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Metabolic dysfunction and obesity-related cancer: beyond obesity and metabolic syndrome

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Abstract

The metabolic dysfunction driven by obesity including hyperglycemia and dyslipidemia increase risk of developing at least 13 cancer types. The concept of “metabolic dysfunction” is often defined by meeting various combinations of criteria for metabolic syndrome. Yet, the lack of unified definition of metabolic dysfunction makes it difficult to compare findings across studies. This review summarizes 129 studies that evaluated variable definitions of metabolic dysfunction in relation to obesity-related cancer risk and mortality after a cancer diagnosis. Strategies for metabolic dysfunction management are also discussed. Metabolic dysfunction, defined as metabolic syndrome diagnosis or any number of metabolic syndrome criteria out of clinical range, inflammatory biomarkers, or markers of metabolic organ function, has been associated with risk of and mortality from colorectal, pancreatic, postmenopausal breast, and bladder cancers. Metabolic dysfunction associations with breast and colorectal cancer risk have been observed

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independently of BMI, with increased risk in individuals with metabolically unhealthy normal weight or overweight/obese compared with metabolically healthy normal weight. Therefore, metabolic dysfunction is a key risk factor for obesity-related cancer, regardless of obesity status. Nonetheless, a harmonized definition of metabolic dysfunction will further clarify the magnitude of the relationship across cancer types, enable better comparisons across studies, and further guide criteria for obesity-related cancer risk stratification.

Keywords

Metabolic dysfunction; cancer; obesity

Introduction

Metabolic conditions like obesity and diabetes account for 6% of all incident cancers worldwide (1), underscoring the importance of metabolic dysfunction for cancer prevention (2-4). While international governing bodies have convened to establish a consensus definition of “metabolic syndrome”, the same has not been accomplished for defining “metabolic dysfunction”, a concept representing disordered metabolism on a continuum rather than a definitive diagnosis. This has limited the ability to evaluate the true extent of cancer and its outcomes that can be attributed to defective metabolism. Components of metabolic dysfunction that are evaluated to diagnose metabolic syndrome (i.e., ≥3 of elevated waist circumference, triglycerides, fasting blood glucose, blood pressure, and/or low HDL-cholesterol or their treatment (5)) are independent cancer risk and prognostic factors (6-8), even among individuals with a body mass index (BMI) in the normal range (9-14). Managing metabolic diseases therapeutically, such as with metformin and statin pharmacologic treatment, has been shown to reduce cancer risk and improve survival for a number of cancer types (15-19). Altogether, these observations provide evidence for a key role of dysfunctional metabolism in cancer development, and underscore the potential of targeting these pathways as a strategy to reduce cancer risk and mortality (20, 21). Additional biomarkers linked to inflammation, insulin sensitivity, and liver function that are commonly dysregulated in metabolic disease (e.g., C-reactive protein, C-peptide, alanine aminotransferase (ALT) and aspartate transaminase (AST)), and more comprehensive indicators of central adiposity (e.g., visceral to subcutaneous adipose tissue ratio (VAT:SAT)) may further bolster obesity-related cancer risk stratification or other cancer prevention efforts (22-26). In addition, the concept of metabolic obesity in the normal weight range is gaining traction as another target for intervention, since up to a third of lean individuals have metabolic syndrome parameters out of clinical range that often go undiagnosed (27). As the worldwide incidence of obesity-related cancer continues to escalate, a consensus definition of metabolic dysfunction would provide a benchmark for studies evaluating its role in the development of cancer and outcomes among cancer patients.

The aim of this comprehensive review is to summarize studies on accepted clinical and broader definitions of metabolic dysfunction and their relationship with obesity-related cancer risk, recurrence, and mortality, and to discuss lifestyle strategies that address metabolic health that have the potential to mitigate cancer risk. We briefly discuss lifestyle-

based strategies for managing or improving metabolic dysfunction among adults and cancer survivors.

Methods

We performed a comprehensive review of studies evaluating metabolic dysfunction and obesity-related cancer risk, recurrence, and mortality.

Inclusion Criteria

Studies were included according to the following criteria: 1) Observational study design (i.e., prospective or retrospective cohort or case-control studies) and clinical trials. 2) Studies on the relationship between metabolic dysfunction (any study-specific definition including metabolic syndrome or its components defined by national or international criteria) and any of the 13 obesity-related cancers (risk or mortality after cancer diagnosis). Obesity-related cancers as defined by the International Agency for Research on Cancer (IARC) and the United States (US) National Cancer Institute include esophageal adenocarcinoma, gastric cardia, colorectal, liver, gallbladder, pancreas, postmenopausal breast, uterus (corpus uteri), ovary, kidney (renal-cell), meningioma, thyroid, and multiple myeloma cancers (28, 29). 3) Studies on the association of other metabolic criteria (e.g., biomarkers of key organs that regulate metabolic homeostasis like the liver, pancreas, gut, and adipose tissue) or obesity-related parameters (e.g., body composition) that are not part of the metabolic syndrome definition in relation to obesity-related cancer risk, recurrence, and mortality. 4) Study population included adults (≥ 18 years), males and/or females, residing in any geographical location. 5) Studies limited to the English language.

