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Obesity and Cancer
A Translational Science Review

Sherry Shen, MD; Kristy A. Brown, PhD; Angela K. Green, MD; Neil M. Iyengar, MD

IMPORTANCE Obesity is associated with increased risk of cancer, including endometrial, esophageal, gastric, kidney, colorectal, liver, gallbladder, pancreas, prostate, postmenopausal breast, ovarian, and thyroid cancers. Overweight and obesity account for approximately 10% of new cancer diagnoses annually in the US and up to 50% of certain cancers such as endometrial and hepatobiliary cancer.

OBSERVATIONS Overweight is defined as body mass index (BMI) of 25 to 29.9 and obesity as BMI of 30 or greater. Obesity and overweight are characterized by excess accumulation of adipose tissue, which disrupts its primary function of energy storage. Excess energy, in the form of free fatty acids, is transferred to developing cancer cells and stimulates cancer development through genomic instability caused by oxidative stress and DNA damage. Other defining features of adipose tissue dysfunction include inflammation and altered hormone production such as increased estrogens and leptin and decreased adiponectin. Inflamed adipose tissue is associated with systemic elevations in inflammatory mediators, such as prostaglandin E_2, the cytokines interleukin 1β and interleukin 6, and tumor necrosis factor α. These mediators promote tumor growth directly or indirectly by stimulating estrogen biosynthesis, which can promote proliferation of hormone-sensitive cancers such as breast, ovarian, and endometrial cancer, or by suppressing immune-mediated elimination of developing cancer cells through accumulation of myeloid-derived suppressor cells and reductions in the amount and function of cytotoxic T cells and natural killer cells. Inflammation and oxidative stress are also stimulated by obesity-associated depletion of gut commensal bacteria species (eg, *Akkermansia muciniphila*) and overgrowth of bacterial populations associated with cancer development in preclinical models (eg, *Bilophila*). In observational studies, patients who lost more than 10% of body weight through bariatric procedures (n = 30 318) or with glucagon-like peptide 1 receptor agonists (n = 1 651 452) had modest reductions in obesity-associated cancer incidence (absolute change, −0.02% to −0.5%).

CONCLUSIONS AND RELEVANCE Overweight and obesity are associated with higher rates of cancer and account for 10% of new cancer diagnoses annually in the US. Weight loss may reduce cancer risk by attenuating adverse effects of obesity, but greater than 10% weight loss may be necessary to reduce cancer risk.

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Author Affiliations: Memorial Sloan Kettering Cancer Center, New York, New York (Shen, Green); University of Kansas Medical Center, Kansas City (Brown); Weill Cornell Medicine, New York, New York (Green); Winship Cancer Institute at Emory University, Atlanta, Georgia (Iyengar).

Corresponding Author: Neil M. Iyengar, MD, Winship Cancer Institute at Emory University, 1365 Clifton Rd NE, Atlanta, GA 30322 (nmiyeng@emory.edu).

Overweight, defined as body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 25 to 29.9, and obesity, defined as BMI of 30 or greater, are associated with approximately 10% of new cancer diagnoses annually in the US and up to 50% of specific cancer types such as endometrial and hepatobiliary cancers.[1-3] By the year 2030, approximately 49% of adults in the US are expected to have obesity, compared with 42% in 2020 and 35% in 2010.[2,4] Worldwide, more than 4 billion people, accounting for 51% of the global population, are expected to be overweight or obese by the year 2035.[5] Cancer incidence rates are also increasing worldwide; by 2050, it is anticipated that more than 35 million new cancers will be diagnosed each year.[6] Obesity-related cancers, such as breast and colorectal cancers, are increasing at faster rates than other cancers among young adults aged 25 to 49 years.[1,7-12] This Review summarizes current evidence about the primary biologic pathways by which obesity may promote development of cancer. Interventions that may reduce obesity-associated cancer risk are also reviewed.

Associations of Excess Body Weight With Cancer Risk

Currently, 12 cancers are classified as obesity-related cancers by the International Agency for Research on Cancer, including colorectal, endometrial, postmenopausal breast, gallbladder, kidney, liver, esophagus, ovarian, pancreas, gastric, multiple myeloma, and thyroid cancers.[13] Obesity and metabolic syndrome were recently

