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Commentary

Metabolic Dysregulation and Cancer Risk Program (MeDOC): a transdisciplinary approach to obesity-associated cancers

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Abstract

With the escalating prevalence of obesity, the association between obesity and cancer is a growing public health concern. Obesity will soon surpass tobacco smoking as the most important preventable cause of cancer. Obesity-driven mechanisms can alter cell functions to induce metabolic changes, chronic inflammation, and insulin resistance that are believed to contribute to cancer risk and development; yet the specific underlying biological mechanisms of obesity-related cancer development are largely unknown. The Metabolic Dysregulation and Cancer Risk Program: a transdisciplinary approach to obesity-associated cancers (MeDOC) is a trans–National Cancer Institute research initiative supported by the Division of Cancer Control and Population Sciences, the Division of Cancer Biology, the Division of Cancer Prevention, and the Center to Reduce Cancer Health Disparities. The overall purpose of the MeDOC Program is to advance our understanding of the underlying mechanisms that connect obesity, metabolic dysregulation, and increased obesity cancer risk as well as identify markers that will enhance cancer risk prediction, improve screening for high-risk individuals, and identify targets for preventive and therapeutic interventions for cancer interception or treatment. This report describes the funded research projects, the Coordinating Center, and the goals of the MeDOC program.

The obesity-cancer link is of pressing concern due to the escalating prevalence of obesity (ie, a state of chronic positive energy balance or an excess of body fat or body adiposity) (1,2). According to data from the 2016-2017 National Health and Nutrition Examination Survey, more than 70% of Americans are currently overweight or obese (1,3,4) and are at higher risk of common chronic diseases, including diabetes, cardiovascular disease, and many types of cancer (5,6). Moreover, considerable differences in obesity rates exist by race, ethnicity, socioeconomic status, and geographical region (7) that may contribute to some of the health disparities and disproportionate burden of cancers observed in racial and ethnic minority groups (4,8-10).

The increased risk of at least 13 different cancers are associated with obesity (11), and emerging data link obesity to the early onset of certain cancers (12). Obesity-driven mechanisms that lead to alterations in normal metabolic functioning rather than adiposity or obesity itself are thought to play a critical role in cancer development. Obesity is typically measured by body mass index; although convenient for rapid and inexpensive estimation of adiposity, body mass index is an imperfect measure, especially for certain races or ethnicities (13). The Metabolic Dysregulation and Cancer Risk: a transdisciplinary approach to obesity-associated cancers (MeDOC), as a research consortium, will address this gap by including more comprehensive measures of obesity or adiposity (eg, waist circumference, dual-energy x-ray absorptiometry) to precisely delineate the role of adiposity and metabolic health in cancer risk. Observational studies suggest that cancer risk may be lower among individuals who are overweight and/or obese and metabolically healthy than among individuals who are overweight and/or obese with metabolic dysregulation (14,15). Although this evidence requires further confirmation, the findings suggest that individuals who are obese but defined as "metabolically healthy" (ie, have high muscle mass or low visceral adiposity) are likely individuals for whom body mass index is a poor measure of cancer risk because these individuals' cancer risk may be driven by a metabolically dysregulated state.

Preclinical and epidemiological studies (14-17) suggest that metabolic dysregulation may be contributing to the initiation and development of obesity-associated cancers. The biological mechanisms driving obesity-related cancer, however, are likely

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to be heterogeneous and complex and vary by duration of obesity, anatomic location and type of adipose tissue, cancer type, genetic background, and metabolic phenotype of the individual. Further, the link between obesity-associated metabolic dysregulation and cancer risk is complicated by other factors (eg, diet, physical activity, genetics, gut microbiota, sleep cycle, environmental pollutants) (18-22) that remain poorly understood. Research that characterizes how dysregulated metabolic states in obesity affect cancer development is an area of opportunity that may identify targeted interventions with strong potential for clinical translation.