Search Methods

We conducted a comprehensive search of relevant publications in MEDLINE (PubMed) and Google Scholar. The complete PubMed and Google Scholar search terms included: (Neoplasm OR cancer OR neoplasia OR adenocarcinoma OR adenoma OR carcinoma) AND (“obesity-related" OR “obesity-related" OR esophageal OR esophag OR “gastric cardia” OR stomach OR gastric OR colorectal OR colon OR rectum OR rectal OR liver OR gallbladder OR “gall bladder” OR pancreas OR pancreatic OR breast OR uterus OR “corpus uteri” OR uterine OR endometri OR ovary OR ovarian OR ovaries OR kidney OR hepatic OR hepatocellular OR renal OR meningioma OR meninge OR thyroid OR “multiple myeloma”) AND (marker OR biomarker OR metabolite) AND (risk OR incidence OR mortality OR survival OR recurrence) AND ("metabolic health" OR “metabolically healthy” OR "cardiometabolic health" OR "metabolic phenotype" OR "metabolic syndrome" OR "metabolic health biomarkers" OR "metabolic health outcomes" OR "metabolic status" OR "metabolic abnormality" OR "metabotype" OR "metabolic dysfunction" OR “metabolic health definition”). Publications until March 31, 2021 were considered.

Data Abstraction

First, articles were screened for relevant titles. Of those, abstracts and then the full text articles were screened for the inclusion criteria. All articles that met the above mentioned inclusion criteria were incorporated. Full text article reference lists were searched for

additional references that met inclusion criteria. Data were extracted from each study and tabulated, including author, year of publication, country, study, sample size, mean age, cancer type, definition used for metabolic syndrome, metabolic health parameters and criteria used to define metabolic dysfunction (Tables 1, 2, 3, and 4 from Supporting Information).

Results

Metabolic syndrome and metabolic dysfunction definitions

Metabolic syndrome.—Metabolic syndrome has been defined by various health organizations: the World Health Organization (WHO) (30), European Group for the Study of Insulin Resistance (EGIR) (31), American Association of Clinical Endocrinology (AACE) (32), American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) (33, 34), International Diabetes Federation (IDF) (35), the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) (36) and a harmonized definition across these organizations (5). Among included studies, there was consensus with respect to five criteria: (1) obesity (elevated waist circumference or body mass index (BMI)); (2) insulin resistance/impaired glucose tolerance (i.e., elevated fasting plasma glucose); dyslipidemia ((3) elevated blood triglyceride and (4) low high-density lipoprotein concentrations); and (5) hypertension (elevated systolic and/or diastolic blood pressure). There were some differences in the definition of obesity. Five of the seven guidelines defined obesity as elevated waist circumference according to population and ethnicity-specific cut-points (5, 31, 33, 35, 36), one as increased BMI (32), and one as elevated waist-to-hip ratio or BMI (30). The criteria for other parameters in the metabolic syndrome definition were more consistent. After the year 2000, dyslipidemia was defined as triglycerides ≥ 150 mg/dL, and HDL-cholesterol ≤ 40 mg/dL in men and ≤ 50 mg/dL in women. Elevated systolic and/or diastolic blood pressure was defined as ≥ 130/85 mmHg, and elevated fasting glucose was defined as concentration ≥ 100 mg/dL. In all guidelines, the presence of at least three of the five elements was required for a metabolic syndrome diagnosis. Three of the guidelines required as one of those three elements impaired insulin or glucose levels (30-32), whereas one required presence of central obesity as indicated by elevated waist circumference (35). Receiving pharmacologic treatment to regulate any of these five metabolic components was an acceptable alternative to elevated clinical biomarkers or measurements in determining the presence of metabolic syndrome.

Metabolic dysfunction.—A modified metabolic dysfunction definition that included markers of insulin resistance and inflammation has been previously proposed by Wildman and colleagues (37). They defined metabolic dysfunction based on six metabolic components including the inflammatory biomarker C-reactive protein (CRP) and the insulin resistance indicator Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), along with two or more of four metabolic syndrome components out of clinical range (fasting glucose, HDL-cholesterol, triglycerides, and blood pressure). Other biomarkers of visceral fat mass, adipose tissue, liver, and pancreatic dysfunction such as leptin: adiponectin ratio, VAT, SAT, VAT: SAT ratio, alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), ALT, AST, insulin, and C-peptide, have also been leveraged as indicators of

metabolic dysfunction. These metabolic markers correlate with metabolic syndrome (38, 39), but have not been widely used when defining metabolic dysfunction.

