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OBESITY AND ITS RELATIONSHIP WITH CANCER: PART III

Breast, Colorectal, Esophageal, Gastric, Gall Bladder, Liver Cancers

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ABSTRACT

Obesity and cancer has been discussed in the first two parts. This part (Part III) deals with six cancers, namely those involving the breast, colorectal tissues, esophagus, stomach. gall bladder, and liver. Their relationship with obesity is discussed. Part IV will look at endometrial, ovarian, pancreatic, prostate, renal, thyroid and lung carcinomas. Meningioma and multiple myeloma are also discussed.

Obesity and breast cancer

Breast cancer is the most prevalent cancer among women worldwide and carries a highest mortality rate (Bray et al., 2018). In 2018, it is estimated that newly diagnosed breast cancers affected nearly 1 in 4 (24.2%) women (Bray et al., 2018). It was the leading cause of female cancer related death in 103 of 172 countries in 2018 (Bray et al., 2018). Obesity affects premenopausal and postmenopausal women differently (García-Estévez et al., 2021). It is estimated that approximately 35% of premenopausal women ages 20 to 59 years in the United States were obese during the years 2011-2014 (Ogden et al., 2015). Obesity is associated with a lower rate of breast cancer in premenopausal women (www.aicr.org). A pooled study of 337,819 women and 4,385 invasive breast cancers, found an inverse association between obesity and premenopausal breast cancer risk (van den Brandt et al., 2000). In this study, the connection was especially noticeable when women who had a BMI >31 kg/m^2 were compared with those who had a BMI <21 kg/m^2. Another meta-analysis of studies that enrolled more than 2.5 million women showed that premenopausal breast cancer risk was reduced by approximately 8% per 5 kg/m^2 BMI increase (Renehan et al., 2008). Obesity however increases the risk of breast cancer in postmenopausal women (Reeves et al., 2007). Menopause occurs with a decline in estrogen production, usually at an average age of 51.3 ± 5 years (García-Estévez et al., 2021). It is usually preceded by a several month periods of irregular menstrual bleeding (García-Estévez et al., 2021). If there is no menstrual period for 12 months, menopause has occurred (www.nichd.nih.gov). The incidence of obesity in women increases with the onset of menopause, mainly due to hormonal changes (Kozakowski et al., 2017). It also rises with increasing age. Obesity incidence is estimated to be 65% among women ages 40 and 65 years and almost 74% over the age of 65 (Flegal et al., 2010). This increase also includes abdominal

obesity - postmenopausal women show a 4.88-fold higher risk of developing abdominal obesity compared to premenopausal women (Donato et al., 2006). A clinical trial of 67,142 postmenopausal women showed that obese postmenopausal women are at greater risk of developing breast cancer compared with their normal weight equivalents (Neuhouser et al., 2015). This increase was confirmed in a meta-analysis of 89 epidemiologic studies (Munsell et al., 2014). Breast cancer is also more aggressive in obese women (Ewertz et al, 2011., Paskett et al., 2012; Chan et al., 2014). The Danish Breast Cancer Cooperative Group (n = 53,816 women) found that obese women had a 46% higher risk of developing metastasis at 10 years follow-up compared to normal weight women (Ewertz et al, 2011). Obesity is also associated with increased risks of treatment-related lymphedema in breast cancer patients (Paskett et al., 2012). Mortality is also higher in these women (Chan et al., 2014). The meta-analysis of 82 studies by Chan et al. reported a 41% and 35% higher risk for all-cause mortality and breast cancer specific mortality, respectively, in obese women compared to normal weight women (Chan et al., 2014). Weight loss helps. Women who lost and maintained >10 kg lower body weight and who did not use postmenopausal hormones demonstrated a lower breast cancer risk than those who did not lose weight (RR= 0.43) (Eliassen et al., 2006). Bariatric surgery appears to have a protective effect in reducing the risk of breast cancer in obese women (Ishihara et al., 2020). A meta-analysis of several studies that incorporated a total of 150,537 patients in the bariatric surgery arm and 1,461,938 women in the control arm, revealed a breast cancer reduction of 49% (RR: .51) in the bariatric surgery group (Ishihara et al., 2020).

