Obesity

The Triple Health Threat of Diabetes, Obesity, and Cancer—Epidemiology, Disparities, Mechanisms, and Interventions

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Obesity and type 2 diabetes are both chronic, relapsing, progressive diseases that are recognized as risk factors for the development of multiple types of cancer. In a recent symposium titled "Hitting A Triple—Diabetes, Obesity, and the Emerging Links to Cancer Risk," convened by The Obesity Society during ObesityWeek 2019, experts in the field presented the current science and highlighted existing research gaps. Topics included (1) the epidemiology of obesity and diabetes and their links to cancer risk; (2) racial and ethnic differences in obesity, diabetes, and cancer risk; (3) biological mechanisms common to obesity and diabetes that may increase cancer risk; and (4) innovative interventions that can be used to prevent the development of cancers related to obesity and diabetes. This report provides an overview of the symposium and describes key research gaps and pressing questions in need of answers to advance the field. The collective burden of obesity, diabetes, and cancer represents one of the largest public health challenges of the century. Although the symposium was titled "hitting a triple," it was recognized that being able to disrupt the linkages among obesity, diabetes, and cancer would be a "grand slam" for public health and medicine.

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Study Importance

What is already known?

- Obesity and type 2 diabetes are both chronic, progressive, and relapsing diseases that increase the risk of developing various types of cancer.
- The collective burden of obesity, diabetes, and cancer represents one of the largest public health challenges of the century.

What does this review add?

- In a symposium titled "Hitting A Triple—Diabetes, Obesity, and the Emerging Links to Cancer Risk," experts presented the current science and highlighted research gaps.
- Topics included the epidemiology of obesity and diabetes and links to cancer risk; racial and ethnic differences in obesity, diabetes, and cancer risk; biological mechanisms common to obesity and diabetes that increase cancer risk; and interventions to prevent the development of cancers related to obesity and diabetes.

How might these results change the focus of clinical practice?

- As the prevalence of obesity and diabetes increases, clinical and public health interventions are urgently needed.
- Identifying how to disrupt the linkages among obesity, diabetes, and cancer has the potential to transform the health and wellness of society.

Introduction

Obesity and type 2 diabetes (hereafter referred to as diabetes) are both chronic, relapsing, progressive diseases (1,2). By the year 2030, it is projected that one in two adults in the US will have obesity, and one in seven will have diabetes (3,4). Obesity is a strong risk factor for the development of diabetes; consequently, half of people diagnosed with diabetes have obesity (5). Multiple racial and ethnic subgroups experience a disproportionate burden of obesity and diabetes in the US (3,6).

Obesity and diabetes have long been recognized as risk factors for cardiovascular morbidity and mortality. In 2002, the International Agency for Research on Cancer reported that obesity was linked with the development of five different cancers (7). In 2016, the International Agency for Research on Cancer and the World Cancer Research Fund reported that obesity was now convincingly linked with the development of 13 different cancers (8). Furthermore, diabetes has been recognized as a risk factor for the development

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of multiple malignancies (9), independent of obesity (10). Similar to obesity and diabetes, underrepresented racial and socioeconomic subgroups experience a disproportionate cancer burden (11).

In a recent symposium titled "Hitting A Triple—Diabetes, Obesity, and the Emerging Links to Cancer Risk" convened by The Obesity Society during ObesityWeek 2019, experts in the field presented the current state of the science and highlighted existing research gaps. Topics that were discussed included (1) the epidemiology of obesity and diabetes and their links to cancer risk; (2) racial and ethnic differences in obesity, diabetes, and cancer risk; (3) biological mechanisms common to obesity and diabetes that may increase cancer risk; and (4) innovative interventions that can be used to prevent the development of cancers related to obesity and diabetes. The purpose of this report is to provide a concise overview of the symposium; it is not intended to serve as a comprehensive review of all aspects of these individual topics.

The Epidemiology of Obesity

Obesity is a multicausal chronic disease of excess adipose tissue that can occur throughout the life-span (12). Obesity is diagnosed using BMI ≥ 30 kg/m^2 (13). Among all weight-to-height indices, BMI has the strongest correlation with measures of total body adiposity (14). Current estimates are that 34% of adults in the US have obesity (15), and this estimate is projected to increase to 48.9% by 2030 (3). Women are more likely to develop obesity compared with men, and this risk is highest among black and Hispanic women (prevalence ratio: 1.44 for black women and 1.21 for Hispanic women, as compared with non-Hispanic white women) (16). Body fat distribution, particularly intra-abdominal visceral adipose tissue, is a strong determinant of the adverse metabolic effects of obesity (17). Abdominal obesity can be defined using the waist circumference or the waist-hip ratio. Similar to BMI, rates of abdominal obesity are increasing in the US (18). The combined use of BMI and waist circumference or the waist-hip ratio can identify population subgroups with a high cancer risk (19,20).

