Published OnlineFirst February 9, 2021; DOI: 10.1158/1940-6207.CAPR-20-0633

Cancer Risk in Normal Weight Individuals with Metabolic Obesity: A Narrative Review

Bethina Liu[1], Hugh E. Giffney[2], Rhonda S. Arthur[3], Thomas E. Rohan[3], and Andrew J. Dannenberg[2]

ABSTRACT

Obesity represents one of the most significant public health challenges worldwide. Current clinical practice relies on body mass index (BMI) to define the obesity status of an individual, even though the index has long been recognized for its limitations as a measure of body fat. In normal BMI individuals, increased central adiposity has been associated with worse health outcomes, including increased risks of cardiovascular disease and metabolic disorders. The condition leading to these outcomes has been described as metabolic obesity in the normal weight (MONW). More recent evidence suggests that MONW is associated with increased risk of several obesity-related malignancies, including postmenopausal breast, endometrial, colorectal, and liver cancers. In MONW patients, the false reassurance of a normal range BMI can lead to lost opportunities for implementing preventive interventions that may benefit a substantial number of people. A growing body of literature has documented the increased risk profile of MONW individuals and demonstrated practical uses for body composition and biochemical analyses to identify this at-risk population. In this review, we survey the current literature on MONW and cancer, summarize pathophysiology and oncogenic mechanisms, highlight potential strategies for diagnosis and treatment, and suggest directions for future research.

Introduction

Obesity is a well-documented risk factor for a wide variety of medical conditions. Although body mass index (BMI) (calculated as weight (kg)/height; m^2) is used to diagnose obesity, it is widely recognized to be a flawed indicator of an individual's health status (1). A growing body of literature has identified subgroups of normal BMI individuals (18.5–24.9 kg/m^2 for non-Asians and 18.5–22.9 kg/m^2 for Asians) who suffer from negative health consequences similar to those seen in the phenotypically overtly obese (≥30 kg/m^2 for non-Asians and ≥27.5 kg/m^2 for Asians; ref. 2). The condition, known as metabolic obesity in the normal weight (MONW), has been associated with excess body fat, dyslipidemia, insulin resistance, elevated blood pressure, and low-grade inflammation (3–5). In addition to higher risks of cardiovascular disease (CVD) and metabolic disorders, growing evidence has shown that MONW individuals also face increased risks of developing several cancers typically associated with obesity (6–9).

Despite these serious health implications, MONW remains under-recognized clinically. Research studies have employed different combinations of anthropometric and laboratory parameters to describe MONW. The absence of a common definition makes measuring the true prevalence of MONW difficult, with findings ranging from under 1% to over 30% of individuals with a normal BMI (10, 11). Variations in prevalence can also be attributed to differences in body composition patterns across ethnicities. Although much MONW research has been conducted in Asian populations, that are known to have more body fat at a lower BMI than other ethnicities (12, 13), studies have revealed similar patterns in body composition and clinical profiles among MONW individuals from European, Latin American, and North American populations (11, 14–17). As such, MONW should be considered a public health problem on a global scale. The failure to recognize it and develop effective interventions represents a missed opportunity for reducing the risk of potentially life-threatening diseases.

In this review, we examine the literature on MONW and its impact on cancer risk, pathophysiology, diagnostic approaches, and intervention strategies (**Fig. 1**). Given the range of definitions used in MONW research, our review includes studies with criteria based on body composition only, cardiometabolic abnormalities only, and combinations of both. We focus on the emerging evidence around MONW's association with cancer, an area of active investigation not yet addressed by existing reviews. By synthesizing current knowledge, we aim to identify challenges in the diagnosis and treatment of MONW and propose directions for future research.

MONW and cancer risk

Obesity is a risk factor for the development of 13 types of cancer and is associated with higher risk of mortality

[1]MD Program, Weill Cornell Medicine, New York, New York. [2]Weill Cornell Medicine, New York, New York. [3]Albert Einstein College of Medicine, Bronx, New York.

Corresponding Author: Andrew J. Dannenberg, Weill Cornell Medical College, 525 E 68th St, Room E-803, New York, NY 10065. Phone: 646-962-2891; Fax: 646-962-0891; E-mail: ajdannen@med.cornell.edu

Cancer Prev Res 2021;14:509–20

doi: 10.1158/1940-6207.CAPR-20-0633

©2021 American Association for Cancer Research.

Downloaded from cancerpreventionresearch.aacrjournals.org on May 17, 2021. © 2021 American Association for Cancer Research.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1940-6207.CAPR-20-0633

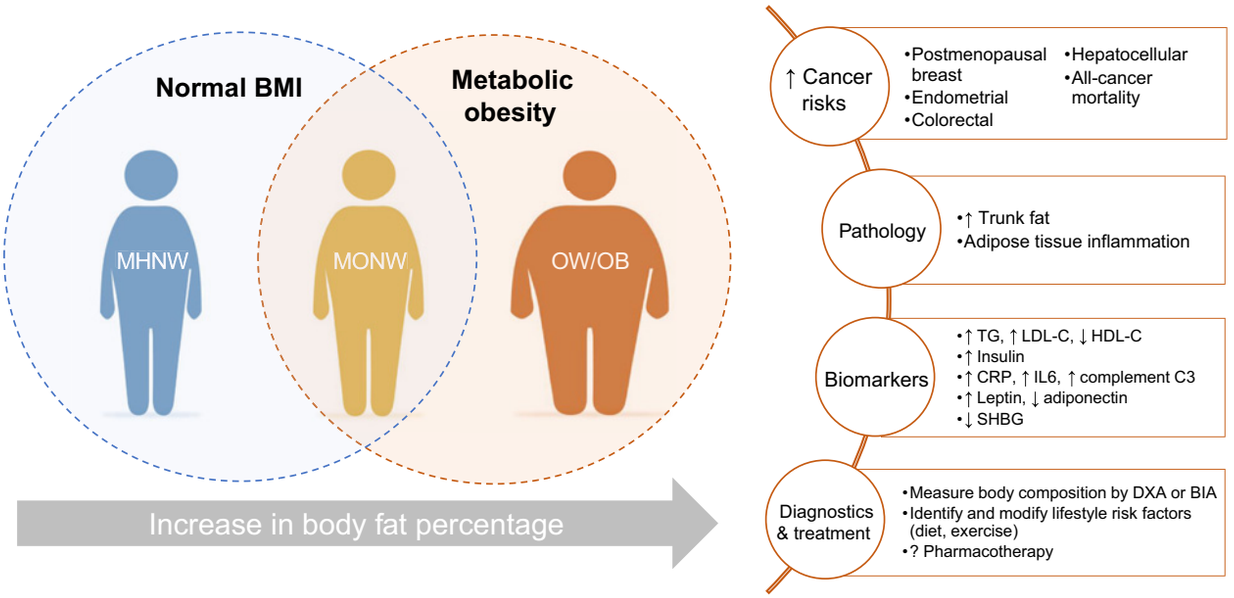

Figure 1.

Metabolic obesity in the normal weight and its clinical significance. Abbreviations: BMI, body mass index; MHNW, metabolically healthy normal weight; MONW, metabolically obese normal weight; OW/OB, overweight/obese; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; SHBG, sex hormone binding globulin; DXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis.

from many of these cancers (18, 19). Evidence from Mendelian randomization (MR) studies on obesity and cancer, which employ known genetic predictors of risk factors to seek evidence consistent with causal effect, has demonstrated significant associations between higher BMI and a number of obesity-related cancers (20). However, because most studies in this field have relied on BMI for defining obesity, the existing evidence has largely highlighted increased cancer risk in those with BMIs ≥ 30 kg/m^2. In individuals with normal BMI, increased adiposity has been associated with risk factors such as insulin resistance, dyslipidemia, and elevated inflammatory markers (11, 14, 15). In MONW populations, elevated cancer risk and increased all-cancer and all-cause mortality rates have been observed (**Table 1**; refs. 21–23).

Breast and endometrial cancers

A growing body of cancer research has focused on breast cancer risk in MONW women. Obesity increases the risk of estrogen receptor–positive (ER$^+$) breast cancer in postmenopausal women and is associated with higher rates of relapse and worse survival outcomes (19, 24). Interestingly, MR studies have shown genetically predicted BMI to be inversely associated with breast cancer risk regardless of menopausal status, a surprising finding that contradicts robust evidence from observational studies linking obesity to increased risk of postmenopausal ER$^+$ breast cancer. It is thought that genetically predicted BMI does not adequately account for the contribution of environmental and lifestyle factors to weight gain later in life, resulting in increased BMI and higher breast cancer risk among older women (20, 25).

