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OBESITY AND ITS RELATIONSHIP WITH CANCER: PART II CANCER

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ABSTARCT

This four-part manuscript briefly reviews the association of obesity with cancer. Part I discussed obesity while this (Part II) will discuss obesity and its impact on cancer. Part III and Part IV will review the association of obesity on fourteen common cancers.

Introduction

Cancer is a dreaded disease and a big barrier to increasing longevity (Capocaccia et al., 2015). It is characterized by uncontrolled cell proliferation that spreads from an initial focal point to other parts of the body, eventually causing death (Steeg, 2016). There were an estimated 19.3 million new cases of cancer diagnosed globally in 2020 (www.iarc.who.int). For both sexes combined, the top 10 cancer types of account for >60% of the newly diagnosed cancer cases and >70% of the cancer deaths (Howlader et al., 2021). Female breast cancer is the most diagnosed cancer (11.7% of total cases), closely followed by lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%) cancers (Sung et al., 2021). In numbers, the World Health Organization (WHO) estimated new cancers in 2020 to be as follows: breast (2.26 million cases); lung (2.21 million cases); colon and rectum (1.93 million cases); prostate (1.41 million cases); skin (non-melanoma) (1.20 million cases); and stomach (1.09 million cases) (www.who.int). Cancer is prevalent all over the world, Africa reported 1,109,209 while Asia had 9,503,710 new cancer cases in 2020 (https://gco.iarc.fr/today/data/factsheets/populations/935-asia-fact-sheets.pdf). Europe reported 4,398,443, while according to the National Cancer Institute there were 1,806,590 new cases of cancer in the USA in 2020 (Fernandez et al., 2021). Cancer contributed to 233.5 million disability-adjusted life-years in 2017 (Wadasadawala et al, 2021). Cancer is a lethal disease, and over 90% of cancer mortality is attributed to its metastasis (Steeg, 2016). There were nearly 10 million cancer related deaths in 2020 (Ferlay et al. 2020). The WHO estimates that in 2019, cancer was the first or second leading cause of death before the age of 70 years, in 112 of 183 countries (WHO, 2020). In the world's most populous country, China, cancer is now the leading cause of death (Feng et al., 2019). The most common causes of cancer death in 2020 were: lung (1.80 million deaths); colon and rectum (935 000 deaths); liver (830 000 deaths); stomach (769 000 deaths); and breast (685 000 deaths) (www.who.int). The global

cancer burden is expected to be 28.4 million cases in 2040, a 47% rise from 2020 (Sung et al., 2021).

Obesity and Cancer

Most cancers arise from a complex etiology involving genetic, environmental, and lifestyle factors (Cogliano et al. 2011). Anand et al reported that up to 95% of cancer events are attributable to lifestyle factors such as physical inactivity, cigarette smoking, poor diet, alcohol, and obesity (Anand et al., 2008). Obesity is an important lifestyle factor and has been linked to an increased risk for several cancers (Bhaskaran et al., 2014; Lauby-Secretan et al., 2016). The United States Cancer Statistics data suggest that overweight and obesity are associated with thirteen different types of cancer, and these cancers made up 40% of all cancers diagnosed in the United States in 2014 (Steele et al., 2017). Worldwide, the burden of cancer attributable to obesity is 11.9% in men and 13.1% in women (Avgerinos et al., 2019). Overweight/obesity was also responsible for 15.1% of all cancer cases in Scotland and 6.3% of all cancer cases in England in 2015 (Brown et al., 2015). In Germany, 7% of the cancers are obesity related (Behrens et al., 2018). According to the American Cancer Society, excess body weight is responsible for about 11% of cancers in women and about 5% of cancers in men in the United States (www.cancer.gov).

Obesity is the third leading cause of cancer globally (after smoking and infections) (De Pergola & Silvestris, 2013). A recently published systematic review found that most cancers were increased by obesity (Gutiérrez-Salmerón et al., 2017). The risk ratio (RR) between obesity and cancer was highest for endometrial cancer (2.54) (Zhang et al., 2014). The RR between obesity and renal cancer was also high (1.77) (Wang & Xu, 2014). This was followed by pancreatic cancer (1.48)[30], breast cancer (1.42) (Munsell et al., 2014), liver cancer (1.35) (Rui et al, 2012), colorectal cancer (1.32) (Okabayashi et al., 2012), melanoma (1.31) (García-Jiménez et al., 2016), ovarian cancer (1.30) (Olsen et al., 2007), thyroid cancer (1.29) (Zhao et al.,2012), leukemia (1.26) (García-Jiménez et al., 2016), prostate cancer (1.16) (Hu et al., 2014), gastric cancer (1.13) (Lin et al., 2014), and bladder cancer (1.10) (Qin et al., 2013). Surprisingly, obese people demonstrate a low RR of 0.79 for getting lung cancer (RR for squamous cell carcinoma, adenocarcinoma, and small cell carcinoma of the lung were 0.68, 0.79, and 0.99) (Yang et al., 2013) compared to the non-obese population, indicating an inverse association.

