Title of the study: Obese but Metabolically Healthy: Impact on the incidence of cancer

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Abstract:
The overwhelming prevalence of obesity has generated widespread alarm in the United States and internationally. Indeed, obesity is associated with the pathogenesis of a host of chronic health conditions including type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), hypertension, stroke and cancer. However, a subset of obese individuals remains metabolically healthy, and empirically, appears protected from a number of obesity-related complications. The objective of this study is to determine whether or not metabolically healthy obese (MHO) individuals are specifically protected from obesity-associated cancers compared to metabolically-impaired obese (MIO) peers using the Rochester Epidemiology Project (REP). In addition, we will use data from the REP to examine what additional patient characteristics may be associated with the prevalence of cancer in MHO and MIO cohorts.

Specific Aims
Specific Aim 1: Determine whether MHO adults experienced a lower incidence of obesity-associated cancers compared to MIO adults.

We will test the null hypothesis that MHO adults have the same cumulative incidence of obesity-associated cancers as MIO adults from 2005 to present. This hypothesis is built upon published and preliminary data that suggest that insulin resistant obesity carries higher risk for cancer than insulin sensitive obesity.

Specific Aim 2: Determine whether MHO adults experienced a higher incidence of obesity-associated cancers compared to metabolically healthy normal weight adults.

We will test the null hypothesis that MHO adults have the same incidence of obesity-associated cancers (i.e., endometrial cancer and breast cancer among post-menopausal women; colorectal cancer; renal, esophageal, gallbladder and pancreatic cancers) as metabolically healthy normal weight adults from 2005 to present. This hypothesis is built upon published and preliminary data that suggest that insulin sensitive obesity still carries metabolic and cancer risks; it follows that compared to lean adults, MIO adults will show the highest incidence of the obesity-associated cancers, whereas MHO adults will show an intermediate incidence of these same cancers.
BACKGROUND AND SIGNIFICANCE

Human metabolism promotes a central tendency in response to high calorie diets and physical inactivity: obesity. Many serious diseases are directly attributable to elevated body mass index (BMI), so that the increased prevalence of overweight (BMI 25 – 29.9), obesity (BMI ≥ 30) and morbid obesity (BMI ≥ 40) has generated widespread alarm in the United States and internationally. The most obvious of these diseases are primarily metabolic in origin, such as insulin resistance, metabolic syndrome, dyslipidemia and ultimately T2DM; but it is also appreciated that obesity promotes cardiovascular disease, hypertension, stroke, sleep apnea, deterioration of musculoskeletal and respiratory function, and a number of cancers (Van Gaal et al 2006; Guh et al 2009). Worldwide, 1.7 billion people are currently classified as overweight (Haslam & James 2009). Some years ago, the World Health Organization estimated that by 2030, 370 million people worldwide would be expected to be suffering from T2DM, driven primarily by obesity, compared to 177 million in 2000 (Wild et al 2004). However, this estimate appears to have been unduly conservative, because as of midway through 2011, the number of diabetic adults worldwide had already reached 347 million. The same report indicates that the United States now has the highest BMI of the high-income countries (Finucane et al 2011). About one in three American adults is now obese. A newly appreciated concern associated with these figures is that, along with smoking, obesity and visceral obesity represent the major preventable cause of most cancers (WCRF/AICR 2007). Indeed, according to the National Cancer Institute, obesity is associated with increased risks of cancers of the esophagus, breast (postmenopausal), endometrium, colon and rectum, kidney, pancreas, thyroid, gallbladder, and possibly other cancer types.

Intriguingly, ~25% of obese individuals have normal glucose concentrations, blood pressures, lipid profiles, and subsequently, appear to be “protected” from T2DM or CVD. Multiple theories abound, however, there is evidence to suggest these individuals have better adipose tissue function, growth pathway regulation, and inflammatory profiles than MIO peers. In addition to using preclinical models to develop an understanding of the biological mechanisms underlying this protection, the investigative team has a strong interest in determining whether or not MHO individuals are also protected from obesity-associated cancers compared to their MIO peers. The REP clearly provides a unique opportunity and effective means to pursue this objective. Collectively, we believe these translational research efforts will lead to novel interventions for obesity and obesity-related conditions and have a significant impact on public health.
PRELIMINARY STUDIES
Not applicable.