Among normal weight women, elevated risks for breast cancer have been reported in association with excess body fat and metabolic abnormalities. Specifically, increased central adiposity has been associated with increased risk of postmenopausal breast cancer across ethnicities, although body composition measurement techniques and criteria for analysis have differed between studies (**Table 1**). Most have relied on operator-dependent techniques such as waist circumference (WC), waist-to-hip ratio (WHR), and skinfold thickness to approximate body composition (26–28). Consistent with these findings, a study of bioelectrical impedance analysis (BIA) of normal BMI UK Biobank subjects found that total body and trunk fat mass indices were positively associated with postmenopausal breast cancer risk (29). In another recent study, using dual-energy X-ray absorptiometry (DXA) to objectively quantify fat mass in a cohort of postmenopausal women with normal BMI, Iyengar and colleagues found that whole-body and trunk fat mass in the upper two quartiles were associated with significantly elevated risks for invasive ER$^+$ breast cancer (7). Whether MONW patients are at increased risk for other subtypes of breast cancer remains to be investigated. Increased trunk fat in these groups was also associated with elevated levels of insulin and triglycerides (TG), and lower high-density lipoprotein cholesterol (HDL-C), reflecting the presence of metabolic dysfunction in these women (7). Research has also shown that, in the absence of documented excess body

Downloaded from cancerpreventionresearch.aacrjournals.org on May 17, 2021. © 2021 American Association for Cancer Research.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1940-6207.CAPR-20-0633

Table 1. MONW and associated cancer risks.

Cancer Type	Cohort		MONW Parameters	Adiposity Measures	Cancer risk, MONW vs. MHNW	Reference
	Name	Characteristics				
Breast cancer, postmenopausal	Women's Health Initiative (USA)	3,460 NW F	BMI 18.5–24.9 kg/m^2 Upper quartiles total fat mass (>22 kg), trunk fat mass (>9.3 kg)	DXA	Q4 vs. Q1 Total fat mass [HR = 1.89 (1.21–2.95)] Trunk fat mass [HR = 1.88 (1.18–2.98)]	Iyengar et al. (2019)
	The Sister Study (USA)	43,599 F (16619 NW)	BMI < 25 kg/m^2 ≥ 1 metabolic abnormality	WC, WHR	≥1 metabolic abnormality [HR = 1.26 (1.01–1.56)] WC ≥ 88 cm [HR = 1.58 (1.02–2.46)]	Park et al. (2017)
	UK Biobank (UK)	149,928 NW (52,729 analyzed)	BMI 18.5–24.9 kg/m^2, BIA adiposity measures, WC, WHR	BIA, WC, WHR	Q5 vs. Q1 FMI [HR = 1.46 (1.20–1.78)]; TFMI [HR = 1.57 (1.20–1.80)]; WC [HR = 1.32 (1.09–1.60)]	Arthur et al. (2020)
	Women's Health Initiative (USA)	3,327 F	BMI 18.5–24.9 kg/m^2 Upper quartiles fasting insulin Upper quartiles HOMA-IR	–	Q3+4 vs. Q1 Fasting insulin [HR = 2.06 (1.01–4.22)] HOMA-IR [HR = 1.80 (0.88–3.70)]	Gunter et al. (2015)
Breast cancer	Nigerian Breast Cancer Study (Nigeria)	2,334 F (1,209 NW)	BMI < 25 kg/m^2 WHR top quartile (> 0.87)	WC, WHR	WHR Q4 vs. Q1 [OR = 2.81 (1.90–4.16)] WC > 81 cm [OR = 1.91 (1.39–2.61)]	Ogundiran et al. (2012)
Endometrial cancer	Alberta Cancer Registry (Canada)	1,477 F (406 NW)	BMI < 25 kg/m^2, MetS	WC	WC > 88 cm [OR = 5.09 (1.04–24.95)]	Friedenreich et al. (2011)
	UK Biobank (UK)	149,928 NW (77,738 analyzed)	BMI 18.5–24.9 kg/m^2, BIA adiposity measures, WC, WHR	BIA, WC, WHR	Trunk fat mass index Q5 vs. Q1 [HR = 1.72 (1.02–2.89)]	Arthur et al. (2020)
Colorectal cancer	EPIC Study (Europe)	1,474 (790 M, 684 F; 523 NW)	BMI < 25 kg/m^2 C-peptide top tertile (>4.74 ng/mL)	WC	C-peptide T3: CRC [HR = 1.59 (1.10–2.28)]; Colon [HR = 1.49 (0.92–2.43)]; Rectal [HR = 1.82 (1.02–3.23)] WC ≥ 80 cm F or ≥ 94 cm M: CRC [HR = 1.35 (0.95–1.91)]; Colon [HR = 1.18 (0.74–1.88)]; Rectal [HR = 1.76 (1.01–3.05)]	Murphy et al. (2016)
	Women's Health Initiative (USA)	21,170 F (5,175 NW)	BMI 18.5–< 25 kg/m^2, MetS	WC	CRC [HR = 1.65 (0.99–2.74)] Colon [HR = 1.79 (1.02–3.12)]	Kabat et al. (2018)
	UK Biobank (UK)	149,928 NW (149,928 analyzed)	BMI 18.5–24.9 kg/m^2, BIA adiposity measures, WC, WHR	BIA, WC, WHR	Men only: CRC, trunk to leg fat mass Q5 vs. Q1 [HR = 1.63 (1.14–2.32)] Colon, trunk to leg fat mass Q5 vs. Q1 [HR = 1.92 (1.20–3.07)] Colon, WC Q5 vs. Q1 [HR = 1.68 (1.05–2.66)] No significant associations among women	Arthur et al. (2020)
Primary liver cancer (HCC and ICC)	Liver Cancer Pooling Project (North America)	1,167,244 (707,281 F, 457,755 M; 338,070 NW)	BMI 18.5–< 25 kg/m^2 WC, WHR	WC	WC per 5-cm increase [HR = 1.14 (1.07–1.21)]	Florio et al. (2020)
Prostate cancer	National Health Check-ups Database (Korea)	11,771,252 M (7,391,410 NW)	BMI < 25 kg/m^2, MetS	WC	HR = 1.14 (1.12–1.17)	Kim et al. (2019)

Abbreviations: MONW, metabolic obesity in the normal weight; MHNW, metabolically healthy normal weight; HCC, hepatocellular cancer; ICC, intrahepatic cholangiocarcinoma; EPIC, European Prospective Investigation into Cancer and Nutrition; NW, normal weight; F, female; M, male; BMI, body mass index; BIA, bioelectrical impedance analysis; WC, waist circumference; WHR, waist-to-hip ratio; HOMA-IR, homeostasis model assessment of insulin resistance; MetS, metabolic syndrome; DXA, dual energy X-ray absorptiometry; FMI, fat mass index; TFMI, trunk fat mass index; CRC, colorectal cancer.

Downloaded from cancerpreventionresearch.aacrjournals.org on May 17, 2021. © 2021 American Association for Cancer Research.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1940-6207.CAPR-20-0633

fat, normal weight women with one or more cardiometabolic abnormalities associated with metabolic syndrome (MetS) had a higher risk of developing postmenopausal breast cancer (28). These findings are consistent with an earlier study that demonstrated increased postmenopausal breast cancer risk among normal-BMI women with relatively elevated fasting insulin levels, while those with lower fasting insulin were not found to have increased risk regardless of weight status (30). Whether MONW also raises the risk of premenopausal breast cancer is less clear, with some studies reporting significant associations (26, 27, 31) while others have not (28). Consistent with the link between MONW and ER^+ breast cancer, there is also emerging evidence of an increased risk of endometrial cancer, another hormonally driven cancer (29, 32).

Colorectal cancer

Observational and MR studies have demonstrated that many malignancies associated with obesity are of gastrointestinal origin, including colorectal, esophageal, liver, and pancreatic cancers, but limited research has been undertaken to understand them in the context of MONW (20, 33). Of these, colorectal cancer has been the best characterized in the MONW population (**Table 1**). While MONW was found to be associated with increased colorectal cancer risk in an analysis encompassing both men and women combined (8), a study using the Women's Health Initiative reported no significant associations among women (34). Another recent study reported positive associations between certain measures of central adiposity and risk of colorectal and colon cancer among men, but not among women (29). The evidence demonstrates an association between MONW and increased risk of colorectal cancer, with strong suggestion of sex dependence such that the association is stronger for males than females, and more specifically for colon than rectal cancer (29). Findings of sex differences have also been reported in the literature on obesity and colorectal cancer, with a stronger association between increased BMI and colorectal cancer reported in men than women (35).