Identifying and addressing obesity-cancer research needs

The National Cancer Institute's (NCI's) investments in obesity-related cancer research vary in scope and focus. Funded research projects cut across multiple disciplines and are supported by various funding mechanisms and activities, including research grant projects, large cooperative agreements, epidemiological and basic science studies, workshops and webinars, and training opportunities. For example, the long-standing Transdisciplinary Research on Energetics and Cancer (https://cancercontrol.cancer.gov/brp/hbrb/trec-centers) initiative currently supports ongoing training workshops for postdoctoral candidates and early-career investigators to enhance their ability to produce innovative and impactful transdisciplinary research in energetics, cancer, and clinical care. In addition, a trans-NCI working group consisting of NCI staff (https://cancercontrol.cancer.gov/brp/hbrb/obesity-energy-balance/working-group) from across multiple divisions and centers was convened to explore ways to address the link between obesity and increased cancer risk in 2020. Grant portfolio analyses and research assessments conducted by NCI staff identified a need for additional human studies focused on understanding molecular mechanisms of obesity-associated cancers. Despite these investments, substantial knowledge gaps remain that have hindered the identification of individuals at risk and the development of effective interventions for obesity-associated cancers. Clinical trials that obtain and bank well-annotated human samples from obese patients and studies of molecular mechanisms in novel animal models are needed to support the development of evidence-based interventions that could specifically reduce cancer burden in obese patients.

To address these gaps, in 2021 the NCI issued companion funding opportunity announcements RFA-CA-21-021 (Metabolic Dysregulation and Cancer Risk Program, Research Grants: a Transdisciplinary Approach to Obesity-Associated Research [U01 Clinical Trial Optional]) and RFA-CA-21-022 (Coordinating Center for the Metabolic Dysregulation and Cancer Risk Program: A Transdisciplinary Approach to Obesity-Associated Cancer Research [U24 Clinical Trial Not Allowed]) to support MeDOC. These Notices of Funding Opportunity solicited applications that pair mechanistic studies with observational or interventional study designs to 1) understand the etiologic role of obesity-associated metabolic dysregulation on the hallmarks of cancer (eg, genomic instability, mutations, tumor-promoting inflammation, immune dysfunction) (23) or markers of increased cancer risk (eg, double-strand breaks, oxidative stress, epigenetic and immune changes); 2) identify profiles of metabolic dysregulation associated with cancer susceptibility (ie, biomarkers to differentiate high-risk individuals); and 3) investigate targeted interventions on markers of metabolic dysregulation for cancer prevention and control. This initiative, described below, is a trans-NCI research program supported by 4 NCI Divisions—the Division of Cancer Control and Population Sciences, the Division of Cancer Biology, the Division of Cancer Prevention, and the Center to Reduce Cancer Health Disparities—that the NCI believes are poised to address this gap in the field to reduced obesity-associated cancer burden and health disparities.

The MeDOC Program

The MeDOC Program consists of 5 individual research projects (funded through RFA-CA-21-021) supported by a separate coordinating center (funded through RFA-CA-21-022) that facilitates research collaboration, data sharing and harmonization, and other postaward activities (https://medoc.bsc.gwu.edu/web/medoc/projects). MeDOC research projects seek to address key questions that will accelerate the discovery of molecular mechanisms linking obesity-associated metabolic changes to cancer. The MeDOC program is designed to foster synergistic interactions among individual projects and combine unique approaches and methods by creating harmonized datasets that can be analyzed to define novel mechanisms of obesity-driven cancer (Table 1). Examples of relevant research questions to be addressed by the individual projects and the MeDOC program are summarized in Table 2.