RESEARCH DESIGN AND METHODS

Overview
We will conduct a retrospective cohort study of adults 40 years of age and older in the 2005 Olmsted County population. We will compare the incidence of metabolically-related cancers among three cohorts: 1. Obese patients (defined by a BMI ≥ 30.0) with a fasting glucose concentration ≥ 100 mg/dl or with a hemoglobin Alc of ≥ 5.7% will be defined as MIO; 2. Obese patients with a fasting glucose concentration ≤ 99 mg/dl or a hemoglobin Alc of ≤ 5.6%, will be defined as MHO; and 3. Frequency-matched metabolically healthy normal weight patients (BMI 18.5-24.9). The incidence of metabolically related cancers after the index date will be assessed for all subjects using ICD-9 codes. Using this information, we will compare the incidence of cancer between MIO, MHO and metabolically healthy normal weight adults from 2004 to present. We will also determine whether there are differences between the three groups regarding the reoccurrence of cancer, and the duration of survival after the onset of cancer.

Setting
There is a long-standing tradition of performing epidemiologic studies in Olmsted County, MN. Its population is served by a largely unified medical care system that has accumulated comprehensive clinical records over a long period of time.24, 25 Olmsted County (2005 population: 135,071) lies 90 miles southeast of Minneapolis/St. Paul. Approximately 70% of the county population resides within the city limits of Rochester, MN, the centrally located county seat. In 2010, the population was 86% white, and the population is largely middle class, with approximately 94% of the adult population having graduated from high school. The characteristics of the Olmsted County population are similar to those of residents from the Upper Midwest.[St. Sauver et al, Mayo Clinic Proceedings, 2011]

Data Resource
Epidemiologic research in Olmsted County is possible because the city and county are relatively isolated from other urban centers and nearly all medical care is delivered to patients in the population by local providers. Medical care is currently provided primarily by the Mayo Clinic and its two affiliated hospitals, Olmsted Medical Center and its affiliated hospital, and the Rochester Family Medicine Clinic. Each health care provider that participates in the REP uses a dossier-type medical record. Together, these medical records contain details of every inpatient hospitalization at the three affiliated hospitals, every outpatient visit to the office, clinic, or emergency department, as well as every laboratory result and correspondence concerning each patient. The medical records are easily retrievable because the Rochester Epidemiology Project has maintained, since the early 1900s, extensive indices based on clinical and histologic diagnoses and surgical procedures. The result is the linkage of medical records from essentially all sources of medical care available to and utilized by the Olmsted County population.
Identification of Study Subjects

Identification of Metabolically Healthy and Metabolically Impaired Obese Adults

Using the REP Census, we have identified a preliminary list of all adults ≥ 40 years old on April 1, 2005 (n = 59,506; 31,326 women and 28,180 men). At this time, it will not be possible to obtain height and weight data electronically from Olmsted Medical Center. Therefore, this study will be limited to patients who have electronic BMI data available from the electronic Mayo medical record. A similar study examining BMI data from the 2009 population indicates that about 70% of the population will have at least one BMI available (personal communication: Dr. Sue Bielinski). We will compare the characteristics of those for whom BMI data are available to those for whom data are not available to assess possible biases.

Therefore, we estimate that the proportion of this population with electronically available BMI data is 70% (21,928 women and 19,726 men). Based on the estimated obesity prevalence of 21% in Olmsted County, approximately 6,123 adults will be obese.

We will obtain lab results for all glucose and hemoglobin A1C tests performed on the study cohort within +/- 1 year of base-line from both Mayo Clinic and Olmsted Medical Center. We estimate that 70% will have fasting glucose or hemoglobin Alc data (15,350 women and 13,808 men). MHO and MIO participants will be identified based on fasting glucose or hemoglobin A1C cutpoints. Participants with a fasting glucose concentration ≥ 100 mg/dl or with a hemoglobin Alc of ≥ 5.7% will be defined as MIO. Participants with a fasting glucose concentration ≤ 99 mg/dl or a hemoglobin Alc of ≤ 5.6%, will be defined as MHO. Based on data from the Framingham population, we anticipate 10-25% (612-1531) of the obese participants will be MHO, and the remainder MIO.

Identification of Metabolically Healthy Normal Weight Adults

An age and sex frequency-matched non-obese sample will be selected from the remaining adults, and will serve as the comparison cohort for this study. All fasting glucose and hemoglobin A1C tests will also be obtained for this sample; however, we expect that these tests may be less likely to be available for this population. If a test is not available, we will assume that the person is metabolically normal, but will also conduct sensitivity analyses to determine the possible effect on results if increasing proportions of the comparison cohort were metabolically impaired.

Identification of Outcomes

Once MHO, MIO, and metabolically healthy normal weight (MHNW) adults have been identified, we will pull all cancer diagnostic codes (ICD-9 codes) of interest for this group from. We’ll exclude those who have a cancer prior to the BMI date. Variables which might confound the association between the exposures and the outcomes will also be obtained electronically, including age, sex, and comorbid conditions. Other important confounders such as alcohol and tobacco use are not available electronically. We will abstract these data from a subset of all three cohorts to obtain these data.

