https://doi.org/10.31925/farmacia.2023.3.1 **REVIEW**

OBESITY AND CANCER: AN UNDERESTIMATED TOXIC RELATIONSHIP

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Abstract

Obesity is a growing global concern, with an estimated one-third of the world's population being overweight or obese. A huge number of studies were conducted to correlate obesity with cancer, mainly with epidemiology, disease progression and survival outcomes. This review article aims at summarising the obesity-related mechanisms associated with cancer development and progression, in addition to investigating the effect of obesity on different types of cancer in terms of disease progression, prognosis and survival outcomes. Confounding factors associated with variability in the obesity-cancer link and outcomes were assessed as well, besides the obesity paradox. Included articles were reached through PubMed, the Cochrane Library and EMBASE for the period between 2017 and 2023 using both the title and keyword functions for the search terms. In conclusion, in this review, obesity was linked to higher overall cancer patient mortality. Patients with lung cancer, renal cell carcinoma and melanoma who also had obesity had a decreased likelihood of dying compared to those with the same diseases who did not have obesity. Weight loss techniques might be an effective way to lower mortality in these populations.

Rezumat

Obezitatea reprezintă o problematică mondială în creștere, estimându-se că o treime din populația lumii este supraponderală sau obeză. Un număr foarte mare de studii au fost efectuate pentru a corela obezitatea cu cancerul, în principal în ceea ce privește epidemiologia, evoluția bolii și rezultatele în materie de supraviețuire. Acest articol își propune să rezume mecanismele legate de obezitate, asociate cu dezvoltarea și progresia cancerului, să investigheze efectul obezității asupra diferitelor tipuri de cancer în ceea ce privește evoluția bolii, prognosticul și rezultatele de supraviețuire. Pe lângă paradoxul obezității, au fost evaluați și factorii de confuzie asociați cu variabilitatea legăturii dintre obezitate și cancer și rezultatele acestuia. Articolele incluse au fost accesate prin PubMed, Cochrane Library și EMBASE pentru perioada cuprinsă între 2017 și 2023, utilizând atât funcția de titlu, cât și cea de cuvinte cheie pentru termenii de căutare. În concluzie, în această analiză, obezitatea a fost corelată cu o mortalitate generală mai mare a pacienților cu cancer. Pacienții cu cancer pulmonar, carcinom cu celule renale și melanom care aveau și obezitate au avut o probabilitate mai mare de a muri în comparație cu cei cu aceleași boli care nu aveau obezitate. Tehnicile de pierdere în greutate ar putea fi o modalitate eficientă de a reduce mortalitatea la aceste tipuri de pacienți.

Keywords: cancer, obesity, mechanisms, progression, survival, confounding variables

Introduction

The obesity pandemic is a concerning health problem worldwide, with an estimated one-third of the world's population being overweight or obese [1]. Obesity affects all age groups, both genders and different ethnicities at variable rates, but the prevalence trend has generally increased by twofold since 1980 [1]. Body Mass Index (BMI) is a universal indicator of adiposity [2]. A person with a BMI of 25 - 29.9 is overweight, and a person with a BMI of 30 or higher is obese [2]. It is a multifactorial disease associated with genetic, psychological, social and economic factors [3]. Obese people are at increased risk of developing dyslipidaemia, diabetes mellitus type 2, hypertension, heart diseases, cerebrovascular accidents, respiratory diseases and different types of cancer [3]. Besides this, obesity places an economic and social burden on the country and the individual [3].

Obesity is the second-most common risk factor for cancer after smoking [4]. Worldwide, obesity-related cancers affect 11.9% of males and 13.1% of females and are found at least in 13 different anatomical sites [5]. The International Association for Research on Cancer proved a link between obesity and oesophageal adenocarcinoma, gastric cardia cancer, colorectal cancer, pancreas cancer, gallbladder cancer, liver cancer, renal cell carcinoma, thyroid cancer, multiple myeloma, meningioma, endometrial cancer, postmenopausal breast cancer and ovarian cancer [6]. This complex association is attributed to many direct and indirect

mechanisms, and it is not fully understood [2]. The most studied mechanisms are sex hormones, insulin and insulin-like growth factors, adipokines and chronic inflammation [7]. These mechanisms are overlapping and have a clinical implication for lowering the incidence of various types of cancer and their mortality rates [8].