The Epidemiology of Diabetes

Diabetes is the result of a progressive loss of adequate β-cell insulin secretion, frequently occurring on the background of insulin resistance (21). Diabetes is diagnosed by plasma glucose concentrations, either fasting or during an oral glucose tolerance test, or by glycated hemoglobin. Current estimates are that 9.1% of adults in the US have diabetes, and this estimate is projected to increase to 13.9% by 2030 (4). Newly released data indicate that the prevalence of diabetes is highest among people of Hispanic origin (14.7%) and non-Hispanic black (16.4%) as compared with other racial and ethnic subgroups (11.9% non-Hispanic white) (22). Overt diabetes is often preceded by a period of prediabetes, characterized by fasting glucose and glucose intolerance that is above normal but below diabetes thresholds, that affects 34.5% of US adults (23). The annual rate of progression from prediabetes to diabetes is 5% to 10% (24).

The Triple Threat of Obesity and Diabetes and Cancer Risk

Obesity defined using BMI is associated with an increased risk of developing at least 13 cancers throughout the body (Figure 1) (8). These 13 obesity-related cancers represent 40% of all malignancies diagnosed in the US (25). Between 2005 and 2014, with the exception of colorectal cancer, the annual incidence of obesity-related cancers increased among persons aged 20 to 74 years (25). Independent of baseline BMI, weight gain across the life-span is associated with risk of cancer (26,27). A higher lifetime BMI and longer duration of obesity are positively related to cancer risk (28-31). Observational studies of Mendelian randomization that use genetic markers known to be associated with obesity or adiposity have reported associations with various types of cancer (32,33).

Diabetes is associated with an increased risk of developing at least six cancers, including breast, endometrial, and several gastrointestinal

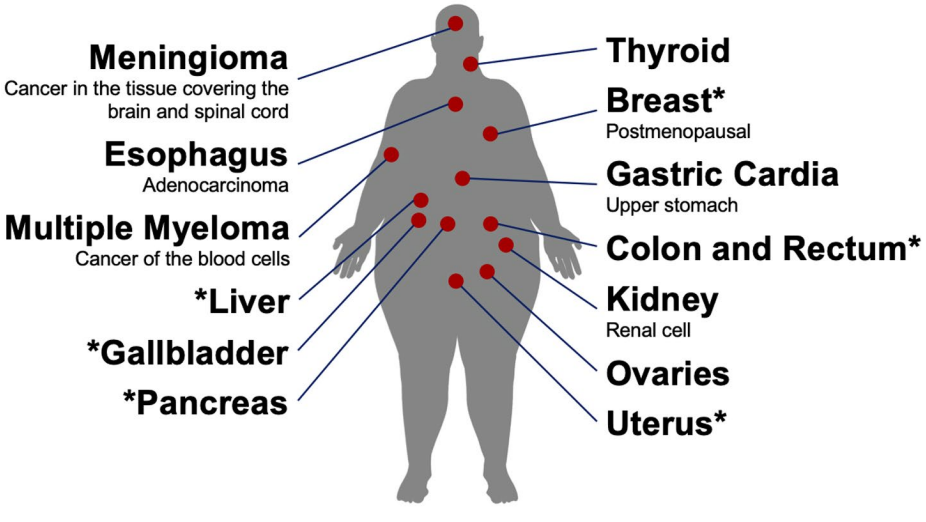

Figure 1 Cancers that have an established relationship with obesity. Cancers that also have an established relationship with diabetes have an asterisk. [Color figure can be viewed at wileyonlinelibrary.com]

malignancies in the colorectum, pancreas, gallbladder, and liver (9). After diagnosis of diabetes, risk of cancer is elevated for ≥20 years, with the highest degree of risk occurring approximately 4 to 8 years after diabetes diagnosis (34). Importantly, prediabetes is associated with an increased cancer risk (35,36). Mendelian randomization studies report that genetic predisposition to diabetes and insulin resistance is associated with cancer risk (37).