Cancer Risk

Metabolic syndrome—There were 63 studies (44 cohort, 19 case-control) with sample sizes varying from 82 to 7,785,098 participants investigating metabolic syndrome and cancer risk. Studies defined metabolic dysfunction as the presence or absence of metabolic syndrome as defined by various health organizations with the exception of some studies that used modified metabolic syndrome criteria such as the Japanese Committee of the Metabolic Syndrome Diagnostic Criteria (2005), the Diabetes Society of the Chinese Medical Association, the Chinese Diabetes Society (CDS). Of these, eight studies computed a continuous metabolic syndrome z-score. Fifteen studies were conducted in the United States, 27 in Europe, 19 in Asia, and one each in Canada, Israel and Australia. Metabolic syndrome was associated with elevated risk of hepatocellular carcinoma and cancers of the breast, colorectum, endometrium, pancreas, and gastric cardia. The association of metabolic syndrome with esophageal adenocarcinoma was somewhat unclear; two of the five studies reported no association, whereas one study showed a small increased risk (OR 1.16, 95% CI: 1.06-1.26). The other two studies showed an association between only the obesity (BMI and waist circumference) component of metabolic syndrome and esophageal adenocarcinoma risk. About 68% of the studies measured these associations while adjusting for smoking and alcohol use. Effect estimates for the risk of cancer among those with compared to without metabolic syndrome ranged from 1.13 to 6.73 for breast, 1.14 to 2.61 for colorectal, 1.37 to 2.20 for endometrial, 1.58 to 2.13 for pancreas, and 1.18 to 2.50 for gastric cancer. and 2.13 to 5.06 for hepatocellular carcinoma. The magnitude of association of metabolic syndrome with obesity-related cancer varied depending on the metabolic syndrome definition used. For example, the strongest associations were observed when metabolic syndrome was defined by IDF, CDS, and NCEP-ATPIII compared with other criteria (40-44). The studies are outlined in Table 1 of Supporting Information.

Other metabolic dysfunction parameters—Eighteen studies (11 cohort and 7 case-control) measured alternative biomarkers than metabolic syndrome components in association with obesity-related cancer risk. Ten studies were conducted in Europe, six in Asia, and three in the United States. Metabolic parameters were evaluated by categorizing individuals according to clinical cut-points or comparing quantiles (e.g., tertiles, quartiles, quintiles, or deciles). Measures included: liver function markers such as ALP, GGT, ALT, AST, total bilirubin (TBIL), total protein (TP) and albumin (ALB) comparing highest/lowest quartile, quintile, and decile, C-reactive protein (CRP) < 10 and ≥ 10 mg/L or top/bottom tertile, HOMA-IR < or ≥ 2.5, C-peptide comparing highest/lowest decile, or < or ≥median concentration, fasting insulin comparing tertiles, or < or ≥ median concentration, IGFBP-rP1 comparing highest/lowest tertile, VAT per standard deviation (SD) or volume ≥1000 cm^3 or tertile or quartile, HbA1c comparing highest and lowest decile, leptin, adiponectin, and leptin: adiponectin ratio comparing top and bottom tertiles or deciles. Other metabolic parameters included pancreatic polypeptide (PP), gut-derived gastric inhibitory polypeptide (GIP), peptide YY (PYY)(23), monocyte chemoattractant protein-1 (MCP-1), and visfatin (an adipose tissue expressed protein). One study showed

that the liver functioning biomarkers ALT, AST, TBIL, GGT, ALP, TP and ALB were inversely associated with colorectal cancer risk, while another study showed no association with colorectal cancer risk. Two studies showed that elevated ALT and GGT were associated with increased risk for multiple cancer types, the strongest association being with liver cancer. For all biomarkers, high compared with low biomarker levels were associated with increased cancer risk (RR range 1.39 to 7.57) (Table 2, Supporting Information). The associations were observed independent of smoking status in 61% of the studies.