Most of the bulk of the evidence relating obesity to cancer risk is accounted for by large cohort studies, a form of observational study. Observational study results, however, do not prove conclusively that obesity clearly increases cancer risk. This is due to the possibility that factors other than body fat – differences between people with obesity or overweight and those without these conditions – may account for the increased cancer risk. Increasing body fat is consistently linked to a higher risk of developing a range of malignancies, according to a working group of the International Agency for Research on Cancer (IARC). The listed malignancies include (starting from being highly related to obesity): endometrial, oesophageal, gastric, liver, kidney, multiple myeloma, meningioma, pancreatic, colorectal, gallbladder, breast (postmenopausal > premenopausal), ovarian and lastly thyroid cancer [6]. Numerous variables of cancer survivorship, including quality of life, cancer recurrence, disease progression, prognosis (survival) and the risk of some second primary malignancies, appear to be negatively impacted by obesity, according to the last published literature [9, 10]. Increased body weight and obesity have been found to possibly raise the risk of mortality from cancer [11]. Additionally, a higher BMI at diagnosis was found to be linked to a higher risk of developing a second unrelated cancer and multiple cancers [12]. In breast cancer patients, for instance, obesity was found to increase the incidence of treatment-related lymphedema [13]. In prostate cancer patients, however, obesity increased the possibility of post-treatment radical prostatectomy (RP) [14]. Comparable negative impacts were also reported in colorectal cancer (CRC) patients in stages I and II of the disease, where patients with a higher BMI at baseline had higher chances of disease recurrence in the same location [15]. Moreover, patients with the highest levels of obesity seem to have a 50% higher risk of mortality from multiple myeloma than people who are within a healthy weight range [16]. The two risk factors that cannot be changed are gender and ethnicity. The prevalence of obesity varies by race and ethnicity, with blacks and Hispanics being more likely than non-Hispanic whites to be obese [17]. Even though some have theorised that obesity may affect survival differently in different racial and ethnic groups, research is scarce and contradictory [18], and there are health inequities among minorities with regard to cancer outcomes, which may cloud the effect of obesity [19]. Over time, being overweight and obese increases the risk of cancer, and a longer period of being overweight and obese during adulthood raises the risk of multiple different cancers. Additionally, it appears that both the length and severity of overweight play a significant role in the likelihood of acquiring cancer [20]. The epidemiological discovery that being overweight or obese is linked to a longer life expectancy than having a normal weight is known as the obesity paradox [21]. Cancer patients who are overweight or obese have higher survival rates for various malignancies [22]. Methodological flaws such as reverse causation, selection bias, confounding and dependence on BMI as a measure of adiposity in cancer patients may account for a major portion of this apparent obesity paradox. Low muscle mass and high adiposity are linked to inferior clinical outcomes in cancer patients, according to a growing corpus of studies that provide encouraging evidence that carefully measured body composition can offer crucial prognostic information in cancer management [22].

This review article discusses the obesity-related mechanisms of developing cancer, the effects of obesity on cancer, other contributing factors besides obesity, points of conflict in this association, future directions and clinical implications of this causality.

Mechanisms Link Obesity and Cancer

Although the link between obesity and increased cancer risk isn't fully understood, many biological mechanisms directly interpret this link [2]. In this review article, we are going to summarise several mechanisms that contribute to the association between obesity and increased cancer risk.

Sex Hormones

This mechanism explains the increased risk of developing hormone-sensitive tumours such as breast, endometrial and ovarian cancers in postmenopausal women [23]. In obese women, there is increased activity of the aromatase enzyme in fatty tissues; this enzyme is responsible for the aromatization process in which androgen is converted to oestrogen, so obesity is associated with increased levels of oestrogen, which induce cell division and mutation, causing tumour progression [23]. Also, high levels of androgens (which are produced mainly by the adrenal gland), and low levels of sex hormone-binding globulin increase the risk of breast cancer in obese women [23]. The Women's Health Initiative randomised clinical trial found that there is an increased risk of developing invasive breast cancer in obese postmenopausal women [24]. Regarding endometrial cancer, oestrogen increases the proliferation of the endometrial tissue and stimulates the local production of IGF-I, which augments the proliferation function of oestrogen [23]. Oestrogen action in the endometrial tissue is opposed by progesterone, which induces oestradiol metabolism and IGF-binding protein 1 production, thus inhibiting

oestrogen and IGF-I action in the endometrial tissue [23]. Obesity causes an oestrogen/progesterone imbalance, and oestrogen action that is not opposed by progesterone increases the risk of endometrial cancer [25]. The Women's Health Initiative randomised clinical trial found that continuous combined hormonal therapy (oestrogen plus progestin) decreases the risk of endometrial cancer in postmenopausal women [26]. Notably, testosterone levels are lower in obese men, and there is no clear association between sex hormone levels and the risk of developing prostate cancer [23]. The available data suggest that low serum testosterone in obese men is associated with poorly differentiated prostate cancer [27].

IGFs Overexpression and Insulin Resistance

Insulin-like growth factors (IGFs) are produced in nearly all tissues, and they play a role in the growth of tumours [28]. Cancer cells overexpress IGFs (especially IGF-I receptors); these molecules directly mediate cell cycle progression and inhibit cell death [28]. As mentioned before, oestrogen stimulates IGF-I production and indirectly mediates cell proliferation [28]. The association between increased IGF levels and cancer risk is variable depending on the anatomical site [29]. Acromegaly is an endocrine disorder that is characterised by increased levels of growth hormone and IGF-I. This disorder is associated with an increased risk of colorectal cancer, thus providing clinical evidence of this mechanism [30]. Diabetes mellitus type 2 is associated with an increased risk of developing oesophageal, pancreatic and biliary tract cancers in males; endometrial and breast cancers in females; and colorectal, kidney and liver cancers in both genders [31]. Hyperinsulinemia in obese individuals also increases the risk of developing cancer, both directly through growth signals and indirectly through decreased production of IGF-binding proteins and increased levels of free IGF, thus promoting cell growth and inhibiting cell death [23]. Metformin administration has reduced IGF-I levels in obese patients who survive cancer, but for only 6 months [32]. A retrospective cohort study conducted in the UK suggests that diabetic patients who take insulin-sensitising drugs like metformin or thiazolidinediones are at lower risk of having cancer compared to those who take insulin or insulin-secreting drugs like sulfonylureas [33].