REMEDY: Reducing Metabolic Dysregulation in Obese Parent and Child Dyads

There has been an increase in incidence rates of early-onset colorectal cancer (CRC) (ie, in individuals younger than 50 years of age) (24), and growing evidence points toward associations between diet, energy imbalance, and adiposity as contributors to metabolic dysregulation and subsequent cancer risk (25-29). Consumption of calorically dense and nutrient-sparse diets is associated with changes in gut microbiota that induce an increase in low-grade inflammation and insulin resistance (30-32). Diet modifications designed to reduce chronic inflammation and reverse metabolic dysregulation may reduce the risk of developing CRC and other obesity-related cancers.

The Reducing Metabolic Dysregulation in Obese Parent and Child Dyads study consists of 2 complementary projects to address the need to identify biomarkers and mediators of CRC risk. The first project will address the absence of critical clinical trials involving lifestyle interventions for early-onset CRC by performing an anti-inflammatory dietary intervention trial in participant-partner dyads who share the same residence and share obesity as an elevated CRC risk factor. The second project will address the gap in mechanistic studies of obesity-associated inflammation by testing whether anti-inflammatory dietary interventions in mice reverse metabolic dysregulation and its associated CRC risk. Results from this study could yield important clues about how diet, energy imbalance, and adiposity increase the risk of early-onset CRC.

CerMet: Ceramides as Novel Drivers of Metabolic Dysfunction and Colorectal Cancer

Ceramides are sphingolipid products of fat and protein metabolism that accumulate in individuals with obesity or dyslipidemia and are strongly linked to insulin resistance (33,34). Preliminary data in preclinical models have implicated ceramides in the formation of hyperproliferative cell clusters that precede the development of CRC. In humans, ceramides and ceramide-

Table 1. How Metabolic Dysregulation and Obesity Cancer Risk program aims address key research needs

Project, institution	Obesity-associated cancer	Study population	Metabolism-related mechanisms and other biological processes	Initiative's goals and objectives			
				Understand mechanism	Develop common metabolic measures	Characterize cross-link between biological processes	Identify and determine utility of metabolic targets
Adipose fatty acid–binding protein, University of Iowa	Breast	N/A	Lipid metabolism, inflammation	✓	—	✓	—
Ceramides as Novel Drivers of Metabolic Dysfunction and Colorectal Cancer, University of Utah	Colorectal	Non-Hispanic White individuals	Lipid metabolism, inflammation, immune function	✓	✓	✓	✓
InflammoDOC, Brigham and Women's Hospital	Colorectal and liver	Non-Hispanic White individuals	Insulin resistance, inflammation	✓	✓	✓	✓
Reducing Metabolic Dysregulation in Obese Parent and Child Dyads, University of South Carolina at Columbia	Early-onset colorectal cancer	African American and non-Hispanic White individuals	Microbiome, inflammation	✓	✓	—	✓
Weight Loss and Cancer Outcomes in the Mid-South, University of Tennessee Health Science Center	Breast	African American and non-Hispanic White individuals	Immune function, inflammation, oxidative stress, microbiome, DNA damage	✓	✓	✓	—

Table 2. Select summary of relevant research questions to be addressed

- How does obesity-associated metabolic dysregulation promote cancer development and progression?
- How can metabolic dysregulation profiles be used as a classification of tumor progression?
- Are diseases linked to metabolic abnormalities causally associated with susceptibility for certain cancer types?
- How does the timing of exposure to metabolic abnormalities across the life course increase cancer risk or markers of carcinogenesis?
- Can weight loss clinical interventions improve metabolic abnormalities and insulin resistance or modify the microbiome?
- What are the biological mechanisms underpinning obesity-associated metabolic dysregulation and cancer?
- What is the influence of extracellular vesicles and their cargo (eg, proteins, microRNA) on obesity-associated metabolic dysregulation and during weight loss and other interventions?
- How does the gut microbiome influence systemic metabolic perturbations and cancer susceptibility?
- How does obesity influence a tumor's use of aerobic and anaerobic metabolism for growth and survival?
- How are obesity, lifestyle factors, metabolic changes, and related pathways affecting cancer risk?
- Which obesity-related risk factors influence metabolism-associated disease progression to cancer across various geographic areas, socioeconomic status, or by racial or ethnic groups?

