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OBESITY AND ITS RELATIONSHIP WITH CANCER: PART IV Endometrial, Ovarian, Pancreatic, Prostate, Renal and Thyroid Cancers Meningioma and Multiple Myeloma

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ABSTRACT

Part I thru III discussed obesity, its general relationship with cancer and its specific impact on six cancers, namely those involving the breast, colorectal tissues, esophagus, stomach. gall bladder, and liver. This part (Part IV) deals with obesity and its relationship with cancers of the endometrium, ovary, pancreas, prostate, kidneys, thyroid, and lung. Meningioma and multiple myeloma are also discussed.

Obesity and endometrial cancer

Endometrial cancer (EC) is the most common gynecological cancer in industrialized countries[1]. It is the second most common gynecological cancer, after cervical cancer, in developing countries (Siegel et al., 2019). Most cancers of the uterus (83%) are endometrioid carcinomas (Mahdy et al., 2021). Other carcinomas affecting the uterus include serous and papillary serous carcinomas (4% to 6%) and clear cell carcinomas (1% to 2%). Treatment is usually surgical and may involve laparoscopic total hysterectomy and bilateral salpingo-oophorectomy (Barcellini et al., 2021).

Endometrial cancer risk has a strong correlation with obesity (Zhang et al., 2014). It is estimated that more than half of all newly diagnosed endometrial cancers are associated with obesity, and this relationship is strongest in postmenopausal patients. In a cohort study of 33,436 postmenopausal patients, McCullugh et al reported that there was a more than fourfold increase in the risk of developing endometrioid adenocarcinoma compared to normal weight patients (McCullough et al., 2008). It has also been calculated that there is a 50% risk increase per 5 increases in BMI units in postmenopausal endometrioid adenocarcinoma (Onstad et al., 2016). The increased risk appears to be linear with increasing body mass index (BMI). Obesity may also increase the risk of premenopausal endometrial cancer (Wise et al., 2016). There is also a strong, negative, linear correlation with oncological outcomes. Cancer-specific mortality increases as the BMI increases - it is more than twice as high for patients with a BMI between 30 and 34.9, almost six times higher in patients with a BMI of >40 kg/m^2 (Calle et al., 2003).

Obesity and meningioma

Meningiomas are the most common primary central nervous system tumors (Ostrom et al., 2019). They affect approximately one per cent of the adult population (Kohler et al., 2011). They

are slow growing, and their incidence increases with age (Ostrom et al., 2019). They arise from the meningothelial (arachnoid) cells (Huntoon et al., 2020). They comprise 37.6% of all primary central nervous system (CNS) tumors and 53.3% of all benign CNS tumors (Ostrom et al., 2019). Although the mortality is low, the associated morbidity is high and serious (Al-Rashed et al., 2019).

In a meta-analysis of 6 studies, Shao et al. found a combined RR of 1.12 for overweight and 1.45 for obesity and meningioma risk (Shao et al., 2014). In a dose-response analysis, Zhang et al estimated that for a 5 kg/m2 increment of BMI, the RR was 1.19 for meningiomas (Zhang et al., 2016). Several studies have been less than clear about the relationship between obesity and meningioma (Wiedmann, et al., 2017; Seliger et al., 2017). A recent Mendelian randomization analysis, however, supports a causal relationship between obesity and meningioma risk (Takahashi et al., 2013; Islam et al., 2020).

Obesity and multiple myeloma

Multiple myeloma (MM) is characterized by a monoclonal proliferation of plasma cells in the bone marrow (Rajkumar et al., 2014). It is usually preceded by a premalignant state - monoclonal gammopathy of undetermined significance (MGUS) (Weiss et al., 2009). Although obesity has a positive association with MM (Yang et al., 2016; Kyrgiou et al., 2017; Marinac et al., 2018), the association between obesity and MGUS is unclear (www.myelomacrowd.org). Obesity, however, is known to enhance the progression of MAGUS to MM (Thordardottir et al., 2017). The biological mechanisms behind this progression are not clear. (Birmann et al., 2014).

Obesity and ovarian cancer

Ovarian cancer is a common cancer in women (Webb & Jordan, 2017; Lheureux et al., 2019). It is highly lethal, with a 5-year survival rate of <45% (Kumar et al., 2008). Most ovarian cancers (90%) are epithelial (Torre et al., 2018). Epithelial cancers are mostly (52%) serous in nature. Other types are endometrioid (10%), mucinous (6%), or clear cell (6%). About 25% are rare subtypes or unspecified (SEER, 2016).

The causal association of obesity with ovarian cancer is inconsistent. In a review of forty-three studies (3,491,943 participants) there was a positive association in 14 studies, no significant association in 26 studies and a negative association in 3 studies – between ovarian cancer risk and higher body mass index (Foong & Bolton, 2017). However, visceral obesity is a risk factor for postoperative complications in ovarian cancer patients undergoing cytoreductive surgery (Heus et al., 2021). Surgical weight loss also appears to help - in a large study, with 150,537 patients in the bariatric surgery arm and 1,461,938 women in the control arm, the risk of ovarian cancer was reduced by 53% in the surgical arm (Ishihara et al., 2020).