Other malignancies

Although MONW has been found to increase the risk of nonalcoholic fatty liver disease and non-alcoholic steatohepatitis (36), investigation of its association with liver cancer, an obesity-associated malignancy, has been limited (37). One study found that central obesity, but not gluteofemoral size, conferred an increased risk of primary liver cancer in both overweight and normal weight individuals (38). MONW has also been shown to be associated with an increased risk of prostate cancer (9).

Associations between MONW and other obesity-related cancers have remained largely unexamined. Further research is needed to determine whether MONW is associated with higher risks of additional cancer types, including hematologic malignancies, and whether it affects clinical outcomes.

Pathophysiology of MONW and Cancer Development

Pathogenesis of MONW

Similar to that of obesity, the pathogenesis of MONW is rooted in the accumulation of excess body fat, leading to a state of metabolic dysregulation and chronic subclinical inflammation that is characterized by abnormal lipidomic, endocrinologic, and immune pathways (6, 7, 39). The physiology of adipose tissue is complex. White adipose tissue (WAT), which acts as a primary site for fat storage, exists underneath the skin as subcutaneous adipose tissue (SAT) or surrounding organs within the abdominal cavity as visceral adipose tissue (VAT). The amount and distribution of these distinct fat depots have substantial clinical implications, as increased VAT confers significantly greater cardiometabolic risk than SAT (40). The observation that some MONW individuals develop metabolic abnormalities without excessive weight gain suggests that different patterns of adipogenesis may underlie MONW pathophysiology in some individuals, leading to the onset of metabolic dysfunction at a lower BMI than observed in their obese counterparts.

Both genetic predisposition and lifestyle choices have been correlated with increased body fat percentages (BF%). The search for the genetic underpinnings of metabolic obesity has uncovered several genetic loci that appear to be implicated in MONW (41). On the basis of genome-wide association study (GWAS) findings, Yaghootkar and colleagues analyzed genetic risk scores for insulin resistance and identified 11 risk alleles in association with abnormal metabolic profiles in conjunction with normal BMI, a lipodystrophy-like phenotype seen in MONW (42, 43). This phenotype is characterized by higher VAT to SAT ratio, increased hepatic steatosis, elevated levels of TG and alanine transaminase, and decreased HDL-C, sex hormone binding globulin (SHBG), and adiponectin (42). The cluster includes common genetic variants involving genes such as *IRS1*, known to increase the risk of diabetes and CVD despite decreased body fat and SAT, and *PPARG*, a crucial regulator of adipocyte differentiation (42). Clinically, these risk alleles are associated with lower BMI but higher risks for cardiometabolic diseases, including type II diabetes mellitus, coronary artery disease, hypertension, and carotid plaque burden (42, 44).

Behavioral factors like lower physical activity levels have been associated with MONW (29, 45, 46). A limited number of studies that examined associations between dietary patterns and MONW have yielded inconsistent findings. Some studies have reported higher carbohydrate and red meat intake and lower fruit and vegetable consumption in MONW individuals compared with healthy controls (29, 47). However, others have reported no significant dietary differences (45, 48). These inconsistent findings likely reflect the challenge of capturing nuanced differences in eating habits given a limited sample size. Notably, many studies have reported small but significantly higher BMI in MONW groups compared with healthy normal BMI subjects (6, 45, 46, 48).

Downloaded from cancerpreventionresearch.aacrjournals.org on May 17, 2021. © 2021 American Association for Cancer Research.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1940-6207.CAPR-20-0633

Mechanisms of carcinogenesis

Growing evidence from the obesity literature has uncovered complex oncogenic mechanisms in the setting of increased adiposity. Such mechanisms are likely applicable to MONW given its overlapping pathophysiology with obesity. Adipose tissue dysfunction and metabolic dysregulation, present in both obesity and MONW, are thought to stimulate carcinogenesis through both local and systemic effects (49, 50). While a detailed review of biological mechanisms is beyond the scope of the present article, we provide below an overview of important factors to highlight the ways in which adiposity contributes to the development and progression of cancer (**Fig. 2**).

Insulin signaling

Insulin resistance is a characteristic feature of metabolic obesity. The resulting elevated levels of circulating insulin are associated with increased cancer risk, including breast, endometrial, colon, and urinary tract cancers (49, 51). MR analyses have further demonstrated genetically predicted higher fasting insulin levels to be associated with increased breast and endometrial cancer risk (25, 52). Insulin exerts mitogenic effects through a number of direct and indirect mechanisms. In addition to binding directly to the insulin receptor, it also increases the availability of insulin-like growth factor (IGF)-1 through upregulation of its synthesis and downregulation of IGF binding protein production (53). Binding of insulin and IGF-1 to their cell surface receptors, which have been shown to be overexpressed in human cancer cells, leads to activation of PI3K/Akt and Ras–Raf–MAPK, pathways known to regulate cell proliferation and play important roles in tumorigenesis and cancer progression (53–55). Insulin and IGF-1 have been shown to induce VEGF, an important mediator of angiogenesis (56). In addition, insulin has been shown to increase glucose oxidation and cell division in cell models of obesity-related tumors (colon, breast, and prostate cancers), while the same effects did not occur in tumors not associated with obesity (57). Elevated insulin levels also reduce hepatic SHBG synthesis, resulting in increased circulating levels of free sex steroid hormones that may additionally predispose to the development of hormone-dependent cancers (51).

Circulating adipokines

Higher leptin and lower adiponectin levels have been observed in metabolically obese individuals (49). Clinically, elevated leptin levels have been found by many studies to be associated with increased risks of postmenopausal breast, endometrial, and colorectal cancers, while others have demonstrated no significant associations (49, 51). Mechanistically, leptin has been shown to exert mitogenic and antiapoptotic effects via activation of the PI3K/Akt, MAPK/ERK, and JAK/STAT pathways in multiple cancer cell models, including breast, endometrial, colon, and androgen-independent prostate cancer (58–61). Leptin also induces VEGF and promotes angiogenesis (49). On the other hand, reduced adiponectin levels have been found to be associated with increased risk of the same cancers (62–64). Adiponectin has been shown to exert growth inhibitory, proapoptotic, anti-inflammatory, and anti-angiogenic effects (65–68). However, contrary to findings from observational studies, recent MR analyses identified no associations to support a causal relationship between genetically determined levels of adiponectin or leptin and the risk of developing five obesity-related cancers (colorectal, pancreatic, renal cell carcinoma, ovarian, and endometrial), highlighting the need for further investigation of the complex roles adipokines may play in cancer biology (69).

Estrogen

The role of estrogen in the development of postmenopausal ER^+ breast cancer and endometrial cancer is well-documented among obese women and supported by evidence from MR analyses (20, 70). Estrogen production occurs through aromatase-mediated conversion of androgens, a process that takes place primarily in the ovary in premenopausal women. Following menopause, adipose tissue acts as a significant site for estrogen production. In metabolically obese individuals, increased adiposity and insulin resistance contribute to elevated free circulating estrogen levels through increased peripheral conversion of androgen to estrogen and reduced blood levels of SHBG (49, 51). The tumor-promoting effects of estrogen are mediated by complex mechanisms and crosstalk between signaling pathways involving insulin/IGF-1, adipokines, and inflammatory mediators. Estrogen promotes cell proliferation and inhibits apoptosis via direct agonism of estrogen receptor-α, and stimulates angiogenesis via VEGF induction (71, 72).

Inflammation

Inflammation is well-documented to occur in obesity and is associated with an increased risk of cancer (51). Inflammatory markers such as C-reactive protein (CRP) and IL6 have been shown by MR studies to potentially increase the risk of colorectal cancer and liver cancer, respectively (20). Under physiologic conditions, adipocytes and stromal vascular cells in adipose tissue play key roles in lipid storage, energy metabolism, and immune function. In obesity, and presumably in MONW, adipocyte hypertrophy leads to the development of cell hypoxia, injury, and eventual adipocyte death, resulting in adipose tissue inflammation (73). Elevated circulating levels of high-sensitivity CRP (hsCRP) and IL6 occur in individuals with increased adiposity, including in postmenopausal women with MONW (7, 70, 74). Interactions between adipocytes and surrounding inflammatory cells are believed to play a role in promoting tumorigenesis. In particular, the presence of crown-like structures (CLS), a histologic biomarker of obesity-related inflammation consisting of macrophages surrounding dead or dying adipocytes, have been associated with an increased risk of breast cancer (ref. 75; **Fig. 2**). Notably, CLS of the breast are associated with MONW (73). In the breast, the presence of CLS is associated with increased levels of aromatase, the rate-limiting enzyme for estrogen biosynthesis. Proinflammatory mediators, including leptin, are known to induce aromatase (76).