Disentangling the joint and independent effects of obesity and diabetes on cancer risk has been challenging, as obesity and diabetes are strongly related. Among women in the multiethnic cohort study, obesity increased risk of breast cancer (hazard ratio [HR]: 1.33 [95% CI: 1.24-1.43]) and was unchanged after adjustment for diabetes (HR: 1.31 [95% CI: 1.22-1.41]) (38). In a meta-analysis of 39 studies, diabetes increased the risk of breast cancer in studies that did not adjust for BMI (risk ratio [RR]: 1.33 [95% CI: 1.18-1.51]), and this risk was attenuated, but remained statistically significant, in studies that did adjust for BMI (RR: 1.16 [95% CI: 1.08-1.24]) (39). It is estimated that as independent risk factors, obesity and diabetes account for 5.7% of all incident cancers (10). After cigarette smoking, obesity is the second strongest modifiable risk factor for cancer (40).

Disparities in Obesity, Diabetes, and Cancer Risk

Racial and ethnic minority subgroups experience a disproportionate burden of cancers (11), including the malignancies that are related to obesity and diabetes (25). BMI does not quantify excess adiposity and metabolic abnormalities consistently across racial populations (41-43). At a specific BMI, black individuals have less visceral adiposity (BMI by race interaction for visceral adipose tissue, $P < 0.05$) and lower insulin sensitivity (BMI by race interaction for skeletal muscle insulin sensitivity, $P = 0.04$) than white individuals (44,45). Among black women, for example, abdominal obesity (e.g., waist circumference or the waist-hip ratio) is a stronger predictor of breast cancer risk than general adiposity measured by BMI (46). Similar findings have been reported for Hispanic women (47). The joint and independent effects of obesity and diabetes on cancer risk may vary by race and ethnicity (38,48). Molecular pathological epidemiology studies have provided important mechanistic insights about how obesity and diabetes impact the molecular tumor characteristics (49) and how these tumor characteristics may vary by racial and ethnic subgroup (for example, black women are more likely than white women to be diagnosed with estrogen receptor negative and triple negative breast cancer, which are biologically more aggressive and have a poorer prognosis) (50).

Mechanisms that Link Obesity and Diabetes with Cancer

The precise biological mechanism through which obesity and diabetes promote tumorigenesis remains incompletely understood but is likely multifactorial. Hypertrophic adipose tissue is associated with altered concentrations of metabolic hormones (e.g., insulin and insulin-like growth factors), adipokines (e.g., leptin, adiponectin), steroid hormones (e.g., estrogen), and inflammatory cytokines (e.g., interleukin-6) (51,52). Multiple intracellular pathways may be activated, including the Janus kinase (JAK)-signal transducers of transcription (STAT), mitogen-activated protein kinase (MAPK), and the phosphatidylinositol 3-kinase, protein kinase B, mammalian target of rapamycin (PI3K-Akt-mTOR) pathway, which are often mutated in cancer (53). By activating these signaling pathways, malignant transformation is supported.

PI3K-Akt-mTOR is perhaps the most intriguing signaling pathway underpinning the effects of obesity and diabetes on cancer risk (Figure 2). This pathway is one of the most commonly activated in cancer (54). mTOR is sensitive to the nutrient status surrounding the cell, such high-energy states (e.g., obesity and hyperinsulinemia), which activate mTOR via Akt, and low-energy states (e.g., caloric restriction and exercise), which inhibit mTOR via 5' AMP-activated protein kinase (AMPK) (55,56). In preclinical models of mammary cancer, suppressing weight gain and accumulation of lipid in adipose depots via dietary energy restriction and/or physical activity reduced tumor incidence (57), mediated in part by activation of AMPK and downregulation of mTOR (58), which reduced rates of cell proliferation and vascularization and increase apoptosis (59-61). These studies suggest that the PI3K-Akt-mTOR pathway is a useful bridge between population studies and mechanistically based interventions because of its central role in cell metabolism, and the host systemic and cell autonomous processes that drive selective growth advantage, and response to therapeutic targeting (62).