Metabolic Health Phenotype—Twenty-five cohort studies evaluated metabolic health phenotype defined by metabolic health status (i.e., healthy or unhealthy) coupled with BMI category (i.e., normal weight, overweight or obese) in relation to cancer risk. Twelve studies were conducted in Asia, eight in the United States, four in Europe, and one in Africa. In all studies, BMI was calculated as kg/m^2. European and North American populations defined BMI according to World Health Organization criteria (normal weight $<25.0\ kg/m^2$, overweight $25.0–29.9\ kg/m^2$, obese $\geq 30\ kg/m^2$) while Asian populations used population-specific cut-points for BMI (normal weight $18.5–23.0\ kg/m^2$, overweight $23.0–<25.0\ kg/m^2$, obese $\geq 25\ kg/m^2$). Among the studies reviewed, four distinctive phenotypes were most often defined: (1) “metabolically healthy normal weight/non-overweight or obese” (MHNW); (2) “metabolically unhealthy normal weight/non-overweight or obese” (MUNW); (3) “metabolically healthy overweight or obese” (MHO); and (4) “metabolically unhealthy overweight or obese” (MUO). Definitions of metabolic dysfunction varied widely across studies. Some studies defined metabolic health as absence of any abnormal metabolic parameters (e.g., glucose, insulin, c-peptide, HOMA-IR, metabolic syndrome components), while others classified being metabolically unhealthy as the presence of ≥ 1, ≥ 2, or ≥ 3 metabolic syndrome criteria out of clinical range. Metabolically unhealthy phenotype has been defined as having an elevated biomarker level, or having ≥ 1, ≥ 2, or ≥ 3 metabolic syndrome criteria out of clinical range in conjunction with BMI category (i.e., normal weight, or overweight and/or obese BMI). Nine studies defined being metabolically unhealthy as having ≥ 1 or 2 out of the four components out of clinical range (i.e., blood pressure, triglycerides, glucose, or HDL-cholesterol). Three studies also considered elevated waist circumference. Consistent with the clinical diagnosis of metabolic syndrome, five studies defined metabolically unhealthy phenotype as the presence of ≥ 3 metabolic syndrome criteria that included waist circumference. Both MUO and MUNW phenotypes were associated with elevated risk of colorectal, pancreatic, postmenopausal breast, and bladder cancer compared with MHNW. The effect estimates for MUNW were similar to that of MUO (range 1.07 to 1.59), while the effect estimates for MHO were closer to MHNW.

Twelve studies evaluated metabolic health phenotypes defined as BMI categories with or without elevation of a single biomarker, including HOMA-IR comparing highest/lowest quartiles, C-peptide comparing highest/lowest tertiles, fasting insulin comparing highest/lowest quartiles, non-fasting glucose (≥125mg/dl), waist circumference (WC) ≥88 cm, waist-hip-ratio (WHR) ≥0.85, VAT per standard deviation (SD) increment, body fat measures (top versus bottom quartiles or quintiles), and basal metabolic rate (BMR). Eight studies defined hyperglycemia according to HOMA-IR ≥ 2.5 or ≥ 3.0, elevated HbA1c ≥6.5%, or a diagnosis of diabetes. One study defined hyperglycemia as having non-fasting

blood glucose ≥125mg/dL. All studies reported higher risk of obesity-related cancer among metabolically unhealthy individuals independent of obesity status (i.e., across all BMI categories) (RR range 1.06 to 3.47). Smoking and alcohol use were adjusted for in 88% of the studies. Four studies evaluated HOMA-IR in relation to breast, colorectal, and thyroid cancer risk. Sixteen studies reported that metabolic dysfunction relative to metabolic health among normal weight individuals (BMI <25 kg/m^2) was associated with increased risk of colorectal, esophageal, pancreas, bladder, endometrial, thyroid, and breast cancer. Some studies also reported differences by sex. For example, metabolic dysfunction independent of BMI was associated with colorectal and bladder cancer risk in men, and with thyroid, colorectal and breast cancer risk in women (Table 3 of Supporting Information).

Cancer Mortality

Multiple prospective studies have reported an increased risk of cancer-related mortality and cancer recurrence among cancer survivors diagnosed with metabolic syndrome compared with those who are metabolically healthy. Added risks of up to 90% have been reported for breast and digestive tract cancer mortality. Metabolic syndrome parameters are cardiovascular disease (CVD) risk factors, and prevalent CVD among patients with cancer increases their risk of all-cause mortality (45, 46). For example, metabolic syndrome has been associated with colorectal cancer-specific mortality and overall mortality, and hepatocellular carcinoma-specific mortality. One meta-analysis observed an association between metabolic syndrome and digestive tract cancer mortality among patients with cancer post-surgery, while another meta-analysis observed an increased risk of cancer recurrence and all-cause mortality, but no association with cancer-specific mortality. Additionally, components of metabolic syndrome including central obesity, hyperglycemia, and hypertension have been reported in multiple studies to be associated with increased cancer-related mortality, and the risk of cancer-related mortality has been reported to increase with increasing numbers of metabolic syndrome components. The studies reviewed are outlined in Table 4, Supporting Information.