In 2018, 67% of cancer survivors in the US were overweight or obese (www.usa.gov/federal-agencies/national-cancer-institute). Obese patients with cancer do not thrive well. Several studies have documented treatment-related toxicity in obese children (Amankwah et al., 2016) and obese adults (Calle et al., 2003). Obesity often results in an increase in cancer recurrence, cancer progression, and a negative prognosis in survivors (Schmitz et al., 2013). It also reduces the quality of life in cancer survivors (Rock et al., 2012)**.** Obese survivors of many obesity-related cancers also have an elevated risk of developing second primary cancers (Sang et al., 2016). Further, more than 40% of the patients diagnosed with cancer also have comorbid diseases, such as diabetes, chronic obstructive pulmonary disease, heart failure, and coronary artery disease – and obesity is detrimental to these conditions as well (Ogle et al., 2000). Obese cancer patients also experience a high mortality rate (Steele et al., 2017). Among patients with a BMI $\geq$40 kg/m^2 compared with patients with a normal BMI, mortality from all causes of cancer

was found to be 52% higher in men and 62% higher in women (Pi-Sunyer, 2009). It is estimated that obesity-related cancer deaths in men and women combined account for 6.5% of all cancer deaths (Islami et al., 2018). Visceral or central obesity is associated with worse cancer outcomes (Allott et al., 2013).

Mechanisms

Most cancers arise from a complex etiology involving genetic, environmental, and lifestyle factors (Cogliano et al.,2011). Lifestyle factors include obesity (www.health.harvard.edu/). Obesity adversely affects cancer in two ways (Lengyel et al., 2018), (i) promoting carcinogenesis resulting in a higher cancer incidence and (ii) cancer progression resulting in an increased risk of mortality. Obesity contributes to a pro-carcinogenic environment by several biological mechanisms. Obesity induces insulin resistance, hyperinsulinemia, and an abnormally increased blood level of insulin-like growth factor (Gallagher et al., 2015). These changes have been linked to the higher cancer risk seen in diabetics (Gallagher et al., 2015). Other cancers affected include pancreatic, biliary tract, and esophageal cancer in men; breast and endometrial cancer in women; and kidney, liver, and colorectal cancer in both genders (Gallagher et al., 2015). They also exhibit a greater mortality rate (Gallagher et al., 2015). Increased serum IGFs levels are associated with an elevated risk for developing prostate, colorectal, and breast cancer (Wolk et al., 1998; Manousos et al., 1999; Renehan et al., 2004). Androgens and androgenic precursors are converted to estradiol by the enzyme aromatase, the activity of which is increased in obese patients (Morris et al., 2011). This leads to higher levels of estrogens (Crosbie et al., 2010), and an increased breast cancer risk in postmenopausal women (Key et al., 2003). Estrogen also promotes tumorigenesis in endometrial tissue by stimulation of cell proliferation and inhibition of apoptosis (Shaw et al., 2016). This increases the risk of endometrial cancer in obese women by almost 2.6-fold (Shaw et al., 2016). Excessive fat accumulation, such as in visceral obesity, is associated with low levels of adinopectin, which has anti-inflammatory and insulin-sensitizing properties (Cnop et al., 2003). Low adinopectin levels coupled with obesity-induced increased leptin levels (pro-inflammatory) results in an increase in several inflammatory factors such as tumor necrosis factor-α (TNF-a) and interleukin (IL-6) (Boutari et al., 2018). The resultant chronic low-grade inflammation encourages cancer development and progression (Hursting et al., 2010). Obesity is also associated with reactive oxygen species production (Manna et al., 2015), which contributes to tumor promotion via mitochondrial and DNA damage (Włodarczyk & Nowicka, 2019). Obesity may also have effects on growth factors such as the mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (Sabharwal et al., 2014). Other factors that play a role are obesity enhanced supply of nutrition (Gómez et al., 2019), angiogenesis (Moodi et al., 2021), local inflammation (Stienstra et al., 2012), inhibition of apoptosis/cell death (Cong et al., 2007), and altered intestinal microbiome (Avgerinos et al., 2019). Altered gut microbiome with obesity (Djuric, 2017) and genetic factors may also play a role (Lan et al., 2020). And finally, excess body fat can induce cancer via mechanical effects. Visceral obesity can induce gastroesophageal reflux, which is associated with Barrett's esophagus and esophageal adenocarcinoma (Emerenziani et al., 2013).