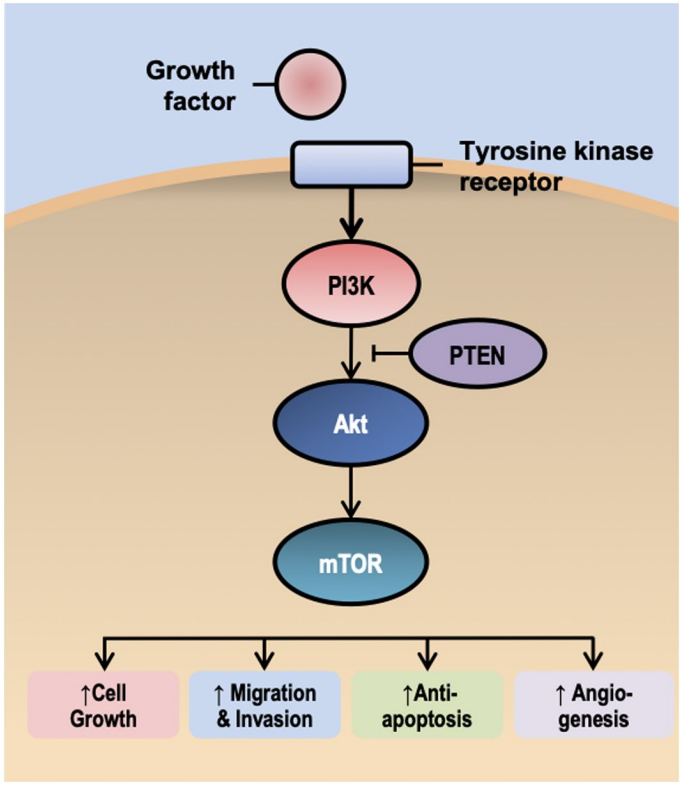

Figure 2 A simplified overview of the PI3K-Akt-mTOR pathway. The PI3K-Akt-mTOR pathway has been implicated in obesity, diabetes, and cancer risk, making this pathway a useful bridge between population studies and mechanistically based interventions. PI3K-Akt-mTOR, phosphatidylinositol 3-kinase protein kinase B, mammalian target of rapamycin; PTEN, phosphatas and tensin homolog. [Color figure can be viewed at wileyonlinelibrary.com]

Interventions to Break the Link Between Obesity and Diabetes with Cancer

The Diabetes Prevention Program (DPP) established that lifestyle modification (7% weight loss and 150 minutes per week of physical activity) or metformin (oral antidiabetes medication) reduced the progression from prediabetes to diabetes by 58% and 31%, respectively (63). Publication of the cancer risk analyses from the Diabetes Prevention Program are pending (64). Observational studies report that weight loss (self-reported as intentional) is associated with a 12% reduction in cancer risk (65). The only randomized trial to address the effect of lifestyle modification (7% weight loss and 175 minutes per week of physical activity) on cardiovascular risk was the Action for Health in Diabetes (Look AHEAD) trial (66). After 11 years of follow-up, data from the lifestyle intervention were associated with a 16% relative risk reduction in obesity-related cancer, though this comparison was not statistically significant (HR: 0.84, 95% CI: 0.68-1.04) (67). The findings from the Look AHEAD trial provide the first evidence that the effects of obesity on cancer risk may be reversible (68).

Metabolic surgery consistently yields ≈25% weight loss at 10 years, induces diabetes remission, with low operative morbidity (5%) and mortality (0.2%) (69,70). Observational studies have reported that patients who undergo metabolic surgery are at a lower risk of developing cancer compared with patients who do not undergo surgery (71,72). A meta-analysis of 13 observational studies reported that surgery was associated with a 44% lower risk of invasive cancer (odds ratio: 0.56 [95% CI: 0.46-0.68]) (73). Metabolic surgery is also associated with a lower risk of malignancies not traditionally considered to be related to obesity and diabetes, such as melanoma and non-Hodgkin lymphoma (74,75).

Inconsistency arises with respect to the anticancer effects of diabetes and obesity medications (76). Many studies that have examined the anticancer effects of diabetes medications use observational designs and have been limited by various types of biases (e.g., immortal time bias) (77). Meta-analyses that combine both observational and randomized designs have demonstrated that, depending on drug class, cancer risk may be increased, decreased, or not changed among observational studies; however, randomized studies have not supported these findings (78,79). For example, in a pooled analysis of 21 cohort studies, metformin was associated with a lower risk of cancer (HR: 0.88, 95% CI: 0.83-0.92), whereas no cancer risk reduction was observed in 23 randomized trials (HR: 1.05, 95% CI: 0.94-1.18) (78). An important limitation is that these trials were not designed to assess cancer risk, and definitive conclusions cannot be made (80). There are also several antiobesity medications that are approved by the Food and Drug Administration (81). Relevant to cancer, lorcaserin was withdrawn from the market in February 2020 because of an increased risk of cancer (82,83).