Obesity and pancreatic cancer

Pancreatic cancer is a deadly disease, with a 5-year survival rate of only around 6% to 9% (Siegel et al., 2017). Its incidence is on the increase, and it is expected to become the second most common cause of cancer related death in the USA by 2030 (McGuigan et al., 2018). Pancreatic duct cell adenocarcinomas are responsible for 90% of the cancers, with other types

being cystadenocarcinoma and acinar cell carcinoma (www.pancan.org). Most pancreatic cancers arise in the pancreatic head (Modolell et al., 1999). There is no known treatment, and surgical resection, the only viable option, is possible in only about 20% of pancreatic cancers at the time of diagnosis (Bausch & Keck, 2018).

Obesity plays a key role in the development and progression of pancreatic cancer (Berger, 2014; Lauby-Secretan et al., 2016; Islami et al., 2018). It is estimated that the risk of pancreatic cancer increases by 10% per 5 kg/m2 excess body weight (www.wcrf.org). The risk is increasing in young American adults - from 1995 to 2014, the average annual percent change in pancreatic cancer incidence increased from 0.77% for the ages of 45–49 years to 2.47% for the ages of 30–34 years and 4.34% for the ages of 25–29 years (Sung et al., 2019). Visceral obesity may be a stronger risk than BMI for these cancers (Jiao et al., 2009). The only therapeutic intervention available is surgery (Téoule et al., 2019), but perioperative morbidity and mortality rates are high in obese individuals (Williams et al., 2008; Nimptsch et al., 2016). Since early diagnosis is difficult the best option to significantly reduce the burden of pancreatic cancer deaths is prevention (Jiao et al., 2009). The risk for pancreatic cancer may be reduced by 25% or more by modifying lifestyle risk factors, including avoiding excess body weight (Jiao et al., 2009; Parkin et al., 2011; Islami et al, 2018).

Obesity and Renal cancer

Renal cell cancer (RCC) is increasing in incidence (Torre et al., 2015; Hsieh et al., 2017). Kidney cancer accounts for approximately 2% of all cancer diagnoses and cancer deaths worldwide (Ferlay et al., 2013). Annually, about 295,000 new kidney cancer cases are diagnosed and about 134,000 deaths are recorded worldwide (Global Burden of Disease Cancer Collaboration, 2015). Men are more affected two times as frequently as women (Hsieh et al., 2017).

There are several meta-analytic studies implicating obesity (increase in body weight - BMI, waist circumference, waist-to-hip ratio) in RCC development (Haggstrom et al., 2013; www.wcrf.org; Lauby-Secretan et al., 2016). Most studies have estimated this risk to be increased by 30% per BMI increase of 5 kg/m2 (www.wcrf.org; Lauby-Secretan et al., 2016).

Obesity and thyroid cancer

Thyroid cancer (TC) represents the most common malignancy of the endocrine system (Cabanillas et al., 2016). Its incidence is rising globally (Siegel et al., 2020). Papillary TC is the most common type and represents approximately 85% of all thyroid cancers (Haugen et al., 2016). It is indolent, with the 5-year relative survival rate of approximately 98% (seer.cancer.gov).

Excess body weight is intricately linked with an increased risk and incidence of thyroid cancer (Hales et al., 2015; Kitahara & Sosa., 2016; Lim et al., 2017). The International Agency for Research on Cancer determined from epidemiological studies that this linkage was causal[81]. This increased risk had an odds ratio 1.17 in men and 1.04 in women (Lauby-Secretan et al., 2016). A systemic review showed that patients who are overweight experience a 25% greater risk while

those who were obese, experienced a 55% risk (Schmid et al., 2015). This review also showed that a 5-unit increase in BMI and a 0.1-unit increase in waist to hip ratio increased the risk of thyroid cancer by 30% and 14%, respectively. Excess body weight is estimated to be responsible for one in six thyroid cancers (Kitahara et al., 2020). Obese thyroid cancer patients tend to have more advanced-stage disease and their cancers are more aggressive (Kim et al., 2013' Tresallet et al., 2014; Choi et al., 2015; Kim and Cheng. 2018).

Obesity and Prostate Cancer

Prostate cancer is the second most common cancer in men (Sung et al, 2021) and a leading cause of cancer-related death (Bray et al., 2018). It was diagnosed in an estimated 1.3 million men worldwide in 2018[89]. Its incidence is increasing (Fillon, 2020).