Discussion

Metabolic dysfunction and cancer

This comprehensive review summarizes studies on metabolic dysfunction in relation to cancer risk, cancer recurrence, and cancer-specific and all-cause mortality after cancer diagnosis (Table 1). A unifying definition of metabolic dysfunction in epidemiological studies is lacking (47). Studies included in this review had a range of definitions for metabolic syndrome and metabolic dysfunction, with or without considering BMI. In common, however, was that the chosen components predominantly derived from the NCEP-ATPIII definition of metabolic syndrome (32). When defining metabolic health phenotypes, one metabolic abnormality generally was enough to classify individuals as being “metabolically unhealthy”, whereas metabolic syndrome classification requires the presence of at least three abnormalities. Despite differences in the definition of metabolic dysfunction, any number of parameters out of clinical range was associated with risk of a number of obesity-related cancers and with mortality after a cancer diagnosis, independent of obesity status.

Metabolic syndrome represents metabolic dysfunction on the continuum between obesity and cardiometabolic disease incidence, including type 2 diabetes, heart disease, and stroke (45). It has been demonstrated that as the number of metabolic syndrome components increases, the severity of each component also increases (48). Cancer-associated metabolic risk factors may be driven by lifestyle factors such as diet, alcohol, smoking, and physical inactivity, biological factors such as central obesity, and/or by non-modifiable factors like age and genetics (34). Smoking status has been positively associated with obesity and either positively or inversely associated with a number of cancer types (49). Most studies we reviewed considered smoking as a covariate in statistical models, but residual or unmeasured confounding by smoking could potentially influence the results. Smoking has been shown to increase risk of insulin resistance, but its inverse association with endometrial cancer suggests potential effects on other relevant pathways like estrogen metabolism (50). Similar to smoking, alcohol use has also been associated with risk of esophageal, colorectal, liver, oral, and breast cancers (51). Several mechanisms have been postulated for the increased cancer risk with alcohol use, including increasing estrogen and androgen levels. In addition to considering them as potential confounders, investigating smoking and alcohol as potential effect modifiers of the relationship between metabolic dysfunction and cancer may be warranted. Further, metabolic syndrome is associated with other biological changes among patients with cancer, including hyperinsulinemia, visceral adiposity, increased circulating estrogen, inflammatory cytokines, and altered circulating adipokines (52-54). Specific mechanisms of interest in the etiology of cancer include the role of insulin and insulin-like growth factor-1 (IGF-1), hyperglycemia, elevated triglycerides, and low HDL-cholesterol. These pathways can influence estrogen signaling, cytokines, and adipokines that can trigger inflammation, and growth and proliferation of tumor cells (55, 56). For example, elevated insulin and IGF-1 can lead to activation of the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway. Adipokines and cytokines like leptin, interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) also promote angiogenesis (55, 56). In addition, people with insulin resistance independent of adiposity experience a cancer-promoting low-grade inflammatory state (57).

An expanding body of research shows an age-period-cohort effect on associations between obesity and cancer risk, whereby the relationship is time-varying (58). Moreover, treating obesity as a homogenous group (i.e., BMI ≥ 30kg/m^2) rather than delineating obesity by severity may lead to inconsistent results. Although cancer is largely a disease of aging, incidence of some cancers has been increasing in younger age groups in recent years. The rising rates of obesity and resulting metabolic dysfunction at younger ages are hypothesized to be one key factor in driving these trends. For example, incidence of colorectal and pancreatic cancer (59, 60) are disproportionately raising in younger adults under 50 years of age, and are associated with metabolic dysfunction (60).

It is well-established that obesity contributes to metabolic dysfunction (54, 61). However, individuals with obesity may be protected against metabolic dysfunction via numerous mechanisms including healthy expansion and distribution of adipose tissue across body depots, regulation of adipose tissue breakdown and macrophage-driven inflammation, and adipokines (47, 62, 63). On the other hand, lean individuals with a “lipodystrophy-like phenotype” comprised of central adiposity and/or ectopic fat accumulation (i.e., in

tissues not suited for fat storage) may be at higher risk for metabolic dysfunction and concomitantly for cancer (27). Dysfunctional metabolism among normal weight individuals could be attributed to genetic or behavioral factors (e.g., physical inactivity and poor diet quality) that influence adipogenesis and visceral fat deposition, and increase propensity for hyperglycemia, hyperinsulinemia, dyslipidemia, and hypertension (64). A caveat is that metabolic health phenotypes also lack clear criteria to define what constitutes as being "metabolically healthy", leading to estimates of the prevalence of MHO ranging from 6 to 75% among individuals with obesity (65) that could give rise to exposure misclassification. It is estimated (based on prevalence of metabolic syndrome) that prevalence of MUNW phenotype is up to 16% in the US (66, 67) and 26% in Europe (67). A harmonized definition for MHO was proposed recently as having a BMI ≥ 30 kg/m^2 and none of the metabolic syndrome criteria or cardiovascular diseases (68-70). Prospective studies have suggested that MHO is likely to convert to MUO given a longer duration of follow-up and therefore represents a temporary phenotype (71, 72). Therefore, identifying and intervening to prevent progression of metabolic dysfunction among individuals with MHO may still offer an opportunity for cancer prevention.