Obesity and colorectal cancer

Colorectal cancer (CRC) is the third most common cancer worldwide (Keum & Giovannucci, 2019). Approximately 1.8 million new cases occurred in 2018 (www.wcrf.org). CRC is associated with approximately 900,000 deaths every year (Fitzmaurice et., 2019). CRCs may occur anywhere in the colon, although most occur in the rectum and distal colon (Lauby-Secretan et al., 2018). Most CRCs are adenocarcinomas (Fleming et al., 2012). It is estimated that the lifetimes risk of developing a CRC is 4.4% (1 in 23) in men and 4.1% (1 in 25) in women (Siegel et al., 2020).

Numerous studies have shown an association between higher BMI and the incidence of colorectal carcinoma (Campbell et al., 2010; Matsuo et al., 2012). In Europe, approximately 11% of CRC cases are associated with obesity and being overweight (Bardou et al., 2013). A large meta-analysis of several studies involving 70,906 individuals estimated that the relative risk of colorectal cancer was 1.19 when comparing obese (BMI = or > 30 kg/m^2) with normal weight (BMI <25 kg/m^2) individuals (Islam et al., 2020; Moghaddam et al., 2007). In the same study, the authors found that comparing those with the highest, to the lowest level of central obesity, the increased risk was 1.45. This study also showed that there appears to be a dose-response relationship between BMI. A 2 kg/m^2 increase in BMI increases the risk of colorectal cancer by 7%. A later study estimated that the overall RR for CRC predicted per 1 kg/m2 of higher BMI was 1.03 (www.wcrf.org), further confirming the dose-response relationship. Men seem to be more at risk than women for the development of CRC (Ma et al., 2013; Bardou et al., 2013). In the study by Moghaddam et al., after correcting for publication bias, the risk of colorectal cancer

was 1.41 in men and only 1.08 for women (Moghaddam et al., 2007). Ma et al, found that obesity was associated with more colon cancer than rectal cancer and a more distal location than proximal location (Ma et al., 2013). Xue et al in 2017 estimated that obese men have about a 50% higher risk of colon cancer and a 25% higher risk of rectal cancer, whereas obese women have about a 10% increased risk of colon cancer and no increased risk of rectal cancer, when compared to individuals with normal body weight (Xue et al., 2017).

As with many other cancers, abdominal fat collection, as seen in visceral obesity, is more strongly associated with CRC than BMI (Song et al., 2016; Aleksandrova et al., 2017; Murphy et al., 2018). One study reported that the risk increased by 4% for every 2-cm increase in waist circumference (Moghaddam et al., 2007). A meta-analysis also reported a link between abdominal obesity and an increase in the risk of colorectal adenomas, with an RR=1.42 (Lee et al., 2011). Overweight and obese individuals with CRC have a poorer prognosis. In one clinical trial, obese individuals, especially men with stage II and stage III rectal cancer, demonstrated an increased risk of local recurrence (Meyerhardt et al., 2004)..

CRC is being increasingly diagnosed at younger ages (Vuik et al., 2019). It is estimated that there will be a marked increase in colon cancer among individuals aged 50 or under (Bailey et al., 2014). Rectal cancer is also increasing and expected to continue doing so in young patients (Siegel et al., 2009). This increased incidence of CRC in people below the age of 50 is only partly due to early screening and improved diagnostic procedures and appears to be due to a true causal relationship to an increase in obesity (Martinez-Useros & Garcia-Foncillas, 2016). A study of 1,794,570 Jewish adolescents found that excess body weight increases the risk of later colon cancers, while obesity increases the risk of later rectal cancer (Levi et al., 2017). Analyses using the Nurses' Health Study II (NHS2) data showed that in women with a higher BMI at 18 years of age, and early adulthood weight gain increased the risk of colorectal cancer developing before the age of 50 (Liu et al., 2018). This study showed 20% increase in the risk of colorectal cancer for each 5-unit increase in BMI. In a prospective cohort of 230,000 Norwegian adolescents, adolescent obesity was associated with increased mortality in patients with colon cancer (males: RR= 2.1, females: RR=2.0) (Bjørge et al., 2008).

Obesity reduction via bariatric surgery appears to reduce the risk of obesity-related cancers, in general (Tee et al., 2013). However, some reports suggest that bariatric surgery results in an increased risk of colorectal cancer (Derogar et al., 2013; Hull et al., 2018). Several explanations exist for this possible deleterious effect (Liu et al., 2017; Sainsbury et al., 2008). The connection is however not confirmed, and more data is awaited. Many reports indicate that the absolute CRC incidence in the obesity surgery group is less than in the obesity non-surgical group (Ostlund et al., 2010; Sjostrom L. 2013; Schauer et al., 2019) The final word is therefore still out (Castagneto-Gissey et al., 2020; Bruno et al., 2020). Currently, data indicates that bariatric surgery does not eliminate or reduce colorectal cancer risk beyond that of the non-obese, normal weight population.