Influence of normal body weight and weight loss on cancer

A normal body mass index (BMI <25 kg/m2) is associated with reduced rates of gastric cardia, gallbladder, pancreatic, ovarian, and thyroid cancers, as well as meningiomas, hepatocellular carcinoma and multiple myeloma (Genkinger et al., 2011; Beral et al., 2012; Arnold et al. 2017). These patients also have a reduced risk of metastasis (Annett et al., 2020). A lower weight gain during adulthood also lowers the risks of colon and kidney cancer, and for postmenopausal women, cancers of the breast, endometrium, and ovaries (Keum et al. 2015).

Intentional weight loss in obese individuals is also beneficial. It specifically reduces the risk of postmenopausal breast and endometrial cancers (Parker & Folsom, 2003). A systematic review that included 34 studies reported that 16 of the evaluated studies confirmed the benefit of intentional weight loss on cancer (Birks et al., 2012). Weight loss with bariatric surgery also helps reduce cancer incidence and mortality (Christou et al., 2008; Schauer et al., 2019., Castagneto-Gissey et al., 2020). In women, it helps reduce the incidence of cancers such as endometrial, breast, colorectal, non-Hodgkin lymphoma and melanoma (Christou et al., 2008; Schauer et al., 2019, Islam et al., 2020; Castagneto-Gissey et al., 2020). Adams et al. reported that bariatric surgery induced weight loss is associated with a lower cancer risk (RR = 0.55) and helps bring their elevated risk of cancer back down to a baseline population risk (Adams et al., 2009). Besides reducing cancer risk, losing weight intentionally has many other health benefits, such as lowering the risk of heart disease and diabetes (Parto & Lavie, 2017; Schnurr et al., 2020).

Cancer patients often notice an unintentional weight loss. Both radiation and chemotherapy may produce nausea and vomiting (Roila et al., 2010), anorexia (DeWys, 1977), and result in decreased food intake (Postma et al., 2020). Cancer may modify GI motility and digestion, and worsen absorption of nutrients, further enhancing weight loss (Shafi, 2019). Mechanical obstruction by the tumor and psychological factors may also be responsible for poor caloric intake (Diamantis et al., 2011; Ehrsson et al., 2021) A wasting syndrome, cachexia, occurs in many cancers, and especially with pancreatic and gastric cancers (Muliawati et al., 2012). The skeletal muscle wasting in cachexia is associated with significant weight loss (Webster et al., 2020). Unintentional weight loss in cancer patients leads to a reduction in the quality of life and is associated with poor outcomes (Martin et al., 2013). Weight loss, especially due to muscle loss, is associated with poorer tolerance to anticancer therapy (Bachmann et al., 2008), increased risk of postoperative complications (Liu et al., 2020), a reduced quality of life (Naito et al., 2017), and increased mortality (Ryan et al., 2019).

Obesity paradox in cancer

The obesity paradox has been well described in the cardiovascular and metabolic literature (Aune et al., 2016). Many reports indicate that it also exists in oncology (Petrelli et al., 2020). A recent meta-analysis of 203 observational studies including 6,320,365 participants observed that an obesity paradox exists with lung cancer and melanoma – obesity apparently has a protective effect in these patients (Petrelli et al., 2020). Some researchers attribute this protection to higher levels of skeletal muscle mass in cancer patients with a higher BMI (Cespedes et al., 2018).

Others claim that this benefit is misleading and is based on several methodological flaws in the studies reporting this phenomenon (Lee & Giovannucci, 2019).

To summarize, cancer is a deadly disease. It is now the second leading cause of death in the world. Its prevalence is growing rapidly, given the growing and aging population, and the adoption of unhealthy lifestyles. Obesity is a major lifestyle that increases cancer risk. It also promotes cancer progression and hastens death. The mechanistic pathways are several, with heightened inflammation, hyperinsulinemia, and alterations in sex hormone levels. Prevention of weight gain and intentional weight loss is beneficial in stemming these deleterious effects.

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