When it comes to risk prediction, clinically-defined metabolic dysfunction based on criteria for metabolic syndrome (5, 73) has good sensitivity but poor specificity for classifying risk of cardiometabolic diseases including cancer among individuals who are either lean or obese (74). Beyond metabolic syndrome criteria, additional indicators may strengthen estimates of the risk of cancer attributable to metabolic dysfunction. In particular, biomarkers that stem from visceral adipose tissue or adipose tissue expansion and/or distribution independent of BMI could be highly informative (27, 75). Leptin: adiponectin ratio, (76) and central obesity (VAT, SAT, VAT: SAT ratio) (24, 26, 77-81) have been associated with cancer risk. Even among normal weight individuals, higher measures of WC, WHR, body fat %, and BMR were associated with increased cancer risk, highlighting the need to risk stratify across BMI categories (82-88).

Considering systemic metabolic crosstalk between key metabolic organs, it may be prudent to consider biomarkers beyond adipose tissue functioning. For example, adipose tissue remodeling is triggered by signals emanating from the liver after sensing nutrition overload (89) that leads to obesity. Liver markers like ALP, GGT, ALT, AST, TBIL, TP and ALB are part of routine health check-ups, but have rarely been incorporated into definitions of metabolic dysfunction. Liver functioning enzymes have been correlated with metabolic syndrome, insulin resistance, binge alcohol drinking, and MUO phenotype. Recent studies suggest that liver function may be associated with colorectal and liver cancer risk (90-92). Pancreas-derived biomarkers like insulin and C-peptide have also been independently associated with cancer risk (23, 93, 94). Sex hormones, especially estrogens, are established risk factors for female cancers like breast, endometrial, and ovarian cancer, and play a role in the etiology of several other cancers (95, 96). Free estradiol is increased with obesity given elevated estrogen production (i.e., aromatase conversion of androgens to estrogen), and depression of sex hormone binding globulin levels. For example, causal mediation analyses have demonstrated that estrogens coupled with inflammatory biomarkers and C-peptide mediate 70% of the increased odds of endometrial cancer among obese compared with normal weight women (96). Such analyses that quantify indirect effects through all

biomarkers with decomposition into pathway-specific indirect effects are novel and may shed light into the metabolic pathways of greatest significance for driving obesity-related cancer risk. Taken together, biomarkers of metabolic regulation by organs like the liver and pancreas may augment the definition of metabolic dysfunction with a potential for better cancer risk stratification if they are found to enhance sensitivity and/or specificity of cancer risk prediction models.

Novel high-throughput technologies like metabolomics (small chemicals in biospecimens) and proteomics may unveil additional biomarkers of metabolic dysfunction, and could unravel the mechanisms linking obesity and/or excess central adiposity with cancer risk and prognosis. Application of metabolomics in cancer research and opportunities in the field have been reviewed previously (97, 98). A metabolite profile of metabolic syndrome components identified 27 commonly linked metabolites, including branched chain amino acids (BCAA), demonstrating convergent biological pathways (99), and over 300 metabolites were associated with individual metabolic syndrome components. The main chemical classes included amino acids, carbohydrates and their derivatives, glycolysis-related metabolites, glycerophospholipids, glycerolipids, sphingolipids, fatty acids, cholesterol, oxysterols, steroids, and peptides. Such findings, when replicated, could be used to generate a metabolite score of metabolic dysfunction. Metabolomics has also been used to define metabolic dysfunction, irrespective of BMI. A high ‘metabolic BMI’ (i.e., BMI-associated metabolites) has been shown to predict anthropometric BMI in only 80% of individuals, underscoring the notion that BMI is an imperfect metric that fails to identify all metabolically unhealthy individuals. Those that had higher circulating obesity-related metabolites, irrespective of their BMI, had a 2- to 5-fold increase in cardiovascular events (100). Furthermore, individuals with obesity may be metabolically healthy according to metabolic syndrome criteria. However, those defined as being metabolically healthy with the strictest of criteria (i.e., no metabolic syndrome criteria out of range), have been shown to have elevated risk of incident morbidity (23). Metabolomics could be leveraged to identify alternate metabolic pathways that could account for this elevated risk.