Adipokines and Systemic Inflammation

Adipose tissue is not only an energy store but also an endocrine organ that secretes adipokines [34]. Adipokines are cytokines that have a role in carcinogenesis, and the most studied types are leptin and adiponectin [35]. Leptin is a potent inflammatory agent, and its level is positively correlated with BMI [23]. Obesity is associated with high levels of leptin, so it has a role in the development of breast, colon and prostate cancers, as it induces cell division, inhibits cell death, promotes angiogenesis and suppresses immune function [23, 36]. However, adiponectin is a potent anti-inflammatory agent with anti-proliferative effects that protect from cancer development, and its level is negatively correlated with BMI [23]. Obesity is associated with low levels of adiponectin, and an increased risk of colorectal cancer, renal cancer, endometrial cancer in premenopausal women, and breast cancer in postmenopausal women [23, 35]. A study proves that weight loss increases adiponectin levels regardless of the diet type [37].

Sub-Clinical Inflammation and Tumour Micro-environment

Obesity is a state of chronic subclinical inflammation, and the tumour microenvironment resembles that of injured tissue [38]. This link may be attributed to immune cell infiltration, such as granulocytes, cancer-associated fibroblasts, endothelial cells, T and B lymphocytes, mast cells, antigen-presenting cells (*i.e.*, macrophages and dendritic cells), extracellular matrix (ECM) and other stromal components [39]. The dysregulation of immune function leads to epithelial dysfunction, and these changes increase the risk of cancer development and progression [39]. C-reactive protein (CRP), tumour necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 and IL-18 levels rise as adipose tissue increases [23]. CRP levels and colon cancer were linked in an early epidemiological study [40]. Additionally, epidemiologic studies have shown a link between chronic inflammation and the risk of several malignancies, including those of the stomach, oesophagus, colon, liver, bladder and lung [41]. Many cancers are associated with a previous infectious inflammatory trigger; for example, *H. pylori* infection increases the risk of gastric cancer and MALT lymphoma; human herpes virus 8 increases the risk of Kaposi's sarcoma, and hepatitis viruses (B and C) increase the risk of hepatocellular carcinoma [41]. Other types of cancer are associated with non-infectious inflammatory triggers, such as lung cancer, which is associated with exposure to asbestos or silica [41]. An association between inflammatory bowel disease and colorectal cancer is noted [41]. Inflammation of the adipose tissue promotes breast cancer development and is associated with a worse prognosis [39]. It's important to note that some people who do not meet the body mass index criteria for obesity or overweight can have adipose tissue inflammation and its tumour-promoting effects [39]. Clinical evidence of this mechanism is that aspirin modulates the inflammatory cytokines and is thought to reduce the risk of colo-rectal cancer if it is taken at higher doses [42].

Oxidative stress

Obesity is a condition that is associated with systemic oxidative stress due to inflammation of the adipose tissue [43]. Oxidative stress is an imbalance between reactive oxygen species (ROS) and the antioxidant actions in the body, leading to impaired cellular functions and an increased risk of cancer [43].

Increased levels of ROS lead to more mutations and DNA damage, thus increasing the risk of cancer development and progression [44]. As well, high production of ROS can stimulate the phosphoinositide 3-kinase/protein kinase B (PI3K/PKB) and mitogen-activated protein kinase (MAPK) signalling pathways, which regulate tumour proliferation and cell apoptosis [45, 46]. In particular, increasing ROS generation may halt the effect of PTEN (tumour suppressor gene) and inhibit ERK1/2 (extracellular signal-regulated kinase 1/2), resulting in the activation of PI3K/Akt expression and stimulating cell growth and tumour development [46, 47]. In addition, oxidative stress is correlated with blocking specific genes such as FoxO3, TP53 and ATM (ataxia telangiectasia mutated) [48]. These genes play a role in preventing DNA damage from intracellular ROS production [49]. Although, the role of oxidative stress in cancer is not fully understood, many studies have proven a link between this mechanism and breast cancer development and progression [50].

Intestinal Microbiome Alteration

The intestinal microbiome consists of around 10^{13} - 10^{14} different types; it forms a symbiotic relationship with the host, maintains the normal immune function of the mucosa, protects the integrity of the epithelial barrier, and helps in nutrient utilisation [51, 52]. Also, it is affected by several factors, including diet and obesity [53]. Obesity, the intestinal microbiome and cancer are linked by two main mechanisms: the stimulation of inflammation and the production of pro-tumour factors [5]. The imbalance of the microbiome, dysbiosis, can trigger multiple digestive issues such as irritable bowel syndrome (IBD) and colorectal cancer (CRC). In this context, dysbiosis plays a role in promoting inflammation and modulating different signalling pathways that may initiate adenoma in the primary stages of CRC [54, 55]. The tumorigenesis impact of dysbiosis is determined by several factors, including the genomic alteration effect of some bacteria and their metabolites, mediating inflammation and eliciting an immune response [55, 56].

It also stimulates oestrogen metabolism and increases oestradiol levels, thus raising the risk of oestrogen-dependent cancers, including endometrial cancer and post-menopausal breast cancer [57].

Mechanical Mechanisms

Obesity is linked to renal cell carcinoma through elevating blood pressure, and obesity is an independent risk factor for kidney cancer [7]. Moreover, obesity is associated with chronic acid regurgitation, which causes Barrett's oesophagus, a precancerous lesion of the oesophageal adenocarcinoma [7]. Obesity is also associated with an increased risk of thyroid carcinoma due to increased iodine uptake by the thyroid gland [7]. Figure 1 depicts the main mechanisms that link obesity and cancer.