Mechanism-related questions

- Which biological mechanisms underpin obesity-associated metabolic dysregulation and cancer?
- How does obesity or weight loss modulate altered metabolic pathways in cancer development?
- How does metabolic dysregulation promote cancer development across the age spectrum?
- What is the influence of biological processes (eg, inflammation, oxidative stress, hormones) on metabolic dysregulation and cancer risk?

Etiology- or epidemiology-related questions

- Are diseases linked to metabolic dysregulation causally associated with susceptibility for certain cancer types? What are the mechanisms underlying the association? What is the role of timing and duration related to onset of metabolic disorders and subsequent cancer risk?
- How do modifiable factors (eg, circadian disruption, microbiome, diet, environmental factors) influence metabolism-related markers (eg, insulin resistance, hyperinsulinemia, metabolic syndrome, adiponectin to leptin ratio) that lead to metabolic dysregulation or cancer risk?
- Which obesity-related risk factors influence metabolism-associated development of cancer across various geographic areas, socioeconomic groups, or racial or ethnic groups (eg, ancestry)?
- Are individuals who are overweight or obese and who have a metabolic dysregulation profile at higher risk of cancer than people who are overweight, obese, or not obese who have a normal metabolic profile?

Intervention-related questions

- Can weight loss or other clinical interventions improve abnormal metabolic profiles, such as insulin resistance, so as to modify cancer risk and progression to cancer?
- Can certain modulating factors (eg, sleep, microbiome, diet, physical activity) and their putative interactions serve as interventions to attenuate the negative effects obesity has on metabolic health and cancer?
- Can chemopreventive agents, with or without dietary modification, improve the metabolic profile of at-risk patients who are obese or overweight and thereby decrease cancer risk?

synthesizing enzymes are upregulated in serum and tissues from patients with adenomas or CRC (35).

The Ceramides as Novel Drivers of Metabolic Dysfunction and Colorectal Cancer project aims to clarify the key role of ceramides in metabolic dysregulation underlying CRC risk, develop a "ceramide risk score" to identify individuals at elevated risk of CRC, and identify novel therapeutic targets for clinical intervention. It will use multiple large-scale epidemiological and clinical cohorts to identify associations of ceramides through a derived ceramide risk score with CRC risk using stored samples from the European Prospective Investigation into Cancer and Nutrition (36) and the Prostate, Lung, Colorectal, and Ovarian cancer cohort (37). Further, the impact of body weight and body composition on the ceramide risk score after bariatric surgery will be evaluated using patient data from the Utah Bariatric Surgery Cohort. Dihydroceramide desaturase-1 knockout mice will also be used to study the efficacy of new ceramide-lowering interventions in preventing the formation of CRC using models harmonized across the MeDOC consortia.

The role of adipose fatty acid–binding protein in linking lipid dysregulation and breast cancer risk

Data from epidemiologic studies have consistently found that obesity increases the risk of and mortality associated with breast cancer in postmenopausal women (38,39), and high-fat diets rich in saturated fats have been associated with increased adipose fatty acid–binding protein (A-FABP) expression and mammary tumor growth (40,41). Thus, A-FABP and high-fat diets may represent potential factors linking dysregulated lipid metabolism with obesity and breast cancer risk.

The objective of this project is to determine how high-fat diet–induced lipid dysregulation links obesity with increased breast cancer risk. Using A-FABP conditional knockout breast cancer mouse models, the investigators will identify which high-fat diets containing different fat sources (eg, cocoa butter, safflower oil, olive oil) promote mammary tumor risk through an A-FABP–dependent pathway. The project will delineate the downstream metabolic changes caused by increased A-FABP levels in high-fat diet–induced breast cancer and test whether immunotherapy and A-FABP inhibition with unique humanized antibodies can improve A-FABP–induced metabolic dysregulation in patient-derived xenograft mouse models. Finally, A-FABP will be evaluated as a biomarker for obesity-associated breast cancer risk by determining the function of A-FABP in peripheral monocytes, measuring the levels of soluble A-FABP in serum, and A-FABP expression in tumor stroma using specimens collected from women who are lean or obese, with or without breast cancer. As such, A-FABP offers a novel therapeutic target and biomarker for obesity-associated breast cancer risk, and results from this project may have substantial clinical implications for the prevention and immunotherapy of obesity-associated breast cancer.