associated with additional cancers, such as prostate cancer, melanoma, and hematologic malignancies (**Table 1**). Body weight and metabolic syndrome are each independently associated with higher rates of obesity-related cancers, with highest risk observed in patients with the metabolically unhealthy overweight/obese phenotype, which is defined as having a BMI greater than 25 and at least 1 component of metabolic syndrome: hypertension, dyslipidemia, or insulin resistance.[17] In a meta-analysis that included 15 cohorts of more than 5 million people, the metabolically unhealthy overweight/obese phenotype was associated with increased risk of any cancer (1264 cases/15 022 participants; summary relative risk [RR], 1.21; 95% CI, 1.02-1.44) and increased risk of 10 individual cancer types. Individuals with overweight and obesity without metabolic syndrome had increased overall risk of obesity-related cancer compared with individuals with normal weight without metabolic syndrome (40 252 cases/1.19 million individuals [absolute rates by group not provided]; summary RR, 1.17; 95% CI, 1.09-1.26).[17] Although obesity has been associated with higher risk of breast cancer in postmenopausal females, obesity is associated with a lower rate of breast cancer in premenopausal females. In the UK Million Women Study, which included 1 222 630 females aged 50 to 64 years with 45 037 total incident cancers diagnosed over 5.4 years, each 10-unit increase in BMI was associated with an RR of postmenopausal breast cancer of 1.40 (95% CI, 1.31-1.49; 5629 total cases; absolute rates per 10-unit increase in BMI not provided). A modestly lower risk of breast cancer was observed per 10-unit increase in BMI among premenopausal females (RR, 0.86; 95% CI, 0.73-1.00; 1179 total cases; absolute rates per 10-unit increase in BMI not provided), and there was a significant difference in trend estimates between premenopausal and postmenopausal females regarding the association of BMI with breast cancer incidence ($P < .001$).[18] The lower risk of breast cancer in premenopausal females with obesity may be related to an increased frequency of anovulatory menstrual cycles, which reduces cumulative breast tissue exposure to the luteal phase, defined as the phase of the menstrual cycle when both estrogen and progesterone levels are high and breast epithelial cell proliferation accelerates.[19,20] Lifetime risk of obesity-associated cancer is influenced by excess body weight in childhood and early adolescence. In a Danish cohort study of 301 927 people, weight change between ages 6 and 15 years was used to generate models of BMI change based on height and weight developmental patterns. Five BMI change categories were modeled: BMI increase below the mean between ages 6 and 15 years, BMI increase comparable with the mean between ages 6 and 15 years, BMI increase above the mean between ages 6 and 15 years, overweight between ages 6 and 15 years, and obesity between ages 6 and 15 years, defined in relation to BMI percentiles 10th, 25th, 50th, 85th, and 95th by age, respectively. Childhood BMI changes over time that were more likely to lead to overweight- and obese-range BMIs were associated with higher rates of obesity-related cancers after age 30 years among females (5.1% for overweight females and 5.0% for obese females, compared with 4.4% for below-mean and 4.9% for mean BMI changes that did not lead to overweight/obesity, over 40 years of follow-up).[21] Among 64 675 males who were followed up from age 7 years to early adulthood (age 17-26 years) in the Danish cohort, only males with overweight-range BMI at both age 17 years and age 26 years had higher rates of adult colon cancer compared with males who were never overweight (23/896 [2.6%]) vs 637/56 525 [1.1%]; hazard ratio [HR], 2.73; 95% CI, 1.80-4.15). Males who were overweight at 1 time point only did not have higher rates of colon cancer in adulthood compared with males who were not overweight or obese at ages 17 or 26 years.[22]

Adipose tissue accumulates due to a combination of factors, including excess caloric intake, diets with low nutrient density (eg, high intake of simple carbohydrates such as monosaccharides), lack of physical activity, and genetic predisposition. Many cancers associated with obesity, such as breast, prostate, and melanoma, occur in tissues that are in close proximity to adipose tissue, suggesting that excess adiposity is a cancer risk factor independent of BMI.[23] For example, a secondary analysis of the Women's Health Initiative prospective observational study that included 3460 menopausal participants with normal BMI (18.5-24.9) and no cancer at the time of enrollment reported that those in the highest quartile of whole-body fat and trunk fat had higher risk of developing breast cancer compared with the lowest quartile (57 cases per 12 816.8 person-years vs 31 cases per 12 384.9 person-years [$P = .004$ for trend] for whole-body fat; 50 cases per 12 325.9 persons-years vs 30 cases per 12 720.9 person-years [$P = .002$ for trend] for truncal fat), and these females had higher circulating levels of insulin, C-reactive protein, interleukin 6 (IL-6), leptin, and triglycerides.[24]

Obesity and Tumorigenesis: Mechanisms and Therapeutic Targets

Cancers have 10 acquired properties, including sustained proliferation, unlimited cell division, resisting cell death, evading growth suppressors, angiogenesis, activating invasion and metastasis, modified energy metabolism to support cellular proliferation, evading immune destruction, genomic instability, and inflammation.[25] Understanding how obesity affects these properties to promote cancer growth may help identify novel therapies to lower cancer risk (**Box**, **Figure**, and **Table 2**).

Adipose Tissue Dysfunction

White and brown adipose tissue are the 2 types of adipose tissue in mammals. White adipose tissue is primarily located in subcutaneous and visceral fat and, to a lesser extent, in bone marrow, and it represents the largest endocrine organ in the human body. The primary role of white adipose tissue is storage and release of energy as lipids and free fatty acids. An additional function is secretion of hormones including adiponectin, leptin, and estrogens. Obesity is associated with decreased levels of adiponectin, which has insulin-sensitizing and anti-inflammatory effects that are antitumorigenic in preclinical models.[35] After menopause, white adipose tissue is the main site of estrogen biosynthesis. With obesity, estrogen production in adipose stromal cells is increased due to elevated expression of aromatase. In people with obesity, adipocytes undergo hypertrophy and hyperplasia, leading to adipocyte cell death and an inflammatory microenvironment characterized by high serum concentrations of leptin and proinflammatory cytokines IL-1β, IL-6, and tumor necrosis factor α (TNF-α).[36,37] White adipose tissue inflammation can be detected by histologic examination of human tissue using light microscopy based on presence of crown-like structures, which are composed of CD68-positive macrophages that encircle dead or dying adipocytes.[38] Consistent with preclinical studies in

