American International Journal of Cancer Studies
Vol. 3, No. 1; 2021
ISSN 2641-5658 E-ISSN 2641-5674
Published by American Center of Science and Education, USA

OBESITY AND ITS RELATIONSHIP WITH CANCER: PART I OBESITY

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ABSTRACT

Cancer is a lethal disease and a strong barrier to a better life expectancy. It is the first or second leading cause of death before the age of 70 years in 112 of 183 countries. Its incidence and mortality continue to grow rapidly all over the world. This manuscript is divided into four parts. Part I discusses obesity while Part II discusses the relationship between obesity and cancer. Part III and Part IV review the association of obesity on fifteen common cancers.

Obesity

An excessive food intake (surplus energy intake) or insufficient physical activity (low energy expenditure) causes obesity (Galgani et al., 2008). Obesity is an expansion of the adipose tissue due to hypertrophy of pre-existing adipocytes or recruitment (hyperplasia) of adipocyte precursors (Jo et al., 2009). This results in various physiological and pathological changes in the human body (Stenkula & Erlanson-Albertsson, 2019). The prevalence of obesity has substantially increased worldwide (Caballero, 2007). Obesity now accounts for more than a third of the world's population (Hruby & Hu, 2015). Its prevalence has nearly tripled between 1975 and 2016 (https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.). This dramatic rise in obesity has been attributed to several factors (Finkelstein et al., 2005; Kimbro et al., 2011; Nestle & Nesheim, 2012; Colabianchi et al., 2014). Technological advancements have led to a decline in manual labor (Finkelstein et al., 2005), and the easy availability of processed and fast foods, and this has resulted in excessive consumption of cheap calories (Nestle & Nesheim, 2012). Modern built environments also limit outdoor physical activity (Colabianchi et al, 2014) and increase indoor time, often spent watching television or playing on the computer (Kimbro et al., 2011). Overweight and obesity now kill more people globally than underweight (www.cdc.gov). According to the World Health Organization, in 2016, 1.9 billion adults were overweight, while 650 million were obese (www.who.int). In countries like the USA, obesity is now present in almost one-half of the population, with the Centers for Disease Control and Prevention of USA estimating that it affected 42.4% of the population in 2017 – 2018 (CDC, 2021). This increase in excess body weight is also being seen in other parts of the world (https://ec.europa.eu/; GBD, 2015). Overweight (including obesity) in the European Union is estimated to have affected 52.7 % of the adult EU's population in 2019 (https://ec.europa.eu/). In

the Eastern Mediterranean Region, the prevalence of obesity registered an increase from 15.1% in 1980 to 20.7% in 2015 (GBD, 2015). The obesity burden is also affecting the less developed countries (NCD, 2016; Bleich et al., 2017). In 2010–2012 the prevalence of overweight and obesity in Chinese adults was 30.1% and 11.9%, respectively (PCNH, 2016). In India, it is estimated that the prevalence of overweight and obesity by 2030, will involve 27.8%, and 5.0% of all Indians, respectively (Kelly et al., 2008; IIPS, 2017). China, India, Pakistan, and Indonesia are now in the top 10 countries with the highest populations of obesity in the world (Ng et al., 2014). Adult obesity has also been increasing at an alarming rate among African countries (Swinburn et al., 2011). Eastern Sudan has a prevalence of 26.8% for overweight and 32.2% for obesity (Omar et al., 2020). Uganda has a 17.8% prevalence of overweight (Kirunda et al., 2015) while in Ethiopia, overweight/obesity increased significantly from 10.9% in 2000 to 21.4% in 2016 (Ahmed et al., 2020).

