis) are also known risk factors. Obesity is an inflammatory state; it is thought that excess fat storage leads to rupture of adipocytes, leading to infiltration by immune cells and secretion of cytokines such as interleukin-6 and tumor necrosis factor, and results in chronic low-grade inflammation.[39] Metabolic and inflammatory changes related to the obese adipose tissue microenvironment are thought to contribute to cancer development and progression.[40] Obesity-related inflammation can also lead to DNA damage and thus cancer.[41]

Table 3: Causation versus association: Hill's criteria

Number	Criterion	Explanation	Obesity and cancer
1	Strength	Difference between exposed versus nonexposed	Significant for select subsets
2	Consistency	Observed by different people at different places	Yes
3	Specificity	Linked to specific outcome	Yes but inconsistent
4	Temporality	Exposure precede the disease	Yes
5	Biological gradient	Dose response curve	Yes, with breast cancer
6	Plausibility	Biologically plausible	Yes
7	Coherence	Cause-effect consistent with known natural history	Yes but further investigations needed
8	Experiment	Intervention change outcome?	Yes
9	Analogy	Similar agents cause similar disease?	Unique experience

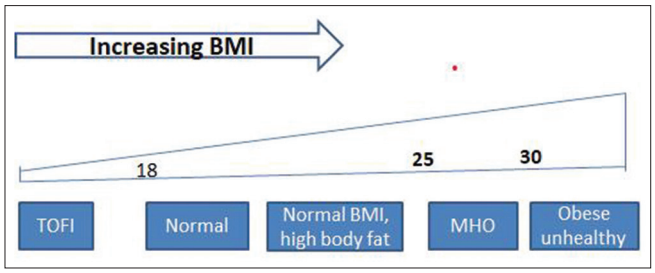

Figure 2: The spectrum of obesity as per body mass index

Gut microbiome

The influence of gut organisms on obesity ("obesogenic bacteria") and on immunity is a matter of ongoing research.[42] Obese people have altered gut bacteria that has been linked to increased risk of gastrointestinal cancers such as of colon, liver, and pancreas.[43,44]

Implications

Obesity is the cause of a significant and growing subset of cancers, and this carries several implications.

Prevention

There is sufficient evidence that weight reduction cuts the risk of cancer.[45] This is best seen in patients of bariatric surgery who undergo significant weight loss and have reduced risk of various cancers, such as that of breast, uterus,[46] colon, and even skin cancer.[47] Intermittent fasting has been suggested as another method of weight control and increasing life span; however, the evidence in humans is limited. The role of insulin in ORCs was mentioned earlier; blocking the insulin pathway is a specific option to treat ORCs. Drugs such as ceritinib, alpelisib, capivasertib, everolimus, and rapamycin (rapalogs) that block proteins along the insulin pathway are effective anticancer drugs; it is unknown if they are more effective in ORCs. Epidemiological studies suggest that metformin may have a preventive role in cancers such as NAFLD-associated HCC, but clinical data are lacking. Clearly, the best preventive method is control of the obesity epidemic, but this requires long-term solutions with social and legal will to enforce measures such as the sugar tax. These measures did work, for instance, in control of tobacco abuse and there is no reason why they should not work to modify unhealthy diets.[48]

Screening

The obese population presents a unique opportunity to screen for specific cancers with the certainty of higher yield. Patients of NAFLD have not only higher risk of liver cancer but also of stomach, pancreas, uterus, and colon;[16] endometrial and thyroid cancers are other high-yield ORCs detectable by screening. The evidence that HI is related to ORCs[49] suggests that insulin levels can be useful as a screening tool; much work needs to be done in this respect. On the flip side, obesity could make screening procedures problematic. In Spanish women, caloric intake above predicted levels seems to increase mammographic density, such that for every 20% increase in relative energy intake, mammographic density increased by 5%.[50]

Second malignant neoplasms

Survivors of childhood cancers have higher risk of second cancers if they put on weight;[51] this presents a challenge as they are prone to weight gain.

Prognosis

As a general rule, obesity predicts poorer survival from various cancers, even in the early stages,[52] and correlates with more visceral metastases.[53] Hyperglycemia itself exerts a negative influence on survival from cancers of breast, liver, and colon.[54] Curiously, some patients of ORCs have better survival which has been termed the "obesity paradox."[55-57] Several explanations have been advanced such as better nutrition, unreliability of BMI, and statistical issues such as reverse causality and collider bias.[58] There is a possibility that obesity gives an advantage to low-grade tumors with inbuilt survival advantage.[59] In renal cell cancer, altered microenvironment of the peritumoral adipose tissue has been suggested as an explanation of this paradox.[60]

Treatment considerations

In addition to its impact on surgery (for example, postoperative infections, anesthetic complications) and radiation (postradiation fibrosis), obesity influences chemotherapy administration.[61] There is a tendency to cap chemotherapy drug dose leading to suboptimal dosage and reduced survival; guidelines recommend full dose as per the individual's actual weight.[62] Despite this, survival can be compromised as drug metabolism may be different in the obese. For instance, adipocytes have been shown to promote doxorubicin resistance by upregulating a drug efflux protein MVP.[63] In addition, adipocytes can sequester chemotherapy drugs and protect cancer cells.[64] Side effects can be more; cardiotoxicity of trastuzumab is increased in obese, dyslipidemic patients.[65] A recent study showed that excess adiposity, detected on usual computed tomography scans as larger visceral and intramuscular fat deposition, was related to reduced relative dose intensity and worse breast cancer-specific survival.[66] Paradoxically, retrospective studies show that immunotherapy may work better in the obese.[67]

Targeted therapy

Upregulation of specific genes related to ORCs present a unique opportunity for targeted therapy; studies are currently ongoing with FASN[68] and FTO[69] inhibitors.

Sarcopenic obesity

About 15% of obese people have limited muscle mass (sarcopenic obesity) and this is further aggravated in patients with cancer cachexia. Sarcopenic obesity confers poorer outcomes in cancer patients including reduced survival.[70] Sarcopenic obesity cannot be detected by clinical examination, but standard imaging done routinely as part of cancer treatment can be used to specifically measure muscle mass and alter management.[71]

Conclusions

The world, and especially the Gulf countries, is in the grip of an obesity pandemic. Metabolic disorders such as NAFLD and T2DM are on the rise and will cost the world economy, billions of dollars. As far as cancers are concerned, obesity is the new smoking and requires equally careful management measures. Several subtypes of cancers will increase and impact the lives of many, unless the importance of ORCs is acknowledged and proactively managed.[72] Oncologists must discuss with the patient importance of weight management as an essential part of cancer treatment, and the need for good glycemic control for better outcomes; these are measures that can be implemented at minimal or no cost. A shared decision on weight and glycemic management and an "exercise prescription" is good clinical practice. Unfortunately, awareness of the link between obesity and cancer is limited, and education, starting at school level, should be an important measure in future programs.[73] Research on the molecular mechanisms of ORCs is crucial.[74] It is well known that Indians develop cardiometabolic complications of obesity at much lower levels of BMI (for which modified criteria have been suggested[75]); whether similar risk exists for ORCs is a potential area for study.

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Conflicts of interest

There are no conflicts of interest.

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