Table 1. Magnitude of Association of Increased BMI on Cancer Risk by Type and Association of Bariatric Surgery and GLP-1 Receptor Agonist Use With Cancer Risk by Type[14-16]

	Incidence and magnitude of association for each 5-unit increase in BMI[16,b]				Association of cancer incidence with bariatric surgery[14,c]		Association of cancer incidence with use of GLP-1 receptor agonist vs insulin[15,d]	
	In males		In females					
Cancer type[a]	Cases/total, No.	Risk ratio (95% CI)	Cases/total, No.	Risk ratio (95% CI)	Cases/total, No.	Difference in event rate (95% CI) per 1000 person-years	Cases/total, No.	Hazard ratio (95% CI)
Postmenopausal breast	NA	NA	23 909/2 559 829	1.12 (1.08-1.16)	21/5053 vs 182/25 265	0.42 (0.10 to 0.74)	13 768/1 651 452 (GLP-1: 427/48 983; insulin: 379/1 044 745)	1.07 (0.93-1.23)
Prostate	70 421/3 029 338	1.03 (1.00-1.07)	NA	NA	12/5053 vs 74/25 265	0.06 (−0.17 to 0.29)		
Colon	22 440/4 833 139	1.24 (1.20-1.28)	20 975/4 833 139	1.09 (1.05-1.13)	13/5053 vs 69/25 265	0.0 (−0.24 to 0.24)	48 443/1 651 452 (GLP-1: 223/48 983; insulin: 391/1 044 745)	0.54 (0.46-0.64)
Melanoma	3492/3 966 859	1.17 (1.05-1.30)	3664/3 966 859	0.96 (0.92-1.01)	14/5053 vs 32/25 265	−0.24 (−0.49 to −0.01)		
Kidney	6073/5 473 638	1.24 (1.15-1.34)	4614/5 473 638	1.34 (1.25-1.43)	10/5053 vs 75/25 265	0.13 (−0.09 to 0.35)	48 322/1 651 452 (GLP-1: 223/48 983; insulin: 284/1 044 745)	0.76 (0.64-0.91)
Non-Hodgkin lymphoma	7041/5 043 747	1.06 (1.03-1.09)	6248/5 043 747	1.07 (1.00-1.14)	In hematologic cancers: 33/5053 vs 113/25 265	−0.36 (−0.73 to 0.01)		
Endometrial	NA	NA	17 084/3 044 538	1.59 (1.50-1.68)	16/5053 vs 215/25 265	0.77 (0.48 to 1.06)	25 750/1 651 452 (GLP-1: 169/48 983; insulin: 210/1 044 745)	0.74 (0.60-0.91)
Pancreatic	2390/3 338 001	1.07 (0.93-1.23)	2053/3 338 001	1.12 (1.02-1.22)	4/5053 vs 30/25 265	0.06 (−0.08 to 0.20)	48 490/1 651 452 (GLP-1: 123/48 983; insulin: 290/1 044 745)	0.41 (0.33-0.50)
Leukemia	3371/4 757 649	1.08 (1.01-1.14)	5317/4 757 649	1.17 (1.04-1.32)	In hematologic cancers: 33/5053 vs 113/25 265	−0.36 (−0.73 to 0.01)		
Rectal	14 894/4 833 139	1.09 (1.06-1.12)	9052/4 833 139	1.02 (1.00-1.05)	3/5053 vs 18/25 265	0.02 (−0.09 to 0.13)	48 443/1 651 452 (GLP-1: 223/48 983; insulin: 391/1 044 745)	0.54 (0.46-0.64)
Thyroid	1212/3 303 073	1.33 (1.04-1.70)	2375/3 303 073	1.14 (1.06-1.23)	21/5053 vs 110/25 265	−0.01 (−0.31 to 0.29)	48 527/1 651 452 (GLP-1: 154/48 983; insulin: 149/1 044 745)	0.99 (0.79-1.24)
Liver	2039/3 319 024	1.24 (0.95-1.62)	31/3 319 024	1.07 (0.55-2.08)	3/5053 vs 26/25 265	0.06 (−0.06 to 0.18)	48 397/1 651 452 (GLP-1: 79/48 983; insulin: 167/1 044 745)	0.47 (0.36-0.61)
Multiple myeloma	4273/5 171 374	1.11 (1.05-1.18)	3664/5 171 374	1.11 (1.07-1.15)	5/5053 vs 22/25 265	−0.02 (−0.16 to 0.12)	48 527/1 651 452 (GLP-1: 80/48 983; insulin: 131/1 044 745)	0.49 (0.44-0.77)
Gastric	817/4 673 213	0.97 (0.88-1.06)	325/4 673 213	1.04 (0.90-1.20)	0/5053 vs 7/25 265	NA	48 449/1 651 452 (GLP-1: 56/48 983; insulin: 75/1 044 745)	0.73 (0.51-1.03)
Esophageal adenocarcinoma	1315/4 673 213	1.52 (1.33-1.74)	735/4 673 213	1.51 (1.31-1.74)	2/5053 vs 5/25 265	−0.03 (−0.12 to 0.06)	48 437/1 651 452 (GLP-1: 49/48 983; insulin: 77/1 044 745)	0.60 (0.42-0.86)
Ovarian	NA	NA	12 208/2 703 734	1.03 (0.99-1.08)	1/5053 vs 33/25 265	0.16 (0.07 to 0.25)	25 739/1 651 452 (GLP-1: 51/48 983; insulin: 94/1 044 745)	0.52 (0.37-0.74)
Gallbladder	928/3 319 024	1.09 (0.99-1.21)	1111/3 319 024	1.59 (1.02-2.47)	0/5053 vs 5/25 265	NA	48 587/1 651 452 (GLP-1: <10/48 983; insulin: 19/1 044 745)	0.35 (0.15-0.83)

Abbreviations: BMI, body mass index; GLP-1, glucagon-like peptide 1; NA, not applicable.