Obesity is also increasing in the younger population (Onywera, 2010; www.who.int; UNICEF, 2020; Danquah et al., 2020). Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016 while 39 million children under the age of 5 were overweight or obese in 2020 (www.who.int). UNICEF estimates that in the pediatric and adolescent population, the prevalence rate of obesity has reached 21.4% (UNICEF 2021). In the US, the prevalence of obesity was 19.3% for children and adolescents aged 2-19 years in the years 2017-2018, and 13.4% among 2- to 5-year-olds (CDC, 2021). According to UNICEF, WHO, and the World Bank, Southern Africa has the highest prevalence of overweight among children under 5 years (14.6%), followed by Central Asia (11.6%) and Northern Africa (11.0%) (Danquah et al., 2020). Cancer risk at an older age may be linked to excess body weight in late adolescence and early adulthood (Genkinger et al., 2015; Park et al., 2018; Colditz & Peterson, 2018) Prevention of early life obesity can thus also help reduce future cancer. Obesity is an expensive disease (CDC, 2021; Withrow & Alter, 2011). The CDC estimates that the estimated annual medical cost of obesity in the United States was $147 billion in 2008 (CDC, 2021). The global costs are much higher (Withrow & Alter, 2011).

Body Mass Index

Actuaries notice an increased mortality of their overweight policyholders after World War II, and the relationship between weight and health became a major subject of epidemiological studies (TIAFT2018). Adolphe Quetelet (1796-1874), a Belgian mathematician, astronomer, and statistician, described a practical index of relative body weight - the ratio of the weight in kilograms divided by the square of the height in meters (or the Quetelet Index) in 1832 (Eknoyan, 2008). This was subsequently termed the Body Mass Index (BMI) in 1972 by Ancel Keys (1904-2004) (Rasmussen, 2019). BMI is nowadays widely used as a measure to define body weight (www.euro.who.int). BMI is categorized into several groups: < 18.5 kg/m^2 (underweight), 18.5–24.9 kg/m^2 (normal weight), and 25 to 29.9 kg/m^2, (overweight). Obesity is defined as a BMI exceeding 30 kg/m^2 and is subclassified into class 1 (30–34.9), class 2 (35–39.9), and class 3 or severe obesity (≥ 40). A BMI >50 Kg/m2 is considered morbid obesity (www.euro.who.int). However, BMI may give erroneous results in the elderly (loss of height and aging-related sarcopenia), extremely tall or muscular individuals; and in overweight individuals that self-report their weight (as they tend to underestimate their weight) (Romero-Corral et al.,

2008). BMI may also be unreliable in individuals of Asian descent (WHO, 2004). Asian populations differ from European populations in the percentage of body fat and health risks (Rush et al., 2009). Compared with other ethnic groups, Asians seem to have higher overall fat levels and abdominal fat as well as lower lean body mass for a given BMI (Lim et al., 2011). The International Obesity Task Force has therefore recommended different BMI categories for them (WHO, 2000). These were as follows: underweight (<18.5 kg/m^2), normal (between 18.5 and 23 kg/m^2), overweight (between 23 and 25 kg/m^2), obese (between 25 and 30 kg/m^2), severe obese (≥30 kg/m^2)[40]. Chinese may use different guidelines, with one study suggesting overweight is defined as a BMI of 24.0–27.9 kg/m2, and obesity is defined as a BMI ≥28 kg/m2 (Zhou, 2002).