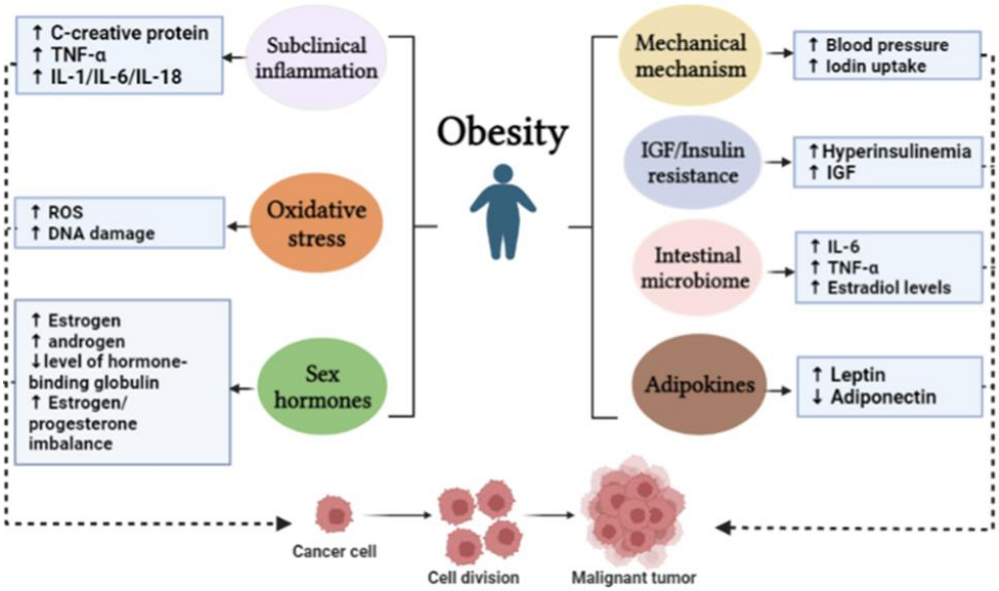

Figure 1.
The main mechanisms that link obesity and cancer

The Correlation Between Obesity and Cancer: Clinical Trials

A relatively recent systematic review and meta-analysis published in 2021 summarised the research findings regarding the association of obesity with survival outcomes in patients with cancer. The review summarised that overall mortality was found to be higher in obese patients diagnosed with either breast, colorectal, or uterine cancers and that mortality due to cancer has increased in patients with breast, colorectal, prostate and pancreatic cancer. Additionally, breast, colorectal, prostate and gastric cancers were found to

have higher relapse rates [58]. In the same review, lung cancer and melanoma were the two cancers where the obesity paradox was registered, while the obesity paradox is referred to as the measure that depicts improved cancer and all-cause death rates among obese individuals; however, this data came from just 12 research items (out of 203 included). For both overall survival (OS) and cancer-specific survival (CSS), the extent of the effect size was comparable in breast, colorectal and lung cancer. Thus, obesity may have an impact on both the natural course of cancer and the death rate from causes other than cancer [58].

Breast cancer

Studies on obesity and survival in breast cancer patients have some inconsistent findings, presumably due to the molecular subtype heterogeneity [59].

In a study conducted in 2017, it was assessed how different Prediction Analysis of Microarray 50 (PAM50) subtypes of breast cancer can affect the relationship between BMI at diagnosis and breast cancer recurrence and survival. The researchers revealed that a BMI higher than 35 kg/m^2 was adversely correlated with outcomes only in patients with luminal A cancer [59]. Similar findings were obtained from a Malaysian study conducted in 2018 on around 3000 (433 were obese) female patients, where breastfeeding and BMI were found to be linked to prognosis in patients with luminal A-like breast cancer specifically [60].

In another study conducted in Italy in 2017 and targeting breast cancer patients (n = 841, obese: 23%), the research team found that patients with obesity and diabetes at diagnosis tended to be older, had larger tumours (> 2 cm), and had worse outcomes than patients without any of them. Researchers pointed out that such findings imply that patients with early breast cancer may have different prognoses depending on their metabolic health [61].

One more retrospective study was conducted in 2017 and involved around 8700 South Korean women with breast cancer (9% were obese). The study aimed at assessing whether there is a particular patient sub-group for which the BMI has an impact on the prognosis of breast cancer. The researchers used the Kaplan-Meier technique and Cox proportional-hazards regression models and compared the outcomes for overall survival (OS) and breast cancer-specific survival (BCSS) among BMI groups. BMI was found to influence the prognosis of breast cancer by interacting with the hormone receptor status in lymph node-positive patients [62].

One more study from New Zealand was conducted in 2018 and involved around 3500 patients diagnosed with invasive breast cancer. In the study population, BMI was measured after diagnosis and was used to estimate mortality from breast cancer, other causes, and all causes of mortality, as well as rates of loco-regional and distant recurrence. The conclusion was that, based on 1049 patients who had chemotherapy and had follow-up for up to 14 years, obesity assessed post-diagnosis did not have an impact on survival or recurrence in that cohort, regardless of the selected treatment plan [63].