[a] Ordered by most prevalent (top) to least prevalent (bottom) in the US.

[b] Mean duration of follow-up per cancer site ranged from 8.4 years to 14.4 years for included studies.

[c] Compared with a matched nonsurgical control group. Median follow-up, 6.1 years.

[d] Over a 15-year follow-up period.

Box. Commonly Asked Questions

Which cancers are more common in people with obesity?
Obesity is associated with a higher incidence of the following types of cancer: endometrial, esophageal, gastric, kidney, colorectal, liver, gallbladder, pancreas, prostate, postmenopausal breast, ovarian, thyroid, and multiple myeloma.

Which biologic pathways may explain the association of obesity with cancer?
Compared with the absence of obesity, obesity is associated with increased inflammation, accumulation of immunosuppressive myeloid-derived suppressor cells and reduced efficacy of T and natural killer cells. These biologic changes may promote tumor development. In the presence of excess adipose tissue, energy storage and production support energy demands of proliferating cancer cells. Other pathways that are more common in people with obesity and associated with tumor development include genomic instability, which is the increased likelihood of DNA damage (eg, double-strand breaks) and accumulation of DNA genetic variants due to impaired DNA repair and increased oxidative stress, and alterations in gut microbiome composition that increase inflammation and oxidative stress.

Can interventions reduce obesity-associated cancers?
In longitudinal and retrospective studies, more than 10% weight loss, such as from bariatric surgery or glucagon-like peptide 1 receptor agonists such as semaglutide and tirzepatide, is associated with reduced cancer risk. However, randomized clinical trials are needed to validate these observations.

animal models and human tissues, white adipose tissue inflammation and elevated levels of estrogen-producing aromatase are associated with an increased risk of invasive breast cancer and breast cancer recurrence.[36,39] Among 86 patients with benign breast disease who developed breast cancer, 10.5% had breast adipose inflammation, characterized as more than 5 crown-like structures per tissue sample, vs 4.7% of 86 patients with benign breast disease who did not develop breast cancer (odds ratio, 6.8; 95% CI, 1.4-32.4; $P = .02$).[39] The importance of aromatase in adipose tissue is underscored by the effectiveness of aromatase inhibitors such as letrozole and anastrozole for treatment of breast cancer, although it is unknown whether aromatase inhibitors reduce adipose tissue inflammation.

Lifestyle interventions are associated with reductions in adipose tissue inflammation. In a systematic review that included 19 clinical trials of 802 patients randomized to aerobic and/or resistance exercise training, dietary modification with or without caloric restriction, or a combination of these interventions, weight loss was associated with reductions in TNF-α, IL-6, and leptin gene expression in subcutaneous abdominal adipose tissue.[40] However, the effects of these behavior changes on obesity-associated cancer risk is unknown.