Downloaded from cancerpreventionresearch.aacrjournals.org on May 17, 2021. © 2021 American Association for Cancer Research.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1940-6207.CAPR-20-0633

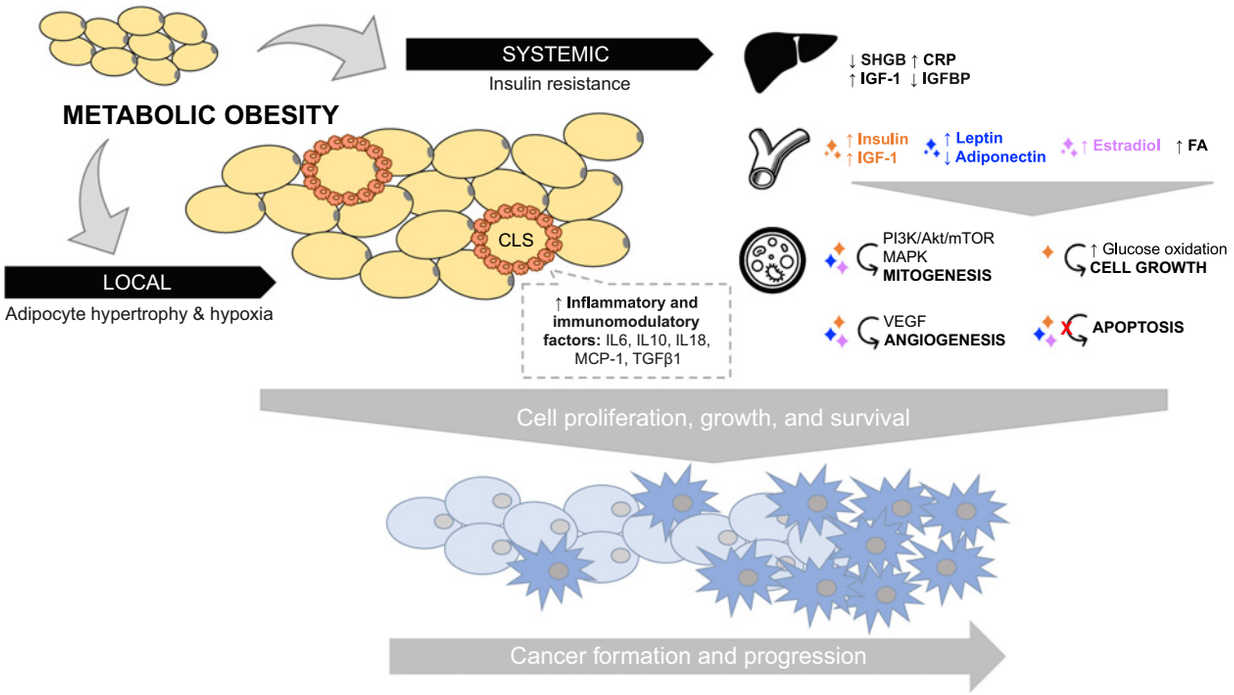

Figure 2.
Local and systemic effects of metabolic obesity and mechanisms for cancer promotion. Abbreviations: CLS, crown-like structures; MCP-1, monocyte chemoattractant protein-1; SHBG, sex hormone binding globulin; CRP, C-reactive protein; IGF-1, insulin-like growth factor-1; IGFBP, insulin-like growth factor binding protein; FA, fatty acids.

Diagnostic Strategies

Body composition measurements

Given the link between altered quantities and distribution of body fat and disease predisposition, the ability to detect increased adiposity in a normal weight individual is crucial for identifying those at risk of adverse health outcomes. Methods for measuring body composition range from anthropometric indices to more advanced technologies, such as BIA, and imaging modalities such as DXA, CT, and MRI (**Fig. 3**).

While CT and MRI provide the most detailed body composition data, including accurate quantifications of SAT and VAT, the high cost of these modalities and the radiation exposure associated with CT imaging limit their use for routine screening. Anthropometric measurements, most commonly WC, WHR, and skinfold thickness, incur negligible cost, are radiation-free, and can be easily obtained during an outpatient visit, but offer only a rough approximation of adiposity status. While WC and WHR are better predictors of health outcomes than BMI (77), their efficacy is heavily dependent on the site of measurement and their precision is limited by inter-operator variability (78).

More objective modalities for body composition measurement include BIA and DXA. BIA is a radiation-free technology that estimates total BF% and fat-free mass by differentiating between nonconductive (fat) and conductive tissues (muscle and bone). BIA measurements are low-cost and can be conveniently performed at the point of care, although the equipment may cost more than $5,000. The reliability of BIA measurements is affected by shifts in water-electrolyte balance, which limits BIA's use in individuals with altered volume status (79).

DXA, readily available at many facilities for routine osteoporosis screening, utilizes X-rays emitted at two energy levels to quantify fat and lean tissue. If equipped with the appropriate computer software, DXA can reliably provide body composition measurements on both whole-body and regional levels, including total fat%, trunk fat%, total fat mass, and trunk fat mass (79). While DXA software can estimate VAT, its ability to discriminate between different types of fat (i.e., visceral, subcutaneous and intramuscular) is less precise than that of CT or MRI (79). However, the radiation exposure from DXA is minimal compared with that from CT. The effective radiation dose from one whole-body DXA scan is under 10 microSieverts, about the same as background radiation at sea level for one day (80). A whole-body scan may cost up to several hundred dollars and would require referral to a facility with DXA equipped to assess body composition.

Blood-based Biomarkers

Lipid and glycemic profiles

Although the presence of dyslipidemia and insulin resistance is well-documented in MONW individuals, the search for a

Downloaded from cancerpreventionresearch.aacrjournals.org on May 17, 2021. © 2021 American Association for Cancer Research.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1940-6207.CAPR-20-0633

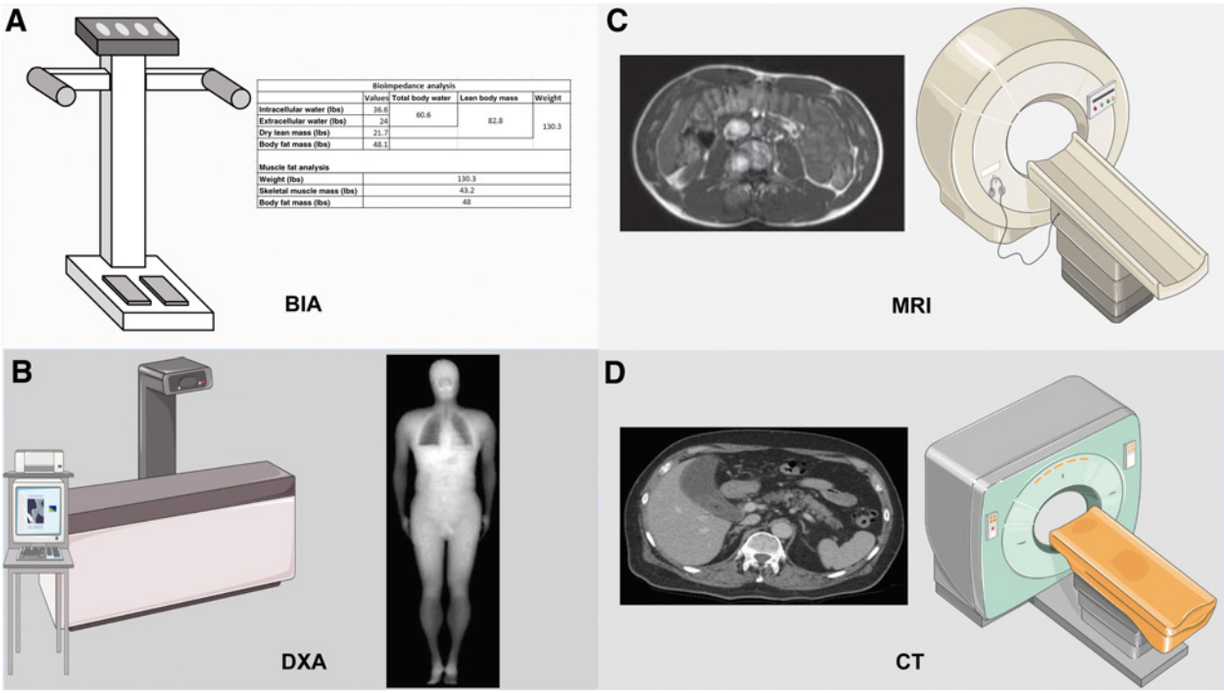

Figure 3.