In a retrospective analysis of hospital cases conducted in China in 2018 and retrieved from around 1000 patients diagnosed with breast cancer, the effects of obesity and overweight on breast cancer prognosis were found to be related more to menopausal status and that both conditions may independently be linked to a worse prognosis for patients [64]. In addition, larger tumour sizes, older age, a higher percentage of postmenopausal women, and a lower proportion of patients choosing anthracycline and/or taxane treatment regimens were all related to increased weight and obesity [64].

About developing a second cancer, one study from the United States revealed a statistically significant link between a high BMI and an increased risk of developing a second malignancy. The retrospective cohort involved around 6500 patients with known baseline BMI who were recently diagnosed with a second cancer after a mean of 88 months of follow-up [9].

Prostate Cancer

A few retrospective studies were conducted in 2017 in multiple regions of the world and targeted prostate cancer (PC) patients who underwent a radical prostatectomy (RP). In one large-scale study from Germany that was conducted on around 16000 patients, obesity was found to possibly increase the likelihood of developing non-organ-confined illness at RP; however, it was not found to be an independent predictor of biochemical recurrence (BCR) following the procedure. Therefore, the detrimental impact of obesity on PC may be restricted to local disease progression and may be offset by RP [65].

In another study from Austria that involved almost 6500 patients, adverse pathological characteristics and BCR after RP were linked to overweight and obesity status. However, a model that was built on established predictors did not significantly benefit from the addition of BMI in terms of prognostic accuracy [66].

In the United States, a study was conducted that involved nearly 4300 patients and found that obesity and increased weight were linked to an increased incidence of PC-specific mortality (PCSM) following RP [67].

A prospective cohort study was conducted in Canada and enrolled nearly 1000 patients with prostate cancer. The patients were followed up for 19 years for survival outcomes, relying on Cox proportional hazards to obtain associations between survival outcomes and anthropometric measures (including the patient's weight, height, BMI, WC and waist-to-hip ratio). The researchers found that anthropometric parameters

after diagnosis were not clearly associated with all-cause mortality, prostate-specific mortality, first recurrence or progression, or new primary cancer, according to survival analyses [68].

Lastly, a study from the USA assessed the relationship between diabetes and obesity and the time for PC progression amongst two racially defined groups (white Americans and black Americans). The study revealed that among participants from the white race group only, obesity was associated with disease progression, and diabetes was not associated with disease progression in either race group [69].

Colorectal Cancer (CRC)

The risk of colorectal cancer is known to be influenced by excess body weight; however, there is minimal evidence that the body mass index (BMI) affects the long-term prognosis of patients with rectal cancer [70].

An Australian study included around 700 participants and aimed to study the correlations between lifestyle variables assessed before diagnosis and colorectal cancer (CRC) survival. The cohort study, which enrolled data on baseline body measures, alcoholic beverage use, cigarette smoking and physical activity, found that waist circumference (WC) was negatively correlated with CRC-specific survival, regardless of tumour stage, anatomic site, or tumour molecular status [71].

In another cohort study conducted in Germany in 2019 that included around 600 patients with CRC under treatment protocols, the effect of BMI on the likelihood of distant metastasis, local recurrence and overall survival in those patients was assessed. CRC patients who were either underweight or overweight had a poorer chance of overall survival and a higher chance of distant metastases, without a significant difference in local recurrence rates [72]. Consistent findings were obtained from a Chinese cohort study conducted in 2017 that investigated the association between pre-diagnostic BMI/waist-hip ratio (WHR) and total or cause-specific mortality, where obesity and underweight were associated with increased mortality among the study population [73].

Endometrial Cancer

In a register study from Denmark that included around 4300 female patients with either type I or type II endometrial cancer (EC), increased mortality in both cancer subtypes was related to abnormal BMI; obesity was found to have a significant impact on mortality in Type II patients, while low body weight was linked to higher overall mortality in both types [74].

Consistent findings related to obesity came from an Australian study aimed at assessing the impact of obesity, diabetes and other lifestyle factors on overall mortality in endometrial cancer patients. Investigated variables (including obesity) were found to act as negative predictors for mortality among women with EC, although the risks varied depending on whether the death was cancer-related or not [75].

Ovarian Cancer

In a study that was published in 2019 in the United States and Australia and retrieved data from thirteen previous studies, the researchers evaluated the correlations between combined exposures to smoking, increased weight or obesity, and not having a sedentary lifestyle and overall survival (OS) and progression-free survival (PFS) in around 7000 female patients diagnosed with invasive epithelial ovarian cancer. Obesity, smoking and physical inactivity, if combined, were found to possibly reduce the survival rate in ovarian cancer [76].

Lung Cancer

One published study summarised the findings from the PLCO (prostate, lung, colorectal and ovarian) screening trial in lung cancer patients. Based on data from 145544 patients, the relationship between BMI measurements during adult life (at 20 years, 50 years and at enrolment into the research) was assessed for associations with lung cancer development and death risks. A higher BMI at diagnosis generally appeared to relate to a decreased risk of lung cancer development and mortality. Additionally, a rising temporal trajectory of pre-diagnostic BMI was found to be linked to a decreased risk of lung cancer development and mortality [77].

Bladder Cancer

A study from Italy conducted in 2019 examined the effect of BMI on survival outcomes in 1200 patients with stage T1 grade 3 (T1G3) non-muscle invasive bladder cancer (NMIBC) receiving immunotherapy. Multiple regression analysis revealed that obesity and overweight were strongly related to a higher risk of disease progression [78]. Table I summarises the recent clinical studies that describe the correlation between obesity and cancer.