Obesity and the Immune System

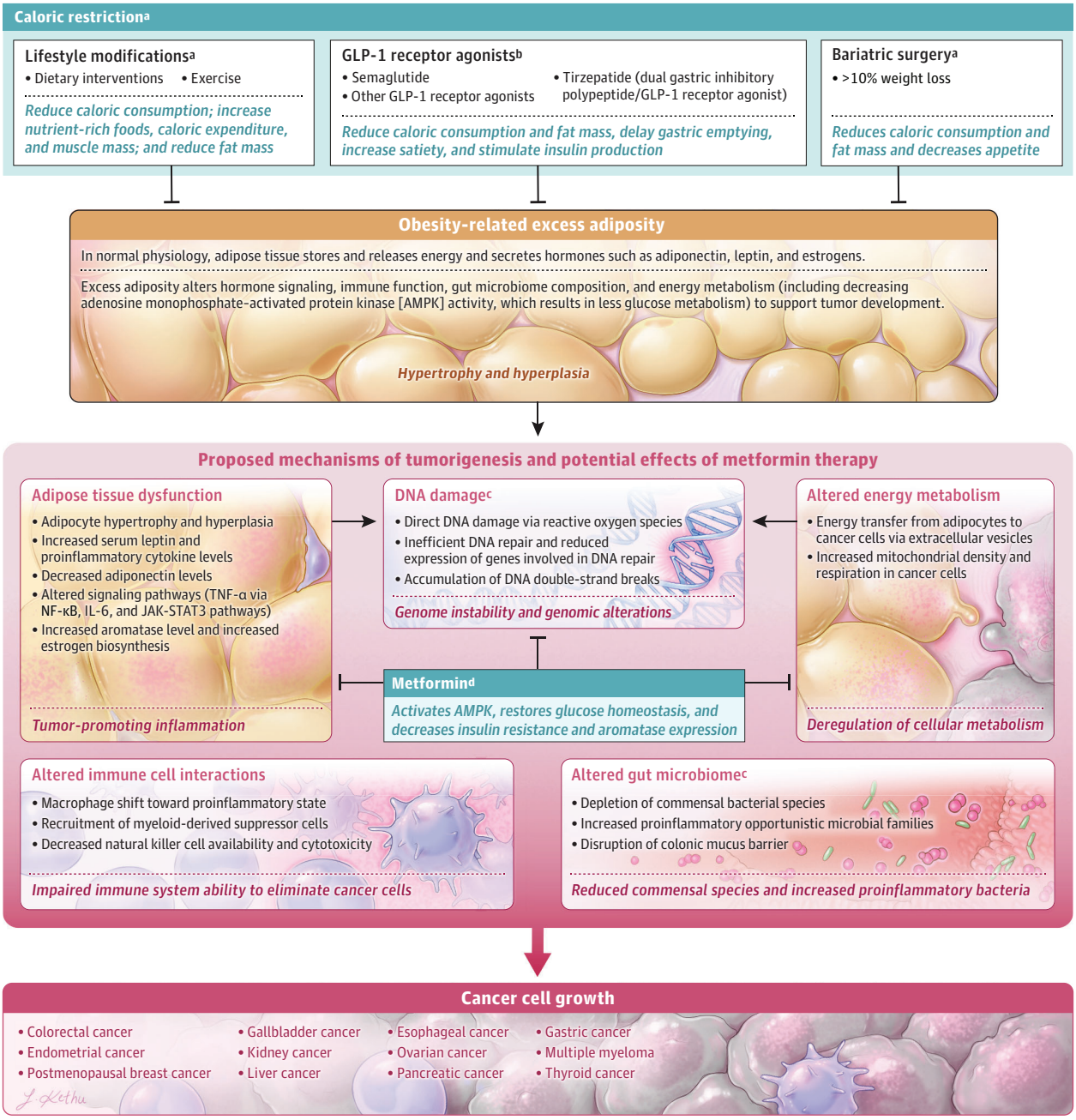
Obesity impairs the ability of the immune system to recognize and eliminate tumor cells by altering the recruitment and function of immune cells such as macrophages, natural killer cells, and myeloid-derived suppressor cells. In the absence of cancer, obesity is associated with a shift of macrophage function toward a proinflammatory state.[41] Conversely, in the setting of neoplasms, in preclinical models, adipocytes derived from patients with obesity shift macrophage function to promote tissue repair/growth, characterized by the production of immunosuppressive factors, such as transforming growth factor β and IL-10.[42-45] In preclinical studies, estrogens and adipose-derived inflammatory mediators, such as leptin and TNF-α, can decrease the ability of the immune system to detect and eliminate abnormal cells by stimulating production of immunosuppressive factors from macrophages, including IL-10 and TNF-α.[46-48] Lipid accumulation and increased lipid uptake by myeloid-derived suppressor cells from diets high in saturated fat enhance immunosuppressive effects, which are characterized in both preclinical models and humans by reduced cluster of differentiation (cell surface markers) 3 ($CD3^+$), $CD4^+$, and $CD8^+$ T cells.[49,50] Increased uptake of lipids by developing cancer cells deprive nearby T cells of essential metabolites including fatty acids. Elevated levels of leptin activate fatty acid oxidation in $CD8^+$ T cells, reducing T-cell cytotoxic function in mouse models of obesity-associated breast and colon cancer.[51,52] Obesity and high fat feeding in mouse models of cancer induce natural killer cell dysfunction, which lowers cytotoxicity, activates macrophages to a proinflammatory state, promotes adipose tissue inflammation, and increases insulin resistance.[53-58] Lower abundance and cytotoxicity of T cells and natural killer cells impair detection and elimination of developing cancer cells by the immune system.

Energy Metabolism

Abundant enlarged adipocytes provide energy for cancer cells, promoting their survival and ability to metastasize.[59-61] Free fatty acids and proteins required for fatty acid oxidation, mitochondrial respiration, and adenosine triphosphate production can be transferred from adipocytes to developing or established tumor cells via extracellular vesicles, which are nanometer-sized particles released from cells that can deliver nucleic acids, metabolites, and proteins to other cells.[60,62,63] Exposure of breast cancer cells in vitro to extracellular vesicles derived from breast adipose tissue of females with overweight or obesity leads to significantly increased tumor cell division and enhanced cell migration. These changes are mediated by greater mitochondrial density, increased mitochondrial adenosine triphosphate production, and significantly higher maximal respiratory capacity in tumor cells, facilitated by transfer of proteins and micro-RNA from vesicles.[64-66] In some cancers, such as prostate and colon, impaired mitochondrial activity within the cancer cell increases lactate production, consistent with a switch toward aerobic glycolysis in tumor cells.[59,67,68] In contrast, obesity was associated with increased β oxidation of fatty acids in a mouse model of triple-negative breast cancer, providing an alternative to glycolysis as a source of energy to cancer cells.[69] Adenosine monophosphate–activated protein kinase (AMPK) is an enzyme that senses energy availability and activates processes that increase glucose uptake and metabolism of fatty acids in settings of low energy availability.[70] People with obesity and insulin resistance have less AMPK activity in adipose tissue, resulting in greater energy availability for cancer cells.[71,72] Thus, energy production and energy use within cancer cells and their surrounding environment may adapt to the available energy supply, permitting cancer cells to use excess energy stores in people with obesity.