Abdominal obesity

BMI may not be a reliable indicator of body fat content and distribution (Allott & Hursting, 2015). It has been estimated by several studies that about 10% of the US population has a normal BMI but increased body fat content (Romero-Corral et al., 2010; Main et al., 2010). This may occur if there is excess adipose tissue (AT) deposition around the abdominal viscera and inside the intra-abdominal solid organs (Tchernof & Després., 2013). Vague in 1947 first suggested the deleterious relationship between subcutaneous and abdominal fat distribution and cardio-metabolic complications (Garg, 2004). Subcutaneous AT is rich in mitochondria and is highly vascularized and innervated. It is mainly involved in heat production (Saely, 2011). Visceral AT is primarily white and serves as a store for excess energy (Saely, 2011). However, it also acts in an autocrine, paracrine, or endocrine organ (Coelho et al., 2016; Finelli, 2020). Visceral AT and its macrophages produce pro-inflammatory cytokines like tumor necrosis factor-alpha and interleukin-6 (Finelli, 2020). It also is associated with an increased expression of fibroblast growth factor 21and insulin-like growth factor-binding protein-5, and decreased levels of hepatocytes, insulin-like-1 growth factors, and adinopectin (Coelho et al., 2016). Adiponectin is anti-inflammatory and helps reduce body fat and to improve hepatic and peripheral insulin sensitivity (Abenavoli & Peta, 2014). The cytokines induce increased inflammation and higher insulin resistance, resulting in endothelial dysfunction (Zhang, 2008). There is also increased pro-atherogenic dyslipidemia (Liu et al., 2010) and a prothrombotic effect (Dosquet et al., 1995). The increased insulin resistance (McLaughlin et al., 2011) and associated atherosclerotic and thrombogenic profile leads to an increase in diabetes mellitus and cardiovascular diseases in these patients (Després, 2011; Yokokawa et al., 2021). Conversely, the subcutaneous adipose tissue in the abdomen and thigh may be protective, as it is associated with a lower risk for insulin resistance (Taksali, 2008; McLaughlin et al., 2011). Visceral fat accumulation is usually independent of age, overall obesity, or the amount of subcutaneous fat (Tchernof & Després, 2013). However, it appears to be more prominent in white men, African American women, and Asian Indian and Japanese men and women (Hamdy et al., 2006). Visceral fat is also closely related to tumorigenesis and the progression of tumors (Crudele et al., 2021).

Central obesity can be objectively ascertained by several anthropometric measurements (Donohoe et al., 2014). The commonest in use is the waist circumference (WC) (NPTD, 2001). Its value for detecting central or visceral obesity has been confirmed by several subsequent studies (Yusuf et al., 2004). WC should ideally be <102 cm in males and <88 cm in females

when measured to the nearest 0.1 cm at the umbilical level in a standing position. In the Asian populations, these numbers are <85 cm for males and, <80 cm for females. Higher values indicate visceral obesity. Many researchers have also used another anthropometric measurement, waist to hip ratio and the normal values for this are 0.85 or less for women and 0.9 or less for men (Wakabayashi, 2013). The waist-height ratio is calculated as WC divided by height. A ratio < 0.5 indicates no visceral obesity and ≥ 0.5 is consistent with visceral obesity and an increased risk for many cardiometabolic diseases and cancer (Ashwell et al., 2012).

Obesity and Health

Obesity deleteriously affects human health. Obesity often causes several health problems in children (Gurnani et al., 2015; Sahoo et al. 2015) including early puberty (De Leonibus et al., 2012), menstruation irregularities (Witchel et al., 2019), sleep disorders (Marcus et al. 2012), hypertension (Wühl, 2019), diabetes (Flodmark, 2018), and non-alcoholic fatty liver disease (Shaunak et al., 2021). Childhood obesity may be associated with reduced self-esteem, low body image, anxiety and depression, poor peer relationships, academic underachievement, and systematic discrimination (Rankin et al., 2016; Topçu et al., 2016). These psychological effects often negatively modify a child's future. Further, childhood obesity also predicts adult obesity (NCD 2017). Obesity in children may therefore also implant the seed for the future development of several non-communicable diseases (Bhave et al., 2004). Elevated BMI in adults is associated with several chronic diseases - these include cardiovascular disorders (Parto & Lavie), diabetes mellitus (Schnurr et al. 2020), depression (Luppino et al., 2010), chronic kidney disease (Ting et al., 2009), obstructive sleep apnea (Tuomilehto et al., 2013), osteoarthritis (Losina E et al., 2013), gout (McCormick et al., 2020), nonalcoholic fatty liver disease (Polyzos et al., 2017), osteoporosis (Friebe & Peters (2005), and infertility (Talmor & Dunphy, 2015);
Kahn & Brannigan, 2017). It causes increased complications related to pregnancy (Schummers et al., 2015). Obesity may also lead to psychosocial distress (Aldossari et al., 2021), and obese people may have low self-esteem and feelings of rejection (KavehFarsani et al., 2020). They often have heightened anxiety (Heidari-Beni et al., 2021), body image dissatisfaction (Makara-Studzińska 2009), and may face weight bias and sigma (Spahlholz 2016). Weight sigma affects approximately 20%–40% of obese persons (Spahlholz 2016). Stigma may also be exhibited by health care providers against obese patients (Gupta 2020). Weight-influenced stigma is stressful (Tomiyama 2014) and often internalized, and this results in adverse health outcomes (Hunger et al., 2015; Pearl et al., 2020). Obesity may also lead to disqualification from the US military (Christeson et al., 2010). It reduces the health quality of life (Meixner et al., 2020). According to recent data, obesity was related to 148 million disability-adjusted life years and 4.72 million deaths worldwide (GBD, 2017). It a major cause of preventable death second only behind smoking (GBD, 2017). It has been estimated that obese individuals (BMI of >30–35 kg/m²) lose about 2-4 years of life while those with severe obesity (BMI >40 kg/m², lose about 8-10 years of life (CPS, 2009). Obesity care is also expensive and imparts a high economic burden on society (OECD 2019). In the US alone, obesity-related direct and indirect health care costs are over $150 billion or even $190 billion yearly (Cawley & Meyerhoefer, 2012) while in Canada, it costs 1.27–11.08 billion Canadian dollars annually (Tran et al., 2013). Obesity is also closely linked with cancer (Avgerinos et al., 2019) and this is discussed in the next three parts of this manuscript.