Table I

The most recent clinical studies showing the correlation between obesity and cancer

Type of cancer	Study group size (n)	Duration of the study	The outcome of the study	Ref.
Breast cancer	1559	17 years (1996 - 2013)	The researchers revealed that BMI higher than 35 kg/m^2 was adversely correlated with outcomes only in patients with luminal A cancer types	[59]
	3012	2 years	Breastfeeding and BMI were found to be linked to prognosis in patients with luminal A-like breast cancer specifically	[60]
	841	4 years (2009 - 2013)	The research team found that patients with obesity and diabetes at diagnosis tended to be older, had larger tumours (> 2 cm), and had worse outcomes than patients without any of them	[61]

Type of cancer	Study group size (n)	Duration of the study	The outcome of the study	Ref.
	8742	11 years (1997 - 2008)	BMI was found to influence the prognosis of breast cancer by interacting with the hormone-receptor status in lymph node-positive patients	[62]
	1049	14 years (2000 - 2014)	The conclusion of this study was that obesity assessed post-diagnosis did not have an impact on survival or recurrence in that cohort, regardless of the selected treatment plan	[63]
	1017	8 years (2004 - 2012)	The effects of obesity and overweight on breast cancer prognosis were found to be related more to menopausal status, and both conditions may independently be linked to a worse prognosis for patients	[64]
	6481	7 years	The study revealed a statistically significant link between a high BMI and an increased risk of developing a second malignancy	[9]
Prostate cancer	16,014	11 years (2004 - 2015)	The unfavourable impact of obesity on prostate cancer might be restricted to the local spread of the disease and might be neutralised after radical prostatectomy (RP)	[65]
	6519	2 years and 4 months	The addition of BMI slightly increased the discrimination of the multivariable clinical prognostic model	[66]
	4268	6.8 years	The study found obesity and increased weight were linked to an increased incidence of PC-specific mortality (PCSM) following RP	[67]
	1000	19 years	The researchers found that anthropometric parameters after diagnosis were not clearly associated with all-cause mortality, prostate-specific mortality, first recurrence/progression, or new primary cancer, according to survival analyses	[68]
	647	5 years	Obesity was associated with disease progression, and diabetes was not associated with disease progression in either race group	[69]
Colorectal cancer	724	10 years	It was found that waist circumference (WC) was negatively correlated with CRC-specific survival, regardless of tumour stage, anatomic site, or tumour molecular status	[71]
	612	7 years (2003 - 2010)	CRC patients who were either underweight or overweight had a poorer chance of overall survival and a higher chance of distant metastases, without a significant difference in local recurrence rates	[72]
	1452	16 years (1997 - 2013)	Obesity and being underweight were associated with increased mortality in the study population	[73]
Endometrial cancer	6003	7 years (2005 - 2012)	Obesity was found to have a significant impact on mortality in Type II patients, while low body weight was linked to higher overall mortality in both types	[74]
	1359	2 years (2005 - 2007)	Investigated variables (including obesity) were found to act as negative predictors for mortality among women with EC, although the risks varied depending on whether the death was cancer-related or not	[75]
Ovarian cancer	7022	NA	Obesity, smoking and physical inactivity, if joined together, were found to possibly reduce an ovarian cancer patient's chance of survival	[76]
Lung cancer	145,544	NA	A higher BMI at diagnosis generally appeared to relate to a decreased risk of lung cancer development and mortality	[77]
Bladder cancer	1155	10 years (2002 - 2012)	Multiple regression analysis revealed that obesity and overweight were strongly related to a higher risk of disease progression	[78]

Other Confounding Factors that Relate to Obesity and Cancer in Clinicals Trail

Ethnicity/Race

The Menikdiwela study was performed between December 14, 2018 and September 5, 2020, across 90 institutions in the United States on around 1928 patients with luminal A-type breast cancer and 1610 patients with luminal B-type cancer. The Declaration of Helsinki ethical guidelines were followed in conducting this study [79]. Based on BMI and race, patients with luminal type A and luminal type B breast cancers were compared. According to their findings, there is a strong correlation between ethnicity and the percentage of luminal A *vs.* luminal B cancer. Compared to Luminal A tumours, Luminal B tumours have more aggressive clinical and biological characteristics and express fewer oestrogen and progesterone receptors, making them less responsive to or effective with endocrine therapy. They found a substantial correlation between race and the prevalence of the more aggressive Luminal B carcinoma subtype, with black and African American women having a much higher risk of developing Luminal B cancer than white and Latino women [79]. Their findings suggested a possible connection between BMI and luminal B cancer, much like the findings regarding race [79]. Breast cancer risk is increased by having an elevated BMI (obesity). A favourable environment

for the onset or spread of cancer may result from metabolic changes brought on by an excess of fat in the adipose tissue of the breast. Compared to women with breast cancer who are not fat, obese women with breast cancer have lower survival rates [79]. The results of this study reveal unequivocally that race and obesity may have a significant role in the development of more aggressive breast carcinomas (Luminal B), besides the presence of biological variations between various subtypes of breast cancer [79].