The causal role of obesity in prostate cancer has been questioned by some studies (Genkinger et al., 2020; Jochems et al., 2020). However, some meta-analyses have clearly shown a connection between obesity and aggressive prostate cancer (MacInnis & English, 2006; Allott et al., 2013). A recent meta-analysis found that obesity was associated with an increase in mortality in prostate cancer patients (Rivera-Izquierdo et al., 2021). In this study a BMI > 30 was associated with a higher prostate cancer mortality and all-cause mortality.

Obesity and Cutaneous Malignant Melanoma

Melanoma arises in the melanocytes – these cells are present in the neural crest located along the choroidal layer of the eye, mucosal surfaces, and meninges in the hair follicles and basal epidermis (Leonardi et al., 2018). Malignant melanoma accounts for only 4% of all skin cancer cases, but because of its high aggressiveness, it is responsible for the highest number of skin cancer deaths (Miller & Mihm, 2006). It is highly lethal in advanced stages. If diagnosed early (stage 0 melanoma), survival is almost 97% – it drops to about 10% for those with stage IV disease (Siegel et al., 2016). Metastasis is common, especially to the lungs, liver, bone, and brain (Tas, 2012). One third of the patients develop a recurrence (Soong et al., 1998). Its incidence is rising globally.

The association between obesity and the risk for malignant melanoma has been questioned by some researchers (Pothiawala et al., 2012; Lauby-Secretan et al., 2016; Præstegaard et al., 2015). However, several epidemiological studies indicate a strong, positive correlation between BMI and the incidence of melanoma (Brandon et al., 2009; Sergentanis et al., 2013; Skowron et al., 2015; Fang et al., 2017) One study also found a positive correlation between obesity and the thickness of the melanoma lesion (Skowron et al., 2015). Studies have noted that diet-induced obesity increases melanoma progression (Pandey et al., 2012). Diet induced obesity in mice with melanoma results in enhanced lymph angiogenesis and lymph node metastasis (Jung et al., 2015). Some researchers have found that obesity significantly increases the risk of melanoma in individuals younger than 50 years old (De Giorgi et al., 2017). Another study noted that a high BMI at age 20 is significantly associated with the risk of future melanoma (Dennis et al., 2007). There is no clear data on the association between obesity and squamous cell skin carcinoma or basal cell skin carcinoma (Pothiawala et al., 2012; Præstegaard et al. 2015).

Obesity and Lung Cancer

Lung cancer is the world's leading cause of cancer death (www.cancerresearchuk.org). It is mainly associated with cigarette smoking, which increases the risk 5- to 10-fold (Schwartz & Cote, 2016). Further, non-smokers exposed to environmental tobacco smoke also have an increased lung cancer risk of about 20%.

The 5-year survival is poor (www.cancer.ne). Several reports report a lower lung cancer risk in individuals with higher BMI, suggesting obesity as a preventive factor for the development of lung cancer (Liu et al., 2004; Samanic et al., 2006). This is contrary to what has been noticed in the previously discussed cancers. Further, several studies have reported reduced mortality (with chemotherapy/lung surgery) in those with lung cancer and a high BMI (25 to 34.9 kg/m^2 (Yang et al., 2011; Leung et al., 2011; Gupta et al., 2016). However, the distribution of fat mass in the body appears to have different effects on lung cancer. In a study **(**involving 1.6 million Americans, Europeans, and Asians with 23,732 incident lung cancer cases during an average 12-year follow-up,**)** published in 2018, that looked at associations of BMI, waist circumference (WC), and waist-hip ratio with lung cancer, some interesting data emerged. The authors found that although high BMI indicated an overall reduced incidence of lung cancer, high WC indicated an increase. Participants with BMIs of less than 25 kg/m2 but high WC had a 40% higher risk (HR = 1.40,) than those with BMIs of 25 kg/m2 or greater but normal/moderate WC. This study was done in never, former, and current smokers (Yu et al. 2018).

Conclusion

Cancer is a major health burden globally. The CDC lists 13 cancers (those involving esophagus, stomach, colon, rectum, liver, gallbladder, pancreas, postmenopausal breast, endometrium, ovary, renal cell, meninges, thyroid, and bone marrow) as being causally related to obesity. Considering the tremendous increase in obesity prevalence all over the world, this causal association indicates that obesity related cancers will continue to increase. Cancer initiation, proliferation, invasion, and metastasis in obesity can be caused by several mechanisms, including increased inflammation, down regulation of adiponectin, and higher insulin resistance. Visceral obesity as measured by waist circumference, appears to be specifically linked with several cancers. Prevention of weight gain in normal weight individuals and weight reduction in overweight/obese individuals is the mainstay intervention to prevent cancer and/or its progression. However, therapies aimed at visceral adipose tissue overgrowth are also being considered. Maintenance of normal body weight should also help reduce the obesity related increased risk and progression of cardiovascular diseases, diabetes, and many other chronic diseases, and premature death. These are often co-morbidly present in cancer patients.

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