Methods of body composition measurement and their diagnostic outputs. **A,** BIA with mock report of body composition data. **B,** DXA machine and a whole-body DXA scan. **C,** MRI machine and an axial abdominal MRI scan. **D,** CT Imager with axial abdominal CT scan. Abbreviations: BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry.

sensitive, specific, and clinically feasible test to identify MONW remains a challenge. For research purposes, studies have frequently relied on components of MetS as indices of cardiometabolic health. Wildman and colleagues proposed the addition of CRP and insulin resistance to the MetS criteria in the evaluation of metabolic obesity, defined as the presence of two or more of these components (81).

The sensitivity and specificity of these criteria are not well characterized and may depend on the ethnicity, sex, and for women, the menopausal status of the individual. Current evidence demonstrates that a relative increase in central adiposity among normal BMI postmenopausal women is associated with higher risks for cardiovascular disease and breast cancer (6, 7). While those with relatively high levels of central adiposity were found to have altered lipid profiles, glycemic traits, and CRP levels, only a subset would meet the thresholds defined by MetS and Wildman's criteria (6, 7). Whether these existing criteria can effectively identify normal BMI individuals at risk for adverse long-term health outcomes requires further investigation.

Inflammatory markers and adipokines

In MONW, a proinflammatory state similar to that seen in obesity has been observed. Elevated blood levels of numerous inflammatory biomarkers, including CRP and hsCRP (6, 7, 82, 83), IL6 (6, 7, 84), TNFα (84), complement C3 (82), white blood cell count (7), and ferritin (85), have been reported in MONW individuals across ethnicities. CRP, IL6, and C3 have additionally been shown to be positively correlated with excess central adiposity in MONW individuals (6, 7, 82, 83).

Alterations in plasma adipokine levels have also been observed in MONW individuals, including decreased adiponectin (6, 7, 84, 86, 87) and increased leptin (6, 7, 84). While the precise criteria for defining MONW vary across studies, changes in adiponectin and leptin levels have been consistently associated with increased adiposity.

Treatments and Interventions

Lifestyle and pharmacologic interventions

While studies have demonstrated associations between behavioral risk factors and adverse health outcomes in MONW individuals (45–47), clinical trials of interventions within this population remain limited. There is emerging evidence that weight reduction may be effective in improving body composition and metabolic function in nonobese individuals (88). A noncontrolled trial of 11 MONW East Asian subjects showed a diet-induced 5% weight loss led to significant decreases in total fat mass, VAT and SAT volumes, and intrahepatic fat (89). Weight reduction was also associated with improvements in lipid and metabolic profiles, with decreases in total cholesterol, TG, and LDL-C, and increases in insulin sensitivity and postprandial insulin clearance rate (89).

Downloaded from cancerpreventionresearch.aacrjournals.org on May 17, 2021. © 2021 American Association for Cancer Research.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1940-6207.CAPR-20-0633

Pharmacologic agents are increasingly prescribed for obese patients who are unable to achieve adequate weight loss through lifestyle changes alone. However, little is known about their efficacy in reducing body fat or mitigating adverse health outcomes in the MONW population. Furthermore, the safety profile and therapeutic index would need to be established in this patient population.

Discussion

Defining the problem

MONW is gaining recognition as a clinically significant condition associated with a growing number of adverse health outcomes, including cancer. Raising awareness among both clinicians and patients about the negative health impacts of MONW should be made a public health priority in areas with relatively high prevalence. Additional efforts to educate the public about metabolic obesity and increased cancer risk, a lesser-known health consequence than CVD, may be beneficial. While MONW has been found to be associated with higher risks of developing postmenopausal breast, colorectal, primary liver, and endometrial cancers (**Table 1**), further research is needed to evaluate MONW as a potential risk factor for other malignancies associated with obesity, such as esophageal adenocarcinoma, renal cell carcinoma, and multiple myeloma, among others. MONW has been found to correlate with increased risk of all-cancer mortality (22, 23), but there are currently no data on whether MONW affects treatment response, recurrence, or cancer-specific survival. Additional research is needed to characterize the full scope of MONW's potential effects on cancer outcomes and determine possible benefits for additional management considerations for patients with cancer with MONW, such as tight glycemic control.

In all likelihood, the mechanisms underlying obesity-related tumor development will be directly relevant to MONW-associated cancers. Evidence from GWAS studies points to a possible genetic basis for the MONW phenotype. Further investigation of the genetic underpinnings of MONW may elucidate its pathophysiology and mechanisms of cancer development. It is conceivable that a greater understanding of mechanism will provide the basis for risk-reducing pharmacological interventions that may complement behavioral approaches.

Challenges in diagnosis

Despite its serious health consequences, MONW remains under-recognized in the clinical setting. The standard practice of relying upon BMI for risk stratification continues to provide false reassurance when evaluating normal weight patients, even though clinicians are aware of BMI's limitations. The heterogeneity of definitions used in the study of MONW has made diagnosing the condition a challenge. Although criteria differ across studies, they can be broadly classified into those that define MONW by increased adiposity and those that are based on indices of metabolic dysfunction. Existing evidence demonstrates these two elements of MONW to be highly correlated; therefore, the presence of increased central adiposity or cardiometabolic abnormality in a normal BMI individual should raise clinical suspicion for MONW.

A standardized definition for MONW is needed to more accurately determine the prevalence of the condition. Further research is required to determine ethnicity- and sex-specific cut-off points for metabolic and inflammatory biomarkers as well as DXA- and BIA-derived measures of adiposity that will help to establish a diagnosis of MONW. Observational cohorts such as the UK Biobank and the Women's Health Initiative have contributed valuable baseline data on body composition, blood analytes, and clinical parameters from large samples of normal weight individuals. However, most MONW studies using such data have relied on intracohort comparisons of adiposity (e.g., top vs. bottom quartiles) to identify associations between indices of MONW and cancer risk. Such analyses result in cohort-specific cut-off points with limited generalizability.

While observational studies have led to the identification of blood biomarkers of MONW such as insulin and CRP, new "omics"-based technologies may vastly expand the scope of novel biomarker discovery to include genomic, epigenomic, transcriptomic, proteomic, metabolomic, and microbiota analyses. Analyses of existing observational cohort biobanks may prove useful in this discovery effort.

Ideally, large-scale prospective cohort studies would enable the development of a common definition for MONW. A possible next step to moving forward with establishing a consensus definition of MONW may be to convene a panel of experts to outline standardized diagnostic criteria for MONW. Precedents for the use of expert panels in establishing clinical criteria include BMI classifications for obesity and NCEP ATP III criteria for metabolic syndrome.

Beyond the lack of standardized criteria for diagnosing MONW, additional unmet challenges limit the widespread recognition of MONW in the clinical setting. The costs associated with DXA will be prohibitive for many in the absence of insurance reimbursement for testing, though BIA offers a viable cost-effective alternative. In addition, given the current absence of effective interventions to treat MONW, further research is needed to identify useful therapeutic approaches. In the absence of proven interventions, simply making the diagnosis of MONW brings little clinical benefit.

Future directions in treatment

Treatment strategies studied in the context of obesity, including lifestyle interventions and pharmacotherapies, should be tested in the MONW population. Among healthy nonobese subjects, daily caloric restriction has been found to reduce CVD risk as well as VAT, SAT, and intramyocellular lipid content (88). A small trial in MONW individuals has shown diet-induced weight loss to result in a reduction in body fat and improvement in clinical parameters (89). However, there are currently no data from larger-scale long-term studies to verify these findings in MONW subjects, though a trial evaluating the effects of caloric restriction has been initiated

Downloaded from cancerpreventionresearch.aacrjournals.org on May 17, 2021. © 2021 American Association for Cancer Research.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1940-6207.CAPR-20-0633

(ClinicalTrials.gov Identifier: NCT03239782). Many dietary approaches have been found to improve body composition in obese subjects, including low-energy, low-fat, low-carbohydrate, high-protein, ketogenic, and whole food plant-based diets (90–92). Intermittent fasting, a caloric restriction paradigm comprising variants of alternating fasting and feeding periods, has recently gained recognition for its potential efficacy in reducing multiple cardiometabolic risk factors, including lowering blood pressure and improving insulin resistance (93, 94). Whether these benefits are translatable to MONW remains to be tested.

