Published in final edited form as:

Cancer Prev Res (Phila). 2021 May ; 14(5): 509–520. doi:10.1158/1940-6207.CAPR-20-0633.

Cancer risk in normal-weight individuals with metabolic obesity: A narrative review

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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.

Keywords

adipose tissue; metabolism; obesity; cancer; body composition

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 (m²)) 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

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Conflict of interest disclosure: The authors declare no potential conflicts of interest

kg/m² for non-Asians and 18.5–22.9 kg/m² for Asians) who suffer from negative health consequences similar to those seen in the phenotypically overtly obese (≥30 kg/m² for non-Asians and ≥27.5 kg/m² for Asians) (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 underrecognized 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 (Figure 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 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/m². 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) (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 et al. 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 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 (CRC) has been the best characterized in the

MONW population (Table 1). While MONW was found to be associated with increased CRC 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 CRC, 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 CRC, with a stronger association between increased BMI and CRC reported in men than women (35).

Other Malignancies

Although MONW has been found to increase the risk of non-alcoholic 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 hematological 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). Based on genome-wide association study (GWAS) findings, Yaghootkar et al. 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 2 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 to 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).

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 (Figure 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 vascular endothelial growth factor (VEGF), an important mediator of angiogenesis (56). Additionally, 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 interleukin (IL)-6 have been shown by MR studies to potentially increase the risk of CRC 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 IL-6 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 histological biomarker of obesity-related inflammation consisting of macrophages surrounding dead or dying adipocytes, have been associated with an increased risk of breast cancer (75) (Figure 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. Pro-inflammatory mediators, including leptin, are known to induce aromatase (76).

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, computed tomography (CT), and magnetic resonance imaging (MRI) (Figure 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 non-conductive (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 \$5000. 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 to 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 are well-documented in MONW individuals, the search for a 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 et al. 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 CVD 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 pro-inflammatory 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), IL-6 (6,7,84), TNF- α (84), complement C3 (82), white blood cell count (7), and ferritin (85), have been reported in MONW individuals across ethnicities. CRP, IL-6, 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 Pharmacological 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 non-obese individuals (88). A non-controlled 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).

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 cancer patients 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 in order to more accurately determine the prevalence of the condition. Further research is required to determine ethnicity- and sex-

specific cut 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 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. Additionally, 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 non-obese 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 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03239782) Identifier: [NCT03239782](https://clinicaltrials.gov/ct2/show/study/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 anti-hyperglycemic 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.

Acknowledgements

Bethina Liu conducted this research as part of the Area of Concentration (AOC) Program of the Weill Cornell MD Curriculum.

Funding: This work was supported by the Breast Cancer Research Foundation (BCRF-19-034 to A.J.D.; BCRF-19-140 to T.E.R.), and NCI U54 CA210184 to A.J.D.

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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.

Figure 2.

Local and systemic effects of metabolic obesity and mechanisms for cancer promotion.

Abbreviations: CLS, crown-like structures; IL-6, interleukin-6; IL-10, interleukin-10; IL-18, interleukin-18; MCP-1, monocyte chemoattractant protein-1; TGF-β1, transforming growth factor-β1; 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; PI3K, phosphoinositide 3-kinase; VEGF, vascular endothelial growth factor.

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; MRI, magnetic resonance imaging; CT, computed tomography.

MONW and Associated Cancer Risks

Table 1.

Cancer Type	Cohort		MONW Parameters	Adiposity Measures	Cancer risk, MONW vs. MHNW	Reference
	Name	Characteristics				
Breast cancer, postmenopausal	Women's Health Initiative (USA)	3460 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 88cm [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)	3327 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)	2334 F (1209 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 > 88cm [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)
	EPIC Study (Europe)	1474 (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)
Colorectal cancer	Women's Health Initiative (USA)	21170 F (5175 NW)	BMI 18.5 to < 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)

Cancer Type	Cohort		MONW Parameters	Adiposity Measures	Cancer risk, MONW vs. MHNW	Reference
	Name	Characteristics				
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 to < 25 kg/m ² WC, WHR	WC	WC per 5cm increase [HR = 1.14 (1.07–1.21)]	Florio et al. (2019)
	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; HR, hazard ratio; OR, odds ratio; FMI, fat mass index; TFMI, trunk fat mass index; CRC, colorectal cancer.