Health diseases/medications causing obesity

Several health conditions and medication can also cause obesity. Implicated medical disorders include hypothyroidism (Hoogwerf & Nuttall,1984), prolactinoma (Ali & Mirza 2021), polycystic ovarian syndrome (Rasquin et al., 2021), depression (Blaine, 2008; Islam el al.,2020), and Cushing's syndrome (www.endocrineweb.com). Cancer survivors may also gain excess body weight more rapidly than the general population (Greenlee 2016). Several prescription drugs are also associated with weight gain. Psychotropic drugs especially clozapine and olanzapine are notorious in this regard (Bak et al., 2014; Zhang et al., 2016). Anti-diabetic medications like insulin, sulfonylurea, and thiazolidinediones may cause substantial weight gain when compared to placebo (Domecq et al., 2015). β-blockers, commonly used to treat hypertension and some cardiovascular disorders, often result in excess body weight (Sharma et al., 2001). Anti-epileptic drugs, especially valproate and carbamazepine, are weight promoting (Ben-Menachem, 2007). Chronic corticoid therapy is associated with weight gain in up to 70% of all patients (Curtis et al., 2006).

Obesity Paradox

In the general population, mortality is higher in both the underweight and overweight, when compared with those with normal weight – indicating a 'U-shaped' relationship (Flegal et al., 2013; Global BMI Mortality (2016). Some diseases however demonstrate improved survival in overweight/obese individuals when compared with normal-weight individuals, while there is still increased mortality in the underweight (Cao et al., 2012; Spelta et al., 2018). This reverse "J-shaped" curve is referred to as the "obesity paradox" and has been described in several other chronic diseases such as heart failure (Khan et al., 2021), coronary artery disease (Akin & Nienaber, 2015), chronic obstructive pulmonary disease (Chittal et al., 2015), and end-stage kidney disease (Park et al., 2014). It has also been noted in several acute conditions such as pneumonia (Nie et al., 2014; Cichon et al., 2021), sepsis (Cichon et al., 2021), and acute respiratory distress syndrome (Liu et al., 2021). Several hypotheses have been advanced to explain this phenomenon. Studies have found that patients demonstrating the obesity paradox have increased lean mass (Lee et al., 2018), despite the obesity, and a better cardiorespiratory fitness (Barry et al., 2018). Other mechanisms may also be involved. Obesity paradox has also been noted with some cancers – this is discussed in Part II.

To summarize, obesity has become a pandemic (Meldrum et al., 2017). It is growing in all ages, populations, and ethnic groups, irrespective of the socioeconomic status. It is associated with severe morbidity and mortality, especially due to cardiovascular diseases and diabetes mellitus (Poirier et al., 2006; Tobias et al., 2014). It is also strongly associated with most cancers (Krupa-Kotara & Dakowska, 2021).

Acknowledgment: None
Funding: None
Conflict of interest: None

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