Obesity and esophageal cancer

Esophageal carcinoma (EC) is one of the most common gastrointestinal malignancies in the world (Bray et al., 2018). It represents the seventh most common malignancy worldwide. The two main histologic subtypes of EC are adenocarcinoma (EAC) and squamous cell carcinoma (ESA), and these account for more than 95% of the cases (Pennathur et al., 2013). ESA arises from cells commonly located at the mid-portion of the esophagus (Recio-Boiles & Babiker, 2021). The reduction in tobacco use and alcohol consumption in the West has resulted in a steady decrease in ESA (Giri et al., 2015). On the other hand, the incidence of EAC has been increasing—primarily due to an increase in body weight (Nimptsch et al., 2016). A meta-analysis of several observational studies estimated that EC had a RR of 1.52 in men and a RR of 1.51 in women per 5Kg/m2 increase in BMI (Kubo & Corley, 2006). A later umbrella review of 204 meta-analyses also showed a strong relationship between excess body weight and EC (Kyrgiou et al., 2017). More recently, Fang et al also found an association of high BMI with EAC (RR=1.45) (Fang et al., 2018). Increasing BMI appears to result in more CRC. The NIH-AARP Diet and Health Study – a prospective study, found EAC risk was highest for those with BMIs > 35 kg/m2 (Abnet et al., 2008). Another study showed that a BMI > 40 kg/m^2 was associated with EC with a RR of 4.8 (O'Sullivan et al., 2018).

Obesity in early life appears to have a relationship with future EAC. The factors influencing the Barrett's/Adenocarcinoma relationship population-based and case-controlled study revealed that EAC was more common among subjects who were overweight or obese 5 y before its diagnosis (Anderson et al., 2007). An earlier study had reported that being overweight (BMI > 25) at age 20 or 10 years before diagnosis, increased the risk of future EAC (de Jonge et al., 2006).

Obesity is associated with a higher prevalence of gastroesophageal reflux disease (GERD) which in turn leads to Barrett's esophagus (BE) and intestinal metaplasia (Gg et al., 2004). BE is a premalignant disorder. Chronic acid exposure in GERD leads to a metastatic columnar replacement of the normal stratified squamous epithelium of the distal esophagus (Zheng et al., 2017). A meta-analysis reported in 2005 indicated a significant and dose-dependent associations between obesity and GERD (RR 1.43-1.94 for BMIs 25–30 kg/m2) (Hampel et al., 2005). BE is associated with an increase in EAC, accounting for most adenocarcinomas of the distal esophagus (Spechler, 2013).

EC is associated with a poor prognosis and the overall 5-year survival rate is only about 10%-20% (American Cancer Society, 2020). It is presently the sixth leading cause of cancer-related death in the world (Ferlay et al, 2010). Besides the influence of the usual obesity related mechanisms, abdominal pressure increase may cause or aggravate GERD, increasing the EC risk (Emerenziani et al., 2013)

Obesity and gastric cancer

Globally, gastric cancers (GC) are the fifth most common cancers, with an estimated 1,000,000 cases in 2018 (Bray et al., 2018). They are more common in men than in women (Bray et al., 2018). GC are categorized as proximal or cardia-GC and distal or non-cardia-GC (Zali et al., 2011). Smoking and obesity are known risk factors for cardia-GC, while Helicobacter Pylori

infection and smoking are risk factors for non-cardia-GC (Karimi et al, 2014). Tumors in the gastric cardia have a poorer prognosis compared with those in the distal part of stomach (Crew & Neugut, 2006). Histopathology reveals that most gastric cancers are adenocarcinomas (90%) (Hu et al., 2012). Unfortunately, the incidence of cardia-GC has been increasing in younger people (Bergquist et al., 2019).

Several epidemiological studies show that increasing body weight and body mass index (BMI) increases the risk of gastric cancer (Yang et al., 2009; Alemán et al., 2014). In a U.S cohort study, obesity increased the risk of gastric cardia adenocarcinoma twofold (Chow et al., 1998). A subsequent study showed that patients with a BMI >29 kg/m2 or highest quartile had a 2.3-fold greater risk of proximal GC than those with BMI >23 kg/m2 or lowest quartile (Lagergren et al., 1999). This association has been confirmed by several recent studies (Islami et al., 2018; Rastaghi et al., 2019). It is estimated that there is a 23% increased risk of gastric cardia cancer per 5 kg/m^2 increase in excess body weight (www.wcrf.org).