Figure. Illustration of How Adiposity Promotes Biologic Pathways Leading to Cancer

Obesity, biologic associations with cancer, and therapeutic interventions



Obesity promotes adipose tissue dysfunction, DNA damage, altered energy metabolism, altered immune cell interactions, and gut microbiome changes. Various interventions have been studied in decreasing excess adiposity and potentially improving cancer risk. GLP-1 indicates glucagon-like peptide 1; IL-6, interleukin 6; JAK, Janus kinase; NF-κB, nuclear factor κB; STAT3, signal transducer and activator of transcription 3; and TNF-α, tumor necrosis factor α.

[a]Studies include preclinical murine data, observational human data, and clinical trial data.

[b]Studies of GLP-1 receptor agonists include observational human data and clinical trial data.

[c]Research is ongoing and further investigation is needed.

[d]Studies of metformin's benefits against altered energy metabolism include preclinical murine data and observational human data, and studies of metformin's benefits against adipose tissue dysfunction include preclinical murine data, observational human data, and clinical trial data.

DNA Damage and Repair

Obesity is associated with impairments in DNA repair. In animal models, obesity-induced reactive oxygen species generation can cause direct oxidative DNA damage or may indirectly damage epithelium via by-products of dysregulated lipid and microbiome-mediated metabolism.[73] Obesity is associated with inefficient DNA repair

Table 2. Potential Therapies That May Mitigate the Association of Obesity With Cancer[a]

	GLP-1 receptor agonists	Metformin	Antioxidants	Probiotics
Mechanisms	• Delays gastric emptying and increases satiety • Increases insulin secretion	• Inhibits glucose production from the liver by activating AMPK, restoring glucose homeostasis • Restores AMPK function in adipose tissue, reducing lipid storage • Decreases obesity-related insulin resistance • Decreases aromatase expression and fibrosis in white adipose tissue[26,27]	• Vitamin E, beta carotene, selenium • Neutralizes reactive oxygen species and may reduce obesity-associated oxidative stress and DNA damage	• Alters gut microbial composition by promoting commensal species • May reduce obesity-associated breakage of the colonic mucus layer and thereby reduce associated inflammation
Evidence in humans	• Induces 10% to 15% weight reduction and adipose tissue reduction • GLP-1 receptor agonist use in patients with type 2 diabetes was associated with lower risk of 10 obesity-associated cancers in a retrospective cohort study[15]	• Associated with 2-kg to 3-kg weight loss[28] • Associated with lower overall cancer incidence in a meta-analysis[29] • 7 Prospective cohorts (n = 646 972; RR, 0.65; 95% CI, 0.37-0.93) • 8 Case-control studies (n = 61 688; RR, 0.55; 95% CI, 0.30-0.80) • Studies limited by publication bias and heterogeneity	• Several studies showed no effect or an increase in incident prostate cancer with daily vitamin E supplementation[30-33] • Multivitamin containing ascorbic acid, vitamin E, beta carotene, selenium, and zinc was associated with decreased total cancer incidence compared with placebo (3.5% vs 4.9%; RR, 0.69; 95% CI, 0.53-0.91)[32]	Associated with reduction in waist circumference (mean difference, −1.13 cm) and fat mass (mean difference, −0.71 kg) in a meta-analysis of 26 randomized clinical trials (n = 1720)[34]
Treatment challenges	• GLP-1 receptor agonist use is limited by gastrointestinal and other toxicity • Discontinuation of GLP-1 receptor agonists typically results in weight gain	• Need for management of metformin dosing, eg, dose escalation and titration, due to adverse effects such as diarrhea • It remains unclear whether other AMPK activators may be limited by similar toxicities, as most studies are limited to rodent models and early human studies	Antioxidant study results are limited by dosing and compound variability, making findings inconclusive and nongeneralizable to class effects of antioxidants	The optimal dose, duration, and vehicle of probiotic delivery for impact on cancer risk remains unclear

Abbreviations: AMPK, adenosine monophosphate–activated protein kinase; GLP-1, glucagon-like peptide 1; RR, relative risk.

[a] Columns are ordered left to right by strength of evidence.

mechanisms, which increase cancer risk through accumulation of aberrant and mutagenic DNA lesions, including double-strand breaks.[74-76]

In humans, preliminary evidence suggests DNA damage accumulation is associated with obesity in people with elevated cancer risk. In a study of healthy breast tissue samples from females with a germline genetic variant in *BRCA1* or *BRCA2*, higher BMI was associated with greater accumulation of DNA double-strand breaks in breast and fallopian tube epithelial cells compared with BMI in the healthy range.[75] The accumulation of DNA damage was reduced by ex vivo treatment of breast tissue explants with fulvestrant, an estrogen receptor degrader, or metformin (which has antioxidant properties). However, lowering oxidative stress with antioxidant supplementation such as vitamin E or selenium has not been reported to decrease cancer risk. For example, among 39 876 females with a mean BMI of 26.04 (SD, 5.06) randomized to receive vitamin E or placebo in the Women's Health Study, 600 IU of vitamin E did not reduce the incidence of total cancers (1437/19 937 [7.2%] vs 1428/19 939 [7.2%]; RR, 1.01; 95% CI, 0.94-1.08) at 10 years of mean follow-up.[30] The SELECT clinical trial randomized 35 533 males aged 50 years or older to receive selenium, vitamin E, both, or placebo; vitamin E was associated with increased risk of prostate cancer (10.9 vs 9.3 cases per 1000 person-years; HR, 1.17; 99% CI, 1.004-1.36) at a mean follow-up of 10.1 years (range, 8.2-10.9 years).[31] In contrast, a clinical trial that randomized 5141 males to receive either placebo or a daily capsule containing 120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 mg of selenium, and 20 mg of zinc reported that the daily vitamin capsule reduced total cancer incidence compared with placebo (3.5% vs 4.9%; RR, 0.69; 95% CI, 0.53-0.91) at a median follow-up of 7.5 years.[32] The difference in outcomes between these studies may be due to differences in vitamin E dosing or use of a single antioxidant vs combinations.