Higher muscle mass is known to be protective against CVD and cancer mortality (95, 96). Therefore, the preservation of total-body lean mass should be prioritized in any MONW therapy. Dietary interventions may be designed to maximize muscle retention, such as increasing protein intake and maintaining a slower rate of weight reduction (90). Studies in overweight and obese populations have shown that exercise in conjunction with dietary changes can increase loss of fat mass, with resistance training resulting in higher preservation of lean mass than aerobic training (97). High-intensity interval training and medium-intensity continuous training have also been found to reduce whole-body fat mass without significant loss of lean mass or changes in body weight (98).

Medications that induce weight loss in obese individuals have yet to be studied in MONW cohorts. Oral antihyperglycemic agents like metformin, sodium-coupled glucose transporter 2 inhibitors, and glucagon-like peptide-1 receptor agonists have been shown to significantly reduce body fat mass but with mixed data on their effects on lean mass reduction (99–101). FDA-approved weight loss medications may be effective, but their significant side effect profiles may outweigh any potential benefits for the MONW population.

Conclusion

MONW is an underdiagnosed condition that significantly increases cancer risk among individuals with normal BMI. Increased awareness of MONW among both healthcare providers and the at-risk demographic is necessary if the long-term morbidity and mortality associated with it are to be reduced. Importantly, future research is needed to establish standardized diagnostic criteria and measure the effectiveness of different lifestyle and pharmacologic interventions in improving body composition and mitigating adverse health outcomes in MONW populations, including the development of MONW-associated cancers. Hopefully, increased awareness of MONW and its complications will lead to an enhanced effort to develop interventions to effectively reduce the risk of preventable life-threatening diseases.

Authors' Disclosures

No disclosures were reported.

Acknowledgments

This work was supported by the Breast Cancer Research Foundation (BCRF-19–034, to A.J. Dannenberg; BCRF-19–140, to T.E. Rohan), and NCI U54 CA210184 (to A.J. Dannenberg). B. Liu conducted this research as part of the Area of Concentration (AOC) Program of the Weill Cornell MD Curriculum.

Received December 7, 2020; revised January 25, 2021; accepted February 3, 2021; published first February 9, 2021.

References

1. Rothman KJ. BMI-related errors in the measurement of obesity. Int J Obes 2008;32:S56–9.
2. Appropriate body-mass index for asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–63.
3. Ruderman NB, Schneider SH, Berchtold P. The "metabolically-obese," normal-weight individual. Am J Clin Nutr 1981;34:1617–21.
4. Stefan N, Schick F, Häring H-U. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab 2017;26:292–300.
5. Franco LP, Morais CC, Cominetti C. Normal-weight obesity syndrome: diagnosis, prevalence, and clinical implications. Nutr Rev 2016;74:558–70.
6. Chen G-C, Arthur R, Iyengar NM, Kamensky V, Xue X, Wassertheil-Smoller S, et al. Association between regional body fat and cardiovascular disease risk among postmenopausal women with normal body mass index. Eur Heart J 2019;40:2849–55.
7. Iyengar NM, Arthur R, Manson JE, Chlebowski RT, Kroenke CH, Peterson L, et al. Association of body fat and risk of breast cancer in postmenopausal women with normal body mass index: a secondary analysis of a randomized clinical trial and observational study. JAMA Oncol 2019;5:155–63.
8. Murphy N, Cross AJ, Abubakar M, Jenab M, Aleksandrova K, Boutron-Ruault M-C, et al. A nested case-control study of metabolically defined body size phenotypes and risk of colorectal cancer in the european prospective investigation into cancer and nutrition (EPIC). PLoS Med 2016;13:e1001988.
9. Kim JW, Ahn ST, Oh MM, Moon DG, Han K, Park HS. Incidence of prostate cancer according to metabolic health status: a nationwide cohort study. J Korean Med Sci 2019;34:e49.
10. Marques-Vidal P, Pécoud A, Hayoz D, Paccaud F, Mooser V, Waeber G, et al. Prevalence of normal weight obesity in Switzerland: effect of various definitions. Eur J Nutr 2008;47:251.
11. Kim MK, Han K, Kwon H-S, Song K-H, Yim HW, Lee W-C, et al. Normal weight obesity in Korean adults. Clin Endocrinol (Oxf) 2014;80:214–20.
12. Wulan SN, Westerterp KR, Plasqui G. Ethnic differences in body composition and the associated metabolic profile: A comparative study between Asians and Caucasians. Maturitas 2010;65:315–9.
13. Rush EC, Freitas I, Plank LD. Body size, body composition and fat distribution: comparative analysis of European, Maori, Pacific Island and Asian Indian adults. Br J Nutr 2009;102:632–41.
14. Romero-Corral A, Somers VK, Sierra-Johnson J, Korenfeld Y, Boarin S, Korinek J, et al. Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. Eur Heart J 2009;31:737–46.
15. Marques-Vidal P, Pécoud A, Hayoz D, Paccaud F, Mooser V, Waeber G, et al. Normal weight obesity: relationship with lipids, glycaemic

Downloaded from cancerpreventionresearch.aacrjournals.org on May 17, 2021. © 2021 American Association for Cancer Research.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1940-6207.CAPR-20-0633