Trained nurse abstractors will collect all data and record abstracted information on data abstraction forms. In preparation for computer entry, the consistency, clarity and completeness of data recording shall be verified by the principal investigator. All data
shall be entered with built-in edit checks into a RedCap data entry system and stored in a SAS data file for analysis.

**Statistical Analyses and Power**

The difference in cancer risk for the three patient groups (MHO, MIO, MHNW) will be assessed using the Cox proportional hazards model with age as the time scale instead of the more typical time from BMI assessment [Therneau and Grambsch 2000]. The Cox model implicitly matches subjects on the time scale that is used. Since cancer rates increase significantly with age and is probably a much larger effect than time since BMI, it is most appropriate to use an age scale for the model. Cancers will be examined overall and by type of cancer. Models will be fit by sex and adjusting for sex and other comorbid conditions as appropriate for the specific cancer type.

For individual risk factors, the power of the Cox model to detect a factor which has an influence on the risk of experiencing the endpoint is dependent on the prevalence of the factor, its level of influence, and the number of observed individuals that experience an endpoint (cancer). Thus, for example, at a significance level of 0.05, a risk factor that occurs in 25% of the cohort (e.g. MHO vs. MIO) and has a true hazards ratio of 2.0 will have an 80% power of being detected if at least 69 cancers are observed [Schoenfeld, 1983].

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Power</th>
<th>Observed number of events (cancers)</th>
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<tr>
<td></td>
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<td>50</td>
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<td>25%</td>
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**Strengths and Limitations:**

The proposed study has a number of strengths. First, it is a novel line of investigation in an area that represents a global epidemic; namely, obesity. Determining whether those who maintain metabolic health in the face of obesity truly have protective mechanisms against a cadre of disabling health conditions, including cancer, compared to their metabolically impaired peers, could provide an important first step to more mechanistic studies of the underlying genetic and epigenetic modulators of health and aging. In turn, this could lead to entirely novel therapeutic strategies for obesity-related diseases. In particular, if we confirm the hypothesis that MHO adults show incidence of obesity-associated cancers that is intermediate between MIO and normal lean adults, we would be justified in studying this group further to learn the protective mechanism, whether it is...
reduced fasting insulin, reduced fasting glucose, less severely lowered adiponectin, or less severely elevated levels of blood pro-inflammatory cytokines. This may be achieved through the analysis of banked samples. The specific protective mechanisms may also vary according to the type of obesity-associated cancer. The translational impact of these results would be that we would have a justification to study the best type of intervention to protect MIO adults from their higher rates of obesity-associated cancer. While not eliminating risk completely, such evidence based recommendations could save lives (e.g., for post-menopausal MIO women who have been treated for breast cancer with surgery and radiation, we may discover evidence to support a recommendation of a regimen of anti-inflammatory drug treatment in addition to tamoxifen.)

Second, this study takes advantage of the population-based medical data available through the Rochester Epidemiology Project resources. The unique strengths of this resource have been previously established. This linked medical records system allows us access to accurate and detailed clinical and laboratory data over many years, which are not typically available in other databases or research settings. This resource also allows us to efficiently examine long-term outcomes of tonsillectomy retrospectively in a well-defined population in a relatively short period of time, while a prospective study would require years to collect complete data.

The primary limitation of this study is due to its retrospective nature. This study relies on complete and accurate recording of pertinent information in the medical record. We expect the record to be reasonably complete and accurate for the data elements most essential to testing our study hypotheses (such as occurrence of cancer). However, other elements, such as complete laboratory test information will be incomplete. Additionally, factors other than obesity and metabolic state may predispose adults to having cancer, and these third variables may confound any associations between metabolic state and reduced cancer. We are therefore collecting information on such variables, and will control for these potential confounders in our analysis. There may be more subtle factors which we are unable to control for. Our data however, will provide preliminary information to support the feasibility and importance of studies to reveal identify protective mechanisms against obesity-related conditions such as cancer.

**HUMAN SUBJECTS**

This project does not involve experimentation on human subjects, and is limited only to a retrospective review of information obtained from medical records. The data will be analyzed anonymously and the usual policies and safeguards enforced by the Department of Health Sciences Research will be used to protect the confidentiality of the patient record. Data on individual patients will not be released, and all results will only be published in aggregate. Additionally, we will not include information from anyone who has denied MN research authorization.

Finally, all data will be analyzed within the Mayo Clinic Division of Biomedical Statistics and Informatics, and data sets will not be released to external investigators.
REFERENCES