Obesity and gall bladder cancer

Gallbladder cancer is a rare cancer that is aggressive and is associated with a poor prognosis (Burasakarn et al., 2021). The 5-year survival is extremely low in advanced cases (Kai et al., 2007). Treatment is primarily surgical (www.cancer.org).

In a prospective study that included 3,658,417 participants, obesity was positively associated with an increased risk of cancers of the gallbladder and biliary tract (Recalde et al., 2021). Another study from UK found that higher levels of adiposity were associated in a linear manner with gall bladder cancer (Parra-Soto et al., 2021). Studies estimate that excess body weight increases gall bladder cancer risk by 25% per increase in BMI of 5 kg/m^2 (www.wcrf.org). An excess risk of intrahepatic cholangiocarcinoma has also been noted with excess body weight (Petrick et al., 2018). It is estimated that reducing BMI to normal in obese individuals should help prevent 29.9% of gall bladder cancer incidence and 39.8% gall bladder cancer related mortality (Parra-Soto et al., 2021).

Obesity and liver cancer

Primary liver cancer is one of the most common malignancies (Wong et al., 2017). The associated mortality rate corresponds to 9% of all cancer-related deaths worldwide (Wong et al., 2017). Hepatocellular carcinoma (HCC) is the most common liver cancer and accounts for approximately 80–90% of all cases of primary liver cancer (Llovet et al., 2021). The common causes of HCC are viral hepatitis (hepatitis B or C virus infection), alcohol, smoking, and diabetes mellitus (Llovet et al., 2016).

Obesity is an independent risk factor for the occurrence of HCC[103]. Sohn et al reported that their study revealed that the risk of occurrence of primary liver cancer was increased in patients with excess body weight, with pooled hazard ratio of 1.36, 1.77, and 3.08 for a BMI >25, >30, and >35 kg/m2, respectively (Sohn et al., 2021). They also found that the risk of mortality from primary liver cancer increased as the BMI increased >25 kg/m^2. This finding is consistent with that reported in previous meta-analyses (Chen et al., 2012; Rui et al., 2012; Wang et al., 2012). Other anthropometric measurements of visceral obesity, indicate that an increase in abdominal

size is also associated with an increased risk of liver cancer. Florio et al estimated that for each 5 cm increase in waist circumference, there was an 11% increased liver cancer risk (Hazard Ratio or HR=1.11). this higher risk persisted when adjusted for hip circumference (HR=1.12) and when restricted to individuals with a normal body mass index (HR=1.14). Hip circumference, per 5 cm increase, was associated with a 9% increased liver cancer risk (HR=1.09), but no association remained after adjustment for waist circumference (HR=0.99) (Florio et al., 2020). These findings suggest that excess abdominal size is associated with an increased risk of liver cancer, even among individuals with a normal BMI (Florio et al., 2020). According to the World Cancer Research fund, there is a positive nonlinear dose-response relation between excess body weight and HCC risk (www.wcrf.org). According to their estimations, the risk for HCC increases by 30% per 5 kg/m2 excess body weight. Excess body weight is also associated with nonalcoholic fatty liver disease (NAFLD), the most common liver disorder in the world (Roeb et al., 2015). NAFLD, may progress to nonalcoholic steatohepatitis (NASH), and NASH may further progress to liver cirrhosis and hepatocellular carcinoma (EASL., 2015). Further, alcohol (Loomba et al., 2013) and smoking (Meyer et al., 2015) enhance the obesity-associated HCC risk in obese patients. Overweight/obese with DM (Baecker et al., 2018) or chronic hepatitis B or C infections (Yu et al., 2017) or with hemochromatosis also see an increase in HCC risk.

In summary, excess body weight increases the risk and progression of cancer of the breast, colorectal tissues, esophagus, stomach. gall bladder, and liver. Avoidance of weight gain, maintenance of normal weight, and reduction of excess body weight – all appear to have a beneficial effect on these cancers. Part IV will look at the impact of obesity on meningiomas, multiple myelomas and endometrial, ovarian, pancreatic, prostate, renal, thyroid and lung carcinomas

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