To summarize, the most commonly leveraged metric for defining metabolic dysfunction is diagnosis of metabolic syndrome, which considers several criteria that have each been associated with cardiometabolic disease risk. Yet, this binary definition of metabolic syndrome may lack the nuance to capture disease risk in the absence of a clinical diagnosis since individual criteria have each been associated with risk of obesity-related cancer (101). Yet, elevation in a single biomarker does not meet criteria for metabolic syndrome diagnosis. Agreement on a harmonized definition of metabolic dysfunction may assist in comparing findings across studies, but there are drawbacks as well. For example, treatments specific to components of metabolic syndrome vary (e.g., metformin, statins, anti-hypertensive drugs, etc.), each with different cancer protective effects (15-19). Moreover, a single metric (either a binary score, or a continuous metric) makes etiological inference more challenging. Nonetheless, conducting studies that test metabolic dysfunction scores comprising various combinations of biomarkers to maximize sensitivity and specificity for cancer risk prediction could have utility for obesity-related cancer risk prediction.

Strategies to improve metabolic dysfunction

Various epidemiological studies and real-world evidence have shown that lifestyle changes can be adopted to manage the components of metabolic dysfunction (e.g., central obesity, insulin resistance, blood pressure, blood lipid profile), prevent cancer, and/or improve health-related outcomes after a cancer diagnosis (102). These strategies may include exercise, diet, or a combination. Aerobic and resistance exercise training, regardless of weight loss or dietary changes, can facilitate attenuation of central obesity, specifically visceral fat (103, 104). Subsequently, reductions in central obesity and visceral fat promote improvements in insulin sensitivity, inflammation, angiogenesis, and tumorigenesis (103, 105). Along with reductions in central obesity, exercise releases cytokines from contracting skeletal muscle (myokines) that have autocrine and endocrine effects on metabolic health, reducing inflammation and promoting whole body insulin sensitivity (103). Evidence also supports the ability of exercise training, regardless of type, to reduce resting blood pressure among individuals with normal blood pressure, pre-hypertension, and hypertension (106). Additionally, regular engagement in exercise slows the progression to hypertension among individuals with pre-hypertension (107). Furthermore, aerobic exercise, regardless of intensity, and resistance training primarily focusing on higher volume (e.g. higher repetitions, moderate to lower weight rather than lower repetitions and higher weight) is associated with favorable changes in blood lipids, notably increases in HDL cholesterol and reductions in triglycerides (108). Taken together, engaging in regular exercise prevents adverse metabolic health outcomes, and may serve as a strategy to attenuate metabolic dysfunction. Moreover, a pooled meta-analysis of 1.44 million adults found that leisure time physical activity was associated with lower risk of 13 cancer types (109). Specific exercise prescription and dose to optimize changes in metabolic dysfunction components are yet to be defined; therefore, it is currently advised for individuals to follow the national physical activity guidelines (110).

Behavior-based weight loss interventions result in significant weight reduction irrespective of macronutrient composition (68), improve metabolic dysfunction parameters, and reduce the risk of subsequent chronic disease (111). The dietary goal for individuals with obesity but are metabolically healthy may be to prevent progression to metabolic dysfunction (112), while individuals with metabolic dysfunction in the normal weight range may benefit from efforts to modify body composition (64). Although there is no consensus on the most effective dietary pattern for optimizing metabolic dysfunction, adherence to a Mediterranean diet improves most risk factors of metabolic syndrome, and has been associated with prevention of cardiometabolic diseases, including cancer (113). The Mediterranean diet emphasizes intake of fish and plant-based foods including wholegrains, fruits, vegetables, pulses, nuts, and olive oil, while minimizing intake of red meat and dairy (114). The dietary approaches to stop hypertension (DASH) diet, which emphasizes a heart healthy dietary pattern and limits sodium intake to 2,300mg/day, has also been associated with improvements in metabolic dysfunction parameters, particularly blood pressure (115). Findings for the role of low carbohydrate diets and cardiovascular risk factors have been mixed, with evidence for significant weight loss but potentially adverse effects on blood cholesterol (116). Manipulating meal timing is gaining traction as a potential strategy for improving metabolic dysfunction (117). Timing of meals and length of overnight fasting can

impact the body's 24-hour biological rhythm or circadian clock that regulates metabolism in liver, adipose and other metabolic tissues (118). Time restricted eating, where daily calories are consumed within 4-10 hours coupled with a prolonged overnight fast, has been associated with improvements in nutrient utilization, energy expenditure, blood pressure, glucose and lipid homeostasis, leptin resistance, hepatic inflammation, steatosis, and ectopic lipid deposition (119). Clinical trials suggest its safety and efficacy in improving body weight, fat mass, energy, glucose and lipid metabolism, inflammation, oxidative stress, blood pressure, and lowering appetite (120). However, few studies have evaluated meal timing in relation to cancer outcomes (121-123). Overall, dietary recommendations for improving metabolic health should be based on metabolic goals, individual and cultural preferences, socioeconomic factors, and food availability (124, 125).