Gut Microbiome

Obesity-associated alterations of the colonic microbiome, such as reductions in commensal species (eg, *Akkermansia muciniphila*) and augmentation of opportunistic populations (eg, *Bilophila*), promote several biologic pathways that increase cancer risk, such as inflammation and oxidative stress.[77] In an animal study, mice that received fecal transplants from humans with obesity experienced reductions in commensal bacteria species such as *Bacteroides vulgatus* and *A muciniphila*, which are associated with tumor suppression.[78] In this study, disruption of the intestinal barrier, which is a selectively permeable layer, allowing for water and nutrient absorption while blocking entry of microbes and harmful substances from the intestinal lumen, led to increased colonic expression of proinflammatory cytokines and subsequent activation of oncogenic Wnt, mitogen-activated protein kinase, and phosphatidylinositol 3 kinase–AKT signaling.[78] In a mouse model of carcinogen-induced breast cancer, mice fed a high-fat diet had reduced fecal commensal *Akkermansia* and *Lactobacillus* populations and increased genotoxic proinflammatory microbial populations such as *Bilophila*. These mice had a greater abundance of proinflammatory macrophages in breast tissue and increased mammary tumor frequency compared with control diet–fed mice ($P < .05$).[79]

Compared with healthy-weight, cancer-free individuals, intestinal microbiota from patients with obesity and colorectal cancer have increased abundance of proinflammatory opportunistic microbial families such as Enterobacteriaceae and Streptococcaceae and fewer microbial populations that produce tumor-suppressive metabolites such as butyrate, an anti-inflammatory short-chain fatty

acid produced by bacterial fermentation of dietary fiber.[80-82] Gut microbial profiles in patients with obesity and colorectal cancer are associated with increased markers of intestinal permeability and higher circulating levels of proinflammatory bacterial metabolites and cytokine IL-1β.[80] Metagenomic functional analyses, a computational approach that can identify the biologic activity of a microbial community through differentially expressed genes, reported that the microbiota profile in obesity-related colorectal cancer is associated with upregulation of pathways involved in disruption of the colonic mucus bilayer. Disrupting this barrier exposes the colonic epithelium to bacteria that induce inflammation and oxidative stress, which generate tumor-promoting cytokines and genomic instability.[80,82] Varied microbial profiles among patients with colorectal cancer across BMI categories suggest that screening to detect obesity-associated colorectal cancer may be facilitated by testing stool samples for the presence or absence of microbial populations.[81,82] Associations of obesity with the microbiome also suggest that probiotic consumption may influence cancer risk, although clinical trial evidence has not been reported.[34]

Weight Loss and Mitigating Obesity-Associated Cancer Risk

Cancer risk may be decreased with weight loss through lifestyle modification, medications, or bariatric surgery.[14,83-85] In the Women's Health Initiative observational study of 58 667 postmenopausal females with a median follow-up of 12 years, intentional weight loss of at least 5% at 3 years from baseline was associated with a lower incidence of obesity-associated cancers compared with stable weight (433/4629 [9.35%] vs 4115/39 424 [10.4%]; HR, 0.88; 95% CI, 0.80-0.98). Intentional weight loss was associated with a lower risk of endometrial cancer compared with stable weight (33/4629 [0.71%] vs 389/39 424 [0.99%]; HR, 0.61; 95% CI, 0.42-0.88).[83] A secondary analysis of cancer risk in the Look AHEAD clinical trial included 4859 patients with overweight or obesity and type 2 diabetes who were randomized to a 1-year intensive lifestyle intervention consisting of reduced caloric intake and increased physical activity with the goal of at least 7% weight loss, followed by a 9-year period consisting of refresher counseling or attention control. Mean weight loss was 6.84 kg (6.5%) in the intervention group compared with 4.87 kg (4.6%) in the control group. Rates of obesity-related cancers did not differ significantly between groups after a median follow-up of 11 years (6.1 and 7.3 per 1000 person-years, respectively; HR, 0.84; 95% CI, 0.68-1.04), although the 4.6% weight reduction in the control group and cancer incidence in the entire cohort (684 cases [14%]) may have affected the ability to detect differences in obesity-related cancer incidence between groups.[85]