WELCOM: Weight Loss and Cancer Outcomes in the Mid-South

Breast cancer is the most common cancer in women in the United States (42), and obesity is 1 of the few modifiable risk factors for this disease. The pathological link between obesity and breast cancer risk is tied to metabolic, inflammatory, and hormone dysregulation (43,44). Yet, the molecular mechanisms linking obesity to breast cancer initiation remain poorly characterized. The goal of the Weight Loss and Cancer Outcomes in the Mid-South project is to test whether modifying obesity-associated host and microbiome metabolic changes will produce effective targets for preventive interventions.

The Weight Loss and Cancer Outcomes in the Mid-South project will examine the role of the microbiome in obesity, chronic inflammation, and breast cancer risk. Specifically, this project will explore associations between altered levels of

microbially modified metabolites and several markers of increased risk of breast cancer, including 1) altered host immunity, 2) obesity-associated chronic inflammatory and immunosuppressive signaling, 3) levels of reactive oxygen species, and 4) oxidative DNA damage and genomic instability. The investigators are recruiting study participants of varying age and adiposity from the Memphis, Tennessee area, as well as patients with obesity before and after bariatric surgery to define whether obesity-mediated dysregulation of microbial-derived metabolites affects cells relevant to antitumor immunity. To study the impact of microbially derived metabolites on breast cancer risk, several preclinical models designed to mimic genetic and dietary differences in human populations will be used to determine alterations in immune cell function, hormone levels, and inflammation. The investigators will also test whether dietary interventions can specifically alter microbially derived metabolites or gut microbes to improve protective immunity in complementary mouse models of obesity-mediated breast cancer. In sum, these studies aim to increase understanding of obesity-associated breast cancer risk and point to potential interventions to reduce risk.

InflammoDOC: Decoding Mechanisms Underlying Metabolic Dysregulation in Obesity and Digestive Cancer Risk

Accumulating evidence implicates visceral adiposity (and its closely related glycemic metabolic dysregulation) as an important factor in the development of CRC and liver cancer (45-47). How visceral adiposity promotes cancer in organs that are encased by visceral fat is largely unknown. Comparing metabolically unhealthy to metabolically healthy obesity is critical to investigating obesity-related mechanisms of CRC and liver cancer risk. Evidence indicates that inflammation plays an important role in the development and progression of CRC and liver cancer, so defining the key inflammatory pathways and markers that indicate a metabolically unhealthy obese state has immense potential to uncover tumor-promoting mechanisms and inform strategies for risk stratification and prevention.

To discover key obesity-linked inflammatory pathways, the InflammoDOC project will first establish "inflammotypes" by characterizing and validating patterns of chronic inflammation in metabolically unhealthy obese patients using an expansive proteomic panel in adults without cancer from the Vitamin D and Omega-3 Trial (48) and the Cocoa Supplement and Multivitamin Outcomes Study (49). Investigators will then examine the relationship between the identified proteomic inflammotypes with long-term risk of incident CRC (1000 cancer patients and 1000 non-cancer participants) and liver cancer (500 cancer patients and 500 non-cancer participants), combining several longitudinal cohorts—the Nurses' Health Study (50); Physicians' Health Study (51); Health Professionals Follow-Up Study (52); Prostate, Lung, Colorectal, and Ovarian; Southern Community Cohorts Study (53); and the Women's Health Study (54)—with stored baseline blood samples and long-term follow-up.