Warner's study was investigated in four randomised clinical trials carried out in the United States and involving 1797 patients to determine whether race, Hispanic ethnicity and/or BMI were related to in-breast pathologic full response to neoadjuvant chemo-therapy and HER2-targeted therapy in patients with HER2+ malignancies. They found no variations in pCR (pathologic complete response) rates when stratified by tumour subtype or overall, by race or ethnicity [80]. However, they did notice tendencies linking rising BMI with lower pCR rates in ER+/HER2+ patients and greater pCR rates in ER+/HER2+ patients, suggesting that there may not be any general differences according to BMI. In their study, pCR rates were comparable in women of both races – black and white, Hispanic and non-Hispanic. Overall, they concluded that there were no differences in breast pCR by race or Hispanic ethnicity and that BMI had little to no effect on the overall pCR rate. These results imply that the biology of the tumour, not the patient, determines how much pCR may be achieved with optimally dosed NST (neoadjuvant systemic therapy) [80].

Between January 2009 and September 2013, Nagrani *et al*. conducted case-control research at TMH that was hospital-based. During the study period, a total of 1659 premenopausal and 1478 postmenopausal women were included. High central obesity (as defined by WHR) was the most significant risk factor, conferring a roughly threefold greater risk of breast cancer, according to the current study on obesity and breast cancer in South Asian women [81]. Even after adjusting for BMI, premenopausal and postmenopausal women still had an increased risk of breast cancer with central obesity. The link between obesity and breast cancer is complicated, and depending on the specific measure of obesity, different ethnic populations exhibit varying patterns of risk. These variations may result from variations in body fatness (in terms of central obesity). Both premenopausal and postmenopausal women showed an increased risk of breast cancer when their WC was higher. After correcting for BMI, their findings demonstrate higher WHR-related risk among both premenopausal and postmenopausal women, which is consistent with the concept that central obesity is strongly associated with a strong breast cancer risk in South Asian women [81].

Wu VJ *et al*. conducted a study in the United States comprised of 1788 men with prostate cancer in total. In terms of weight, about 37.5% of the patients were overweight and about 32.9% were obese. Caucasians and African Americans made up 76% of the patients who were included in the study [82]. According to this study, ethnicity and obesity are significant variables that are connected to the clinical characteristics of prostate cancer patients with stage T3 or Gleason score $\geq$ 7. They discovered that Gleason scores were correlated with ethnicity, with more African American patients having Gleason scores $\geq$ 7. They also discovered that African American males have a threefold increased risk of prostate cancer and frequently present with a more aggressive disease. And the findings of the study showed that African Americans had somewhat more obese patients than Caucasians, although this difference was not statistically significant [82].

Gender

Investigations into gender disparities in cancer prevalence have been active. In the USA in 2014, obesity and being overweight were linked to 40% of all cancer diagnoses (55% of cancers in women and 24% of cancers in men). Endometrial, ovarian and postmenopausal female breast cancers made up 42% of newly diagnosed instances of cancers linked to being overweight or obese, suggesting that females have a greater overall prevalence of malignancies linked to being overweight or obese [83]. Notably, malignancies that affect both sexes have a higher prevalence in men [83]. Obese men appear to have a higher risk of acquiring biologically aggressive prostate cancer and being diagnosed with an advanced form of the illness [84]. At the time of diagnosis, women who are obese and have breast cancer are more likely to die than patients who are of normal weight [85]. Gastrointestinal cancers are obesity-related cancers that affect both genders. Obesity is associated with a striking 30 - 70% increased risk of colon cancer in men [86], although the association is less clear in women [87]. Along with lung and breast cancer, colorectal cancer is the third most frequent cancer in the world and one of the leading causes of cancer mortality in women [88]. A clinical trial has been done to show the correlation between obesity and breast cancer in women. The findings showed that, compared to women with stable weight, women who gained more than 5% of their initial weight during follow-up had a little higher risk [24]. Women with a BMI greater than 35.0 showed the highest connections; these women had a 58% higher chance of developing invasive breast cancer than those with a BMI less than 25.0. They discovered that post-menopausal women who are overweight or obese are substantially more likely to develop invasive breast cancer, especially estrogen receptor-positive tumours. Women with a body mass index higher than 35.0

are in the greatest danger; their risk is 1.58 times larger than that of normal-weight women [24].

The correlation between BMI and survival was not constant among cancer types or stages in an examination of 22 clinical trials encompassing 14 different disease and treatment combinations [89]. At a cut-point of 25 kg/m^2, there was no statistically significant evidence linking BMI to overall survival. However, there was solid proof that there were gender-specific differences in the association between BMI and cancer survival. In general, elevated BMI was not linked to either better or worse overall survival in women, whereas it was linked to better overall survival in men. When early-stage cancers were omitted, gender-related cancers were excluded, and treatment regimens were limited to doses based on BSA, this connection remained. The findings were true when analyses were limited to people who survived for at least a year after trial participation and when a BMI cut-point of 30 kg/m^2 was looked at. They discovered that, when the association between BMI and overall survival was broken down by gender, baseline BMI had a different association with survival for male and female patients. Elevated BMI was found to be neither harmful nor beneficial for overall survival in females, whereas it tended to be protective for overall survival in males. After potential confounding variables such as gender-related cancers, medications not dosed on BSA, and early-stage cancers that might have had a better prognosis were eliminated from the analysis, the conclusion remained valid. The biology of the disease may differ across the sexes, or chemotherapy dose, distribution, or tolerance may be connected to gender differences [89].