status, liver enzymes and inflammation. Nutr Metab Cardiovasc Dis 2010;20:669–75.
16. De Lorenzo A, Martinoli R, Vaia F, Di Renzo L. Normal weight obese (NWO) women: An evaluation of a candidate new syndrome. Nutr Metab Cardiovasc Dis 2006;16:513–23.
17. Guerrero-Romero F, Rodriguez-Moran M. Serum magnesium in the metabolically-obese normal-weight and healthy-obese subjects. Eur J Intern Med 2013;24:639–43.
18. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer—viewpoint of the iarc working group. N Engl J Med 2016;375:794–8.
19. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–38.
20. Pierce BL, Kraft P, Zhang C. Mendelian randomization studies of cancer risk: a literature review. Curr Epidemiol Rep. 2018/05/18 ed. 2018;5:184–96.
21. Sahakyan KR, Somers VK, Rodriguez-Escudero JP, Hodge DO, Carter RE, Sochor O, et al. Normal-weight central obesity: implications for total and cardiovascular mortality. Ann Intern Med 2015;163:827–35.
22. Zhang C, Rexrode KM, van Dam RM, Li TY, Hu FB. Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality. Circulation 2008;117:1658–67.
23. Sun Y, Liu B, Snetselaar LG, Wallace RB, Caan BJ, Rohan TE, et al. Association of normal-weight central obesity with all-cause and cause-specific mortality among postmenopausal women. JAMA Netw Open 2019;2:e197337–.
24. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat 2010;123:627–35.
25. Shu X, Wu L, Khankari NK, Shu X-O, Wang TJ, Michailidou K, et al. Associations of obesity and circulating insulin and glucose with breast cancer risk: a Mendelian randomization analysis. Int J Epidemiol 2019;48:795–806.
26. Ogundiran TO, Huo D, Adenipekun A, Campbell O, Oyesegun R, Akang E, et al. Body fat distribution and breast cancer risk: findings from the Nigerian breast cancer study. Cancer Causes Control 2012;23:565–74.
27. Ronco A, Boeing H, Schulz M, Schulze M, Pischon T. A case-control study on fat-to-muscle ratio and risk of breast cancer. Nutr Cancer 2009;61:466–74.
28. Park Y-MM, White AJ, Nichols HB, O'Brien KM, Weinberg CR, Sandler DP. The association between metabolic health, obesity phenotype and the risk of breast cancer. Int J Cancer 2017;140:2657–66.
29. Arthur RS, Dannenberg AJ, Kim M, Rohan TE. The association of body fat composition with risk of breast, endometrial, ovarian and colorectal cancers among normal weight participants in the UK Biobank. Br J Cancer 2020.
30. Gunter MJ, Xie X, Xue X, Kabat GC, Rohan TE, Wassertheil-Smoller S, et al. Breast cancer risk in metabolically healthy but overweight postmenopausal women. Cancer Res 2015;75:270.
31. His M, Biessy C, Torres-Mejía G, Ángeles-Llerenas A, Alvarado-Cabrero I, Sánchez GI, et al. Anthropometry, body shape in early-life and risk of premenopausal breast cancer among Latin American women: results from the PRECAMA study. Sci Rep 2020;10:2294.
32. Friedenreich CM, Biel RK, Lau DCW, Csizmadi I, Courneya KS, Magliocco AM, et al. Case–control study of the metabolic syndrome and metabolic risk factors for endometrial cancer. Cancer Epidemiol Biomark Amp Prev 2011;20:2384.
33. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579–91.
34. Kabat GC, Kim MY, Stefanick M, Ho GYF, Lane DS, Odegaard AO, et al. Metabolic obesity phenotypes and risk of colorectal cancer in postmenopausal women. Int J Cancer 2018;143:543–51.
35. Abar L, Vieira AR, Aune D, Sobiecki JG, Vingeliene S, Polemiti E, et al. Height and body fatness and colorectal cancer risk: an update of the WCRF–AICR systematic review of published prospective studies. Eur J Nutr 2018;57:1701–20.
36. Tobari M, Hashimoto E, Taniai M, Ikarashi Y, Kodama K, Kogiso T, et al. Characteristics of non-alcoholic steatohepatitis among lean patients in Japan: Not uncommon and not always benign. J Gastroenterol Hepatol 2019;34:1404–10.
37. Sun B, Karin M. Obesity, inflammation, and liver cancer. J Hepatol 2012;56:704–13.
38. Florio AA, Campbell PT, Zhang X, Zeleniuch-Jacquotte A, Wactawski-Wende J, Smith-Warner SA, et al. Abdominal and gluteofemoral size and risk of liver cancer: The liver cancer pooling project. Int J Cancer 2020;147:675–85.
39. Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. The concept of normal weight obesity. Obes Obes Paradox Cardiovasc Dis 2014;56:426–33.
40. Cornier M-A, Després J-P, Davis N, Grossniklaus DA, Klein S, Lamarche B, et al. Assessing adiposity. Circulation 2011;124:1996–2019.
41. Huang LO, Loos RJF, Kilpeläinen TO. Evidence of genetic predisposition for metabolically healthy obesity and metabolically obese normal weight. Physiol Genomics 2017;50:169–78.
42. Yaghootkar H, Scott RA, White CC, Zhang W, Speliotes E, Munroe PB, et al. Genetic evidence for a normal-weight "metabolically obese" phenotype linking insulin resistance, hypertension, coronary artery disease, and type 2 diabetes. Diabetes 2014;63:4369.
43. Kilpeläinen TO, Zillikens MC, Stančáková A, Finucane FM, Ried JS, Langenberg C, et al. Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. Nat Genet 2011;43:753–60.
44. Yaghootkar H, Lotta LA, Tyrrell J, Smit RAJ, Jones SE, Donnelly L, et al. Genetic evidence for a link between favorable adiposity and lower risk of type 2 diabetes, hypertension, and heart disease. Diabetes 2016;65:2448–60.
45. Conus F, Allison DB, Rabasa-Lhoret R, St-Onge M, St-Pierre DH, Tremblay-Lebeau A, et al. Metabolic and behavioral characteristics of metabolically obese but normal-weight women. J Clin Endocrinol Metab 2004;89:5013–20.
46. Eckel N, Mühlenbruch K, Meidtner K, Boeing H, Stefan N, Schulze MB. Characterization of metabolically unhealthy normal-weight individuals: Risk factors and their associations with type 2 diabetes. Metabolism 2015;64:862–71.
47. Choi J, Se-Young O, Lee D, Tak S, Hong M, Park SM, et al. Characteristics of diet patterns in metabolically obese, normal weight adults (korean national health and nutrition examination survey III, 2005). Nutr Metab Cardiovasc Dis 2012;22:567–74.
48. Dvorak RV, DeNino WF, Ades PA, Poehlman ET. Phenotypic characteristics associated with insulin resistance in metabolically obese but normal-weight young women. Diabetes 1999;48:2210.
49. Hursting SD, DiGiovanni J, Dannenberg AJ, Azrad M, LeRoith D, Demark-Wahnefried W, et al. Obesity, energy balance, and cancer: new opportunities for prevention. Cancer Prev Res (Phila Pa) 2012;5:1260.
50. Quail DF, Dannenberg AJ. The obese adipose tissue microenvironment in cancer development and progression. Nat Rev Endocrinol 2019;15:139–54.
51. Gucalp A, Iyengar NM, Hudis CA, Dannenberg AJ. Targeting obesity-related adipose tissue dysfunction to prevent cancer development and progression. Mol Targets Cancer Prev 2016;43:154–60.

Downloaded from cancerpreventionresearch.aacrjournals.org on May 17, 2021. © 2021 American Association for Cancer Research.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1940-6207.CAPR-20-0633