MeDOC Coordinating Center

The Coordinating Center at George Washington University has extensive scientific expertise in obesity, body composition, metabolism, nutrition, cancer, biostatistics, and bioinformatics. It provides overarching project management for the MeDOC studies that includes guiding the selection of common measures, developing consistent protocols and manuals of operations, maintaining websites, establishing working groups, and leading outreach activities. The Coordinating Center facilitates a range of post-award activities, including standing up the consortium with agreed by-laws; convening working groups; establishing the external advisory board; providing scientific contributions and coordination of the collaborative projects; and facilitating activities such as data harmonization, data sharing, and results dissemination across the funded sites and NCI. In collaboration with all the projects, the MeDOC Coordinating Center will lead the integration of animal and human data produced in the consortium to improve our understanding of how the role of metabolic dysregulation affects obesity cancer risk. The Coordinating Center will house MeDOC datasets and establish a MeDOC knowledge base, to be made available to the public as a resource for continued data mining and hypothesis generation.

The multiteam structure, organization, and activities of MeDOC build on experiences from previous transdisciplinary initiatives, such as NCI's Transdisciplinary Research on Energetics and Cancer initiative (55), and best practices from Science of Team Science (55-58). For instance, MeDOC's steering committee, with the support of NCI leadership and the external advisory board, provide guidance and leadership designed to help enhance the consortium's focus on its cross-project goals. In addition, monthly working group calls and annual meetings allow for formal and informal exchange of information across project teams to foster collaboration—a hallmark of NCI's multiteam initiatives. Junior investigators are also encouraged to capitalize on new training opportunities and resources to form new partnerships that advance the goals of the consortium and support their development as transdisciplinary researchers (58).

Summary

The MeDOC consortium presents a unique opportunity to identify biological mechanisms by which obesity increases the risk of cancer in humans, an area traditionally understudied and in great need of advancement. In keeping with this goal, each funded research project evaluates data from human samples, using mechanistic findings obtained through preclinical investigations to better understand human disease. The inclusion of preclinical and human studies should allow more rapid translation of study findings to the clinic and the community. Furthermore, informed by research and lessons learned from the Science of Team Science (59), this initiative is designed to encourage collaboration across projects and between investigators with differing expertise and training. The partnerships between investigators in the post-award collaborative projects will answer scientific questions that are too complex for 1 group or discipline to address. MeDOC will allow participating research teams to take advantage of novel shared resources, such as common data elements that have been harmonized across studies that would not be available at any 1 site. Bringing together several research groups that investigate different obesity-associated cancer types could lead to breakthroughs in the understanding of how obesity alters immune and metabolic pathways that increase cancer risk.

To align the goals of individual projects, the MeDOC consortium defined its mission to reduce the cancer burden in obese populations by advancing our understanding of how metabolic dysregulation affects cancer risk across diverse populations. The MeDOC consortium embraces a core set of values (pillars) to guide its scientific engagement: openness and inclusivity, trust and confidentiality, collaboration and sharing, continuous learning, and compassion. To complement and enrich the scientific

diversity of the consortium, an external advisory board of eminent investigators in obesity-relevant research will aid NCI in evaluating MeDOC's progress. Affiliate members—investigators not funded through the MeDOC consortium—will also be invited to participate in consortium activities and to introduce fresh ideas and allow the consortium to expand and innovate as appropriate.

The NCI is committed to advancing research on obesity-associated cancers and identifying opportunities to mitigate the impact of obesity in populations of diverse backgrounds. Not only does the MeDOC consortium build on the knowledge gained from prior NCI initiatives on obesity and cancer, but its focus on metabolic dysfunction as a key mechanism linking obesity to cancer risk provides a foundation for future transdisciplinary research that reduces the obesity-related cancer burden.

Data availability

Because of the nature of the report, which described the MeDOC consortium and associated funded grants, no new data were generated or analyzed for this article.

Author contributions

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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Commentary