Weight-loss surgeries typically result in more than 20% weight reduction from baseline compared with lifestyle interventions, which induce approximately 4% to 6% weight reduction.[14,86,87] Therefore, bariatric surgery may be more effective to reduce cancer risk than lifestyle changes (Table 1).[14] In an observational study of 30 318 patients with a BMI of 35 or greater; those who underwent bariatric surgery were matched 1:5 to individuals who did not undergo bariatric surgery.[14] At 10 years, mean weight change was −27.5 kg in the bariatric surgery group and −2.7 kg in the control group (mean difference, 24.8 kg [19.2%]; 95% CI, 24.6-25.1 kg). At a median follow-up of 6.1 years, bariatric surgery was associated with a 32% reduction in the incidence of obesity-associated cancers (a rate of 3.0 vs 4.6 per 1000 person-years; cumulative incidence at 10 years, 2.9% vs 4.9%; HR, 0.68; 95% CI, 0.53-0.87). However, analysis by individual cancer type showed reduced risk only for endometrial cancer (a rate of 0.49 vs 1.26 per 1000 person-years; cumulative incidence at 10 years, 0.5% vs 1.3%; adjusted HR, 0.47; 95% CI, 0.27-0.83) but not for other cancers, including breast and colon cancers.

Pharmacologic approaches for weight management may also lower cancer risk. Metformin, a first-line treatment for type 2 diabetes, may lower cancer risk by reducing BMI, hyperglycemia, and hyperinsulinemia.[28] In a meta-analysis that included 166 studies, metformin was associated with lower overall cancer incidence in prospective observational studies (7 studies with 646 972 individuals; RR, 0.65; 95% CI, 0.37-0.93; I^2 = 98.0%; absolute rates not reported) and case-control studies (8 studies with 61 688 individuals; RR, 0.55; 95% CI, 0.30-0.80; I^2 = 98.5%; absolute rates not reported).[29] However, these observations were limited by publication bias (Egger P < .001), heterogeneity, and the observational study design, and results may be due to confounding. Selective sodium-glucose cotransporter 2 (SGLT-2) inhibitors (such as dapagliflozin or canagliflozin) are associated with weight loss of approximately 1.5 kg to 2 kg over 12 to 26 weeks. In a meta-analysis of 20 randomized clinical trials that included 48 895 participants with type 2 diabetes randomized to either an SGLT-2 inhibitor or placebo and at least 52 weeks of follow-up, SGLT-2 inhibitor use was associated with reduced risk of any cancer compared with placebo (1478/34 967 vs 997/14 018; risk ratio, 0.35; 95% CI, 0.33-0.37).[88]

Glucagon-like peptide 1 (GLP-1) receptor agonists such as semaglutide and dual gastric inhibitory polypeptide/GLP-1 receptor agonists such as tirzepatide have been approved by the US Food and Drug Administration for weight loss and diabetes treatment. These medications are associated with weight loss of approximately 10% to 15%.[89-92] In a retrospective cohort study including 1 651 452 US patients with type 2 diabetes identified from a nationwide multicenter electronic health record database, GLP-1 receptor agonist use, compared with insulin, was associated with a lower risk of 10 obesity-associated cancers, such as pancreatic cancer (123/48 490 [0.25%] vs 290/48 490 [0.60%]; HR, 0.41; 95% CI, 0.33-0.50), liver cancer (79/48 397 [0.16%] vs 167/48 397 [0.35%]; HR, 0.47; 95% CI, 0.36-0.61), and colorectal cancer (223/48 443 [0.46%] vs 391/48 443 [0.81%]; HR, 0.54; 95% CI, 0.46-0.64)[15] (Table 1). A cohort study with a target trial emulation design that matched 43 317 individuals taking GLP-1 receptor agonists with 43 315 not taking GLP-1 receptor agonists from a Florida state research database reported that the overall cancer incidence in those taking GLP-1 receptor agonists was reduced compared with those not taking GLP-1 receptor agonists (891/43 317 [2.1%] vs 1022/43 315 [2.4%]; HR, 0.83; 95% CI, 0.76-0.91).[93] Reduced incidence of specific cancers, however, was observed only for endometrial cancers (86/29 379 [0.29%] vs 115/29 741 [0.39%]; HR, 0.75; 95% CI, 0.57-0.99) and ovarian cancers (17/29 379 [0.06%] vs 32/29 741 [0.11%]; HR, 0.53; 95% CI, 0.29-0.96) with GLP-1 receptor agonist use vs nonuse, and longer follow-up may be needed to assess the effects of these medications on other cancers.

Future Directions

First, future clinical trials for cancer prevention should study interventions that reduce myeloid-derived suppressor cell activity, such as aromatase inhibitors, chemokine and chemokine receptor blockade, and all-*trans* retinoic acid, which induces terminal differentiation into mature immune cells.[94] Second, metformin reduced estrogen production and repaired DNA damage in preclinical studies of human breast tissue from females with germline *BRCA1* or *BRCA2* genetic variants.[75] Future studies should consider testing metformin for cancer prevention in people with obesity. Third, combining weight-loss treatments, such as GLP-1 receptor agonists or bariatric procedures, with weight maintenance treatments, such as lifestyle modification by diet and exercise interventions, is a potential strategy for maintaining weight loss and reducing cancer risk.[95]

Limitations

This Review has several limitations. First, some topics related to obesity and cancer were not discussed. Second, the quality of included evidence was not formally reviewed. Third, some relevant references may have been missed.

Conclusions

Overweight and obesity are associated with higher rates of cancer and account for 10% of new cancer diagnoses annually in the US. Weight loss may reduce cancer risk by attenuating adverse effects of obesity, but greater than 10% weight loss may be necessary to reduce cancer risk.

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