Lifetime obesity

In the Arnold study, they looked at the effects of adult overweight and obesity on the likelihood of developing cancer. It was reported that 73913 women from the United States were included in the analyses, with a mean follow-up of 12.6 years [20]. Additionally, they noted that postmenopausal hormone treatment significantly reduced or even eliminated the chances of postmenopausal breast and endometrial cancer linked to the length of overweight and obesity. The outcomes of this study demonstrated that being overweight and obese increases the chance of developing cancer over time and that the longer a patient is overweight and obese as an adult, the higher their risk of developing a number of malignancies [20].

A cohort study was conducted in Europe and the United States, and throughout the follow-up period, 16520 incidences of cancer linked to obesity were diagnosed [90]. They claim that having been overweight for a longer period of time increases the chance of developing cancer in older people in both Europe and the US, with 8.4% of obesity-related malignancies occurring at any point after the age of 50. Thus, very cautiously, it is possible to infer that being overweight for a long time increases the risk of developing cancer. These findings give existing therapeutic guidelines for weight loss in obese people and maintaining a healthy weight in non-obese people, regardless of age, more support. Therefore, the incidence of obesity-related cancer was substantially correlated with a longer period of overweight [90].

Does weight loss modulate cancer risk?

A study carried out by Emaus *et al.* included 205723 women from nine different European nations [91]. The study examined the link between weight change in middle adulthood and the risk of breast cancer and found no conclusive link. However, losing weight in middle age does not reduce the risk of developing breast cancer. But lean mass loss may occur when someone loses weight, especially if they are elderly. Aside from that, underlying medical issues may also be the reason for weight loss. The underlying link may have been obscured by the diversity of reasons for weight loss. Intentional weight loss, established as a breast cancer risk factor, significantly lowers endogenous sex hormone and insulin levels while raising sex hormone-binding globulin levels, according to several intervention trials [91].

The Luo study found that purposeful weight loss was linked to a reduced overall risk of malignancies connected to obesity among the 58667 postmenopausal women who participated in the study [92]. There was a linear relationship between weight change, or WC change and total risk. Of all the tumours, purposeful weight loss showed the greatest risk reduction for endometrial cancer. Additionally, they noted a lower risk of colorectal cancer related to WC reduction and a lower risk of breast cancer associated with weight loss regardless of purpose [92].

The Swedish Obesity Subjects (SOS) study, which included 2010 obese patients who underwent surgical bariatric procedures and 2037 identically obese controls, discovered that after 10.9 years of follow-up, women had lost an average of 31.9% of their body weight and men had lost 19.3% [93]. Men essentially saw no change, but women had a 42% decrease in overall cancer incidence. There was no correlation between this relationship and any specific type of cancer in women [93].

Obesity Paradox in Cancer

In terms of prevalence and as a risk factor for a number of chronic illnesses, such as diabetes, cardiovascular disease and several cancers, overweight and obesity represent a growing global health problem [94]. Obesity is defined by the World Health Organisation as a body mass index (BMI) greater than or equal to 30 kg/m^2 [94]. Recent research has revealed that obese cancer patients do better than those with low, normal BMIs (or those who have lost weight). These

findings, known as the “obesity paradox”, imply that fat has a protective impact [95].

The incidence of cancer may be influenced by BMI, according to the World Cancer Research Fund (WCRF) and the International Agency for Research on Cancer (IARC). [6] In this regard, a high BMI is linked to an increased risk of a number of cancers, such as breast cancer, especially hormone receptor-positive illness in post-menopausal women, endometrial, ovarian, advanced prostate, renal and gastrointestinal cancers. On the other hand, the presence of obesity appears to be a paradoxical protective factor in other cancer types [94].

According to the findings of Attaran's study, an obesity survival paradox occurred between high BMI and lung cancer patients undergoing resection [96]. The study concentrated on the survival following surgical resection of lung cancer in people with a high BMI. It was found that obesity has a protective impact after the surgery (lung resection) and positively affects the survival rate of the patients [96]. These results may be due to the good nutritional status of the patients, which made them tolerate the postoperative treatment, or they could be associated with the specific hormones released by the adipose tissue [96].

Conclusions

Multiple studies have linked obesity to an increased risk of several types of cancer, including oesophageal adenocarcinoma, gastric cardia cancer, colorectal cancer, pancreatic cancer, gallbladder cancer, liver cancer, renal cell carcinoma, thyroid cancer, multiple myeloma, meningioma, endometrial cancer, post-menopausal breast cancer and ovarian cancer. The exact mechanisms by which obesity contributes to the development of cancer are still not fully understood, but there are several theories. One of the most commonly cited mechanisms is chronic inflammation, insulin resistance, adipokines and changes in sex hormone levels caused by excess body fat. In order to reduce the risk of obesity-related cancer, a multi-disciplinary approach is necessary. This includes interventions at the individual level, such as adopting a healthy lifestyle, including a healthy diet and regular physical activity, and interventions at the population level, such as improving access to healthy food options and physical activity opportunities. Overall, addressing the obesity epidemic will be a critical component of efforts to reduce the burden of cancer in the coming years. By promoting healthy behaviours and reducing the number of individuals who are overweight or obese, it may be possible to reduce the incidence of cancer and improve the health of populations around the world. Despite the strong evidence linking obesity and cancer, there is still much that is not understood about the relationship between the two, and there are many questions that remain to be answered. Future research directions in this area should focus on identifying the specific mechanisms by which obesity contributes to the development of cancer and developing new treatments to prevent or slow the progression of obesity-related cancers.

Conflict of interest

The authors declare no conflict of interest.

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