Pressing Questions to Advance the Field

Throughout all presentations, existing research gaps and pressing questions in need of answers to advance the field were highlighted. There was agreement by all presenters that to move the field forward in a transformative and rapid manner will require the assembly of diverse teams of scientists, such as that made possible by the National Cancer Institute-sponsored Transdisciplinary Research on Energetics and Cancer consortium (84). There was also agreement that because of the diverse causes of obesity, diabetes, and cancer, an array of innovative study designs, such as multilevel or adaptive approaches, would be likely to offer unique and complementary evidence to advance the field (85).

There is an important need to determine which measures of obesity and diabetes status are best to prognosticate cancer risk, when, and for whom. The majority of studies to date have used a single assessment of BMI as a measure of adiposity and a single fasting glucose with/without insulin as a measure of insulin resistance. The introduction of optical imaging technology to quantify body composition, continuous glucose monitors, and accelerometry embedded into digital devices, for example, offer the potential to obtain high-dimensional data to glean additional mechanistic insights (86,87).

The importance of measures across the life-span have been appreciated. Among children, 12.4% have obesity when they enter kindergarten (88), with the most rapid weight gain occurring between 2 and 6 years of age (89). It is predicted that 57.3% of children today will have obesity at the age of 35 years (90). Children with obesity have a similar cardiometabolic risk factors profile as adults, including prediabetes and diabetes (91,92). Adolescent obesity predicts midlife cancer risk (93) and has been hypothesized as a possible cause of the increase in early onset cancer (cancers occurring before the age of 50 years) (94).

Many studies to date have been insufficiently racially and ethnically diverse to identify clinically meaningful heterogeneity of effects (95). Diverse subgroups will also enable molecular pathological epidemiology studies to identify differences in tumor subtypes (96). Enrolling study participants from diverse backgrounds in sufficient numbers will enable the identification of distinct obesity and diabetes phenotypes that may offer important clues to social determinants of disparities, mechanisms of action, and identify population subgroups most likely to benefit from intervention (97). Interventions should be tailored to include culturally relevant design approaches to increase their relevance, appeal, and effectiveness (98).

Given the relative infrequency and long latency interval required for cancer to occur, there is a critical need to identify additional biomarkers that can be validated and used as surrogate cancer risk end points for intervention trials. The identification and characterization of such surrogate end points will reduce study length, sample size, and cost. An example of a unique surrogate measure was the use of recurrent polyps as an end point to characterize the potential colorectal cancer benefit of metformin (99). As mechanisms of action continue to be identified, the potential opportunities to identify surrogate end points may increase.

It remains unknown how much weight loss or what degree of glycemic control is required to reduce cancer risk. Greater clarity is needed to define the role of antiobesity or antidiabetes medications as potential cancer risk reduction strategies. Lastly, the observational data supporting the anticancer potential of metabolic surgery should continue to be investigated (100).

Conclusion

Obesity and diabetes are complex diseases that are independently and jointly risk factors for cancer. The collective burden of obesity, diabetes, and cancer represents one of the largest public health challenges of the

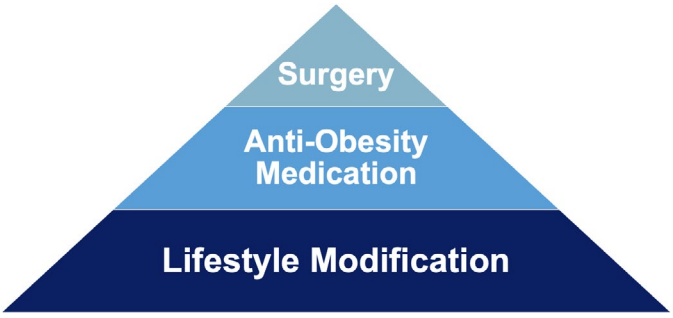

Figure 3 Managing obesity and diabetes as a cancer prevention and control strategy will likely require a multimodal approach that utilizes lifestyle modification as a foundation and offers evidence-based antiobesity or antidiabetes medication and metabolic surgery, as appropriate. [Color figure can be viewed at wileyonlinelibrary.com]

century. As the prevalence of obesity and diabetes increase, clinical and public health interventions are urgently needed (Figure 3). Identifying how to disrupt the linkages among obesity, diabetes, and cancer has the potential to transform the health and wellness of society. Although the symposium was titled "hitting a triple," it was recognized that being able to break the linkages among these three chronic diseases would be classified as a "grand slam" for public health and medicine.O

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