52. Nead KT, Sharp SJ, Thompson DJ, Painter JN, Savage DB, Semple RK, et al. Evidence of a causal association between insulinemia and endometrial cancer: a mendelian randomization analysis. J Natl Cancer Inst 2015;107:djv178.
53. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev Cancer 2008;8:915–28.
54. Wong K-K, Engelman JA, Cantley LC. Targeting the PI3K signaling pathway in cancer. Genet Cell Mech Oncog 2010;20:87–90.
55. Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. Nat Rev Mol Cell Biol 2011;12:21–35.
56. Miele C, Rochford JJ, Filippa N, Giorgetti-Peraldi S, Van Obberghen E. Insulin and insulin-like growth factor-I induce vascular endothelial growth factor mRNA expression via different signaling pathways. J Biol Chem 2000;275:21695–702.
57. Rabin-Court A, Rodrigues MR, Zhang X-M, Perry RJ. Obesity-associated, but not obesity-independent, tumors respond to insulin by increasing mitochondrial glucose oxidation. PLoS One 2019;14: e0218126.
58. Jardé T, Caldefie-Chézet F, Damez M, Mishellany F, Penault-Llorca F, Guillot J, et al. Leptin and leptin receptor involvement in cancer development: a study on human primary breast carcinoma. Oncol Rep 2008;19:905–11.
59. Sharma D, Saxena NK, Vertino PM, Anania FA. Leptin promotes the proliferative response and invasiveness in human endometrial cancer cells by activating multiple signal-transduction pathways. Endocr-Relat Cancer Endocr Relat Cancer 2006;13:629–40.
60. Hoda MR, Keely SJ, Bertelsen LS, Junger WG, Dharmasena D, Barrett KE. Leptin acts as a mitogenic and antiapoptotic factor for colonic cancer cells. BJS Br J Surg 2007;94:346–54.
61. Onuma M, Bub JD, Rummel TL, Iwamoto Y. Prostate cancer cell-adipocyte interaction: leptin mediates androgen-independent prostate cancer cell proliferation through c-jun NH2-terminal kinase. J Biol Chem 2003;278:42660–7.
62. Miyoshi Y, Funahashi T, Kihara S, Taguchi T, Tamaki Y, Matsuzawa Y, et al. Association of serum adiponectin levels with breast cancer risk. Clin Cancer Res 2003;9:5699.
63. Soliman PT, Wu D, Tortolero-Luna G, Schmeler KM, Slomovitz BM, Bray MS, et al. Association between adiponectin, insulin resistance, and endometrial cancer. Cancer 2006;106:2376–81.
64. XU XT, XU Q, TONG JL, ZHU MM, HUANG ML, RAN ZH, et al. Meta-analysis: Circulating adiponectin levels and risk of colorectal cancer and adenoma. J Dig Dis 2011;12:234–44.
65. Grossmann ME, Nkhata KJ, Mizuno NK, Ray A, Cleary MP. Effects of adiponectin on breast cancer cell growth and signaling. Br J Cancer 2008;98:370–9.
66. Cong Li, Gasser J, Zhao J, Yang B, Li F, Zhao AZ. Human adiponectin inhibits cell growth and induces apoptosis in human endometrial carcinoma cells, HEC-1-A and RL95–2. Endocr Relat Cancer 2007; 14:713–20.
67. Kim AY, Lee YS, Kim KH, Lee JH, Lee HK, Jang S-H, et al. Adiponectin represses colon cancer cell proliferation via AdipoR1- and -R2-mediated AMPK activation. Mol Endocrinol 2010;24:1441–52.
68. Bub JD, Miyazaki T, Iwamoto Y. Adiponectin as a growth inhibitor in prostate cancer cells. Biochem Biophys Res Commun 2006;340: 1158–66.
69. Dimou NL, Papadimitriou N, Mariosa D, Johansson M, Brennan P, Peters U, et al. Circulating adipokine concentrations and risk of five obesity-related cancers: A Mendelian randomization study. Int J Cancer 2021;148:1625–36.
70. Iyengar NM, Hudis CA, Dannenberg AJ. Obesity and cancer: local and systemic mechanisms. Annu Rev Med 2015;66:297–309.
71. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. N Engl J Med 2006;354:270–82.
72. Péqueux C, Raymond-Letron I, Blacher S, Boudou F, Adlanmerini M, Fouque M-J, et al. Stromal estrogen receptor-α promotes tumor growth by normalizing an increased angiogenesis. Cancer Res 2012; 72:3010–9.
73. Iyengar N, Brown K, Zhou X, Gucalp A, Subbaramaiah K, Giri D, et al. Metabolic obesity, adipose inflammation and elevated breast aromatase in women with normal body mass index. Cancer Prev Res 2017;10.
74. Brestoff JR, Artis D. Immune regulation of metabolic homeostasis in health and disease. Cell 2015;161:146–60.
75. Carter JM, Hoskin TL, Pena MA, Brahmbhatt R, Winham SJ, Frost MH, et al. Macrophagic "crown-like structures" are associated with an increased risk of breast cancer in benign breast disease. Cancer Prev Res 2018;11:113–9.
76. Catalano S, Marsico S, Giordano C, Mauro L, Rizza P, Panno ML, et al. Leptin enhances, via AP-1, expression of aromatase in the MCF-7 cell line. J Biol Chem 2003;278:28668–76.
77. Dobbelsteyn C, Joffres M, MacLean D, Flowerdew G., The Canadian Heart Health Surveys Research Group. A comparative evaluation of waist circumference, waist-to-hip ratio and body mass index as indicators of cardiovascular risk factors. the canadian heart health surveys. Int J Obes 2001;25:652–61.
78. Bosy-Westphal A, Booke C-A, Blöcker T, Kossel E, Goele K, Later W, et al. Measurement site for waist circumference affects its accuracy as an index of visceral and abdominal subcutaneous fat in a caucasian population. J Nutr 2010;140:954–61.
79. Ceniccola GD, Castro MG, Piovacari SMF, Horie LM, Corrêa FG, Barrere APN, et al. Current technologies in body composition assessment: advantages and disadvantages. Nutrition 2019;62:25–31.
80. Shepherd JA, Ng BK, Sommer MJ, Heymsfield SB. Body composition by DXA. Bone 2017;104:101–5.
81. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). Arch Intern Med 2008;168: 1617–24.
82. Karkhaneh M, Qorbani M, Mohajeri-Tehrani MR, Hoseini S. Association of serum complement C3 with metabolic syndrome components in normal weight obese women. J Diabetes Metab Disord 2017; 16:49–49.
83. Bednarek-Tupikowska G, Zdrojowy-Weøna A, Stachowska B, Kuliczkowska-Pøaksej J, Matczak-Giemza M, Kubicka E, et al. Accumulation of abdominal fat in relation to selected proinflammatory cytokines concentrations in non-obese wrocøaw inhabitants. accumul abdom fat relat sel proinflammatory cytokines conc non-obese wroc inhabitants. Endokrynologia 2014;65:449–55.
84. Hyun YJ, Koh SJ, Chae JS, Kim JY, Kim OY, Lim HH, et al. Atherogenecity of LDL and unfavorable adipokine profile in metabolically obese, normal-weight woman. Obesity 2008;16:784–9.
85. Kim J-W, Kim DH, Roh YK, Ju SY, Nam H-Y, Nam G-E, et al. Serum ferritin levels are positively associated with metabolically obese normal weight: a nationwide population-based study. Medicine 2015;94:e2335.
86. Katsuki A, Suematsu M, Gabazza EC, Murashima S, Nakatani K, Togashi K, et al. Decreased high–molecular weight adiponectin–to–total adiponectin ratio in sera is associated with insulin resistance in Japanese metabolically obese, normal-weight men with normal glucose tolerance. Diabetes Care 2006;29:2327.
87. Zachariah Justin P, Rene Q, Nelson Kerrie P, Zhaoyang T, Keaney John F, Sullivan Lisa M, et al. Prospective relation of circulating

Downloaded from cancerpreventionresearch.aacrjournals.org on May 17, 2021. © 2021 American Association for Cancer Research.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1940-6207.CAPR-20-0633

adipokines to incident metabolic syndrome: the framingham heart study. J Am Heart Assoc 2017;6:e004974.
88. Most J, Gilmore LA, Smith SR, Han H, Ravussin E, Redman LM. Significant improvement in cardiometabolic health in healthy non-obese individuals during caloric restriction-induced weight loss and weight loss maintenance. Am J Physiol Endocrinol Metab 2017;314: E396–405.
89. Chooi YC, Ding C, Chan Z, Choo J, Sadananthan SA, Michael N, et al. Moderate weight loss improves body composition and metabolic function in metabolically unhealthy lean subjects. Obesity 2018;26: 1000–7.
90. Aragon AA, Schoenfeld BJ, Wildman R, Kleiner S, VanDusseldorp T, Taylor L, et al. International society of sports nutrition position stand: diets and body composition. J Int Soc Sports Nutr 2017;14:16.
91. Gershuni VM, Yan SL, Medici V. Nutritional ketosis for weight management and reversal of metabolic syndrome. Curr Nutr Rep 2018;7:97–106.
92. Kahleova H, Fleeman R, Hlozkova A, Holubkov R, Barnard ND. A plant-based diet in overweight individuals in a 16-week randomized clinical trial: metabolic benefits of plant protein. Nutr Diabetes 2018; 8:58–58.
93. Gabel K, Varady KA. Current research: effect of time restricted eating on weight and cardiometabolic health. J Physiol 2020.
94. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. N Engl J Med 2019;381:2541–51.
95. Caan BJ, Cespedes Feliciano EM, Kroenke CH. The importance of body composition in explaining the overweight paradox in cancer-counterpoint. Cancer Res 2018;78:1906–12.
96. Srikanthan P, Horwich TB, Tseng CH. Relation of muscle mass and fat mass to cardiovascular disease mortality. Am J Cardiol 2016;117: 1355–60.
97. Beavers KM, Ambrosius WT, Rejeski WJ, Burdette JH, Walkup MP, Sheedy JL, et al. Effect of exercise type during intentional weight loss on body composition in older adults with obesity. Obesity 2017;25: 1823–9.
98. Wewege M, van den Berg R, Ward RE, Keech A. The effects of high-intensity interval training vs. moderate-intensity continuous training on body composition in overweight and obese adults: a systematic review and meta-analysis. Obes Rev 2017;18:635–46.
99. Feng W-H, Bi Y, Li P, Yin T-T, Gao C-X, Shen S-M, et al. Effects of liraglutide, metformin and gliclazide on body composition in patients with both type 2 diabetes and non-alcoholic fatty liver disease: a randomized trial. J Diabetes Investig 2019;10:399–407.
100. Yanovski JA, Krakoff J, Salaita CG, McDuffie JR, Kozlosky M, Sebring NG, et al. Effects of metformin on body weight and body composition in obese insulin-resistant children. Diabetes 2011;60:477.
101. Sargeant JA, Henson J, King JA, Yates T, Khunti K, Davies MJ. A review of the effects of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors on lean body mass in humans. Endocrinol Metab Seoul Korea 2019;34:247–62.

Downloaded from cancerpreventionresearch.aacrjournals.org on May 17, 2021. © 2021 American Association for Cancer Research.

Published OnlineFirst February 9, 2021; DOI: 10.1158/1940-6207.CAPR-20-0633

AACR American Association for Cancer Research

Cancer Prevention Research

Cancer Risk in Normal Weight Individuals with Metabolic Obesity: A Narrative Review

Bethina Liu, Hugh E. Giffney, Rhonda S. Arthur, et al.

Cancer Prev Res 2021;14:509-520. Published OnlineFirst February 9, 2021.

Updated version Access the most recent version of this article at: doi:10.1158/1940-6207.CAPR-20-0633

Cited articles This article cites 98 articles, 20 of which you can access for free at: http://cancerpreventionresearch.aacrjournals.org/content/14/5/509.full#ref-list-1

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link http://cancerpreventionresearch.aacrjournals.org/content/14/5/509. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.

Downloaded from cancerpreventionresearch.aacrjournals.org on May 17, 2021. © 2021 American Association for Cancer Research.