In addition to physical activity and dietary recommendations, the World Cancer Research Fund/ American Institute for Cancer Research cancer prevention guidelines include avoiding smoking and limiting alcohol consumption to no more than two drinks a day for men and one drink a day for women (126). These guidelines, based on rigorous systematic review with meta-analysis of available literature, have been shown to be beneficial for not only cancer prevention but also to improve survival among cancer survivors (102, 127, 128).

Limitations

The present review provides a comprehensive summary of studies on metabolic dysfunction (both accepted clinical and broader definitions) in relation to obesity-related cancer risk, recurrence and mortality. The review was not systematic, however, and the selected studies are limited to English language. Therefore, some studies may have been missed.

Conclusion and future perspectives

This review summarizes 129 studies that evaluated metabolic dysfunction in relation to obesity-related cancer risk and mortality after cancer diagnosis. Current evidence supports that being metabolically unhealthy (including having a diagnosis of metabolic syndrome or having elevated levels of metabolic syndrome components), regardless of BMI category, is associated with a higher risk of at least four cancer types (colorectal, pancreatic, postmenopausal breast, and bladder) and increased mortality after diagnosis of breast and digestive tract cancers. Existing studies on metabolic health phenotype and cancer are limited to breast and colorectal cancers, thus more research is needed for other obesity-related cancer types. Determining the impact of metabolic dysfunction on cancer recurrence and mortality could be imperative to designing interventions to improve prognosis in cancer survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study importance questions

What is already known about this subject?

- The obesity pandemic has led to a surge in incidence of obesity-related cancers.
- Metabolic syndrome, a clinical diagnosis based on having at least three metabolic criteria (i.e., ≥3 of elevated waist circumference, triglycerides, fasting blood glucose, blood pressure, and/or low HDL-cholesterol or their treatment) out of clinical range, is independently associated with cancer risk and mortality.
- Metabolic dysfunction sits on a continuum, and the presence of one, or various combinations of two or more metabolic criteria out of clinical range have been associated with cancer risk. Yet, there is no unified definition of metabolic dysfunction, which complicates studies evaluating its association with cancer.

What are the new findings in your manuscript?

- We review the definitions of metabolic dysfunction used in studies of obesity-related cancers, discuss the lack of harmonized definition, and how this may influence results from studies evaluating its relationship with cancer risk and survival.
- We summarize studies of metabolic syndrome and cancer, and discuss emerging studies on obesity phenotype (i.e., lean but metabolically unhealthy; obese but metabolically healthy), and alternative metrics beyond metabolic syndrome criteria that could provide more comprehensive measures of metabolic dysfunction.
- We discuss novel strategies for managing metabolic dysfunction for cancer prevention such as meal timing.

How might your results change the direction of research or the focus of clinical practice?

- The findings highlight the need to evaluate metabolic health at any level of body mass index relative to cancer risk or outcomes, which has clinical implications for screening for obesity-related cancers.
- Future studies could consider novel means of evaluating metabolic dysfunction to provide a more nuanced evaluation, such as metabolic obesity defined by obesity-related metabolites, or biomarkers marking metabolic dysfunction in organs like the liver and pancreas.

Table 1.

Summary of studies reviewed relating to metabolic dysfunction definitions and obesity-related cancer (ORC) risk, recurrence, and mortality.

	MetS - ORC risk	Alternate biomarkers - ORC risk	Metabolic health Phenotypes - ORC risk	Metabolic dysfunction (MetS/ other) - mortality after ORC diagnosis
No. of studies reviewed	63 studies (44 cohort, 19 case-control)	18 studies (11 cohort; 7 case-control)	25 cohort studies	23 cohort studies
Sample size (range)	82 to 7,785,098	82 to 1,662,087	1,474 to 11,781,768	101 to 290,000
Country of origin	15 USA, 27 in Europe, 19 in Asia, 1 each in Canada, Israel and Australia	10 in Europe; 6 in Asia; 3 in USA	12 in Asia; 8 in USA; 4 in Europe;1 in Africa	8 USA; 8 Asia; 5 Europe
Age (% studies with mean age <50 years)	40%	22%	32%	52%
Lifestyle factors- (% studies adjusted for smoking and alcohol)	68%	61%	88%	48%
Cancer types with significant associations	HCC, breast, CRC, endometrial, pancreas and gastric cardia	Liver, pancreas, breast, endometrial	CRC, esophageal, pancreas, bladder, endometrial, thyroid and breast	Breast, CRC, HCC
Range of effect estimates	Breast (1.13 - 6.73); CRC (1.14 - 2.61); endometrial (1.37 - 2.20); pancreas (1.58 - 2.13); gastric cancers (1.18 - 2.50); HCC (2.13 - 5.06)	1.39 to 7.57	1.06 to 3.47	-

MetS: metabolic syndrome; ORC: obesity-related cancers; USA United States of America; HCC: hepatocellular carcinoma; CRC: colorectal cancer