



Big society

Associate Professor Gerald Denis is investigating obesity's connection to cancer and how it affects population differences in cancer risk. He discusses his multifaceted, innovative approach

To begin, can you give examples of populations that are most vulnerable to obesity and its associated cancers?

In the US, some urban African Americans and Hispanic families have higher rates of obesity and its complications than some urban Caucasian families. In the UK, families of South Asian origin, and in France, families of North African origin often have higher health risks, not just for obesity and metabolic disease, but for a range of health challenges. Clearly then, obesity is not a simple problem of willpower and portion control; it is a difficult disease of interacting social, environmental, behavioural, medical and genetic factors, and lacks a straightforward, effective treatment.

It is worth noting that obesity does not always carry the same cancer risk. For example, a minority of severely obese people are metabolically healthy, with normal glucose tolerance, a lack of metabolic complications and reduced risks for obesity-associated cancers, including breast cancer. On the other hand, African-American women make up a population of particular concern, as they are more likely to be obese and to experience its inflammatory complications than many other populations. Therefore, new methods to stratify cancer risk using blood profiling will have important benefits for improved cancer outcomes in this disadvantaged group, including reduced breast cancer mortality.

Can you elaborate on why African-American women are more prone to obesity and its inflammatory complications? To what extent do you consider socioeconomic factors in this study?

Both overweight and obese have high prevalence among adults and children of African American origin in the US, and weight loss interventions are less effective in these groups. There is some evidence that compliance in weight loss trials is a factor here, as well as discouragement from prior experiences of weight loss. We are interested in the role of demographic variables; there is evidence that African American women tend to be diagnosed with breast cancer later than Caucasian women. This later diagnosis is associated with reduced survival. Some of these

differences may be due to eroded trust in the medical system.

What are the study's core objectives and how have these evolved since it began?

Our long-term goal is to understand and use the relationships among obesity, inflammation and breast cancer outcomes to reduce the effects of obesity on cancer mortality. We use both basic laboratory and epidemiological population data to identify mechanistic relationships and pharmacological solutions. Obese, underserved women are uniquely impacted by breast cancer and suffer worse outcomes, but identification of critical immunological and metabolic factors that exacerbate risk will enable focused and effective intervention for this at-risk group. This multifaceted approach is highly novel and important.

How can a better understanding of cancer risk reduce the effects of obesity on cancer mortality?

The current recommendations of the US Preventive Services Task Force calls for American women to have a mammogram every two years between the ages of 50 and 74; early detection of breast cancer saves lives. We think mammography could be supplemented with blood profiles for inflammation and metabolism that would be very easy to perform at the same time as a mammogram, and greatly refine our recommendations for risk management.

What do you hope to achieve in the next phase of this project?

We are developing models of metabolic disease, and testing to see how different types of human breast cancer cells respond. We expect to identify a small number of inflammatory and metabolic cancer risk factors that will allow us to look for those same signatures in the blood of women who do not yet have cancer. These signatures would form the basis for a new clinical trial to evaluate the association with risk for breast cancer occurrence. Ultimately, we want to use blood signatures to warn certain women that they are at elevated risk. A more personalised approach should help reduce disease and costs.



An expanding problem

Obesity is linked to several forms of cancer, but certain subgroups of people are more vulnerable than others. Researchers at **Boston University School of Medicine** are identifying population differences in obesity-linked inflammatory blood profiles. These signatures will aid the fight against obesity-related malignancy

WITH THE WORRISOME epidemic of obesity sweeping the globe, modern society is experiencing an acute health crisis. Recent statistics from the US Centers for Disease Control and Prevention estimate that at least 20 per cent of US adults have a Body Mass Index (BMI) greater than 30 kg/m², the clinical benchmark for obesity. In addition to the day-to-day disadvantages of overweight, obesity has been strongly linked with metabolic problems such as stroke and cardiovascular risk, hypertension, insulin resistance and, significantly, type 2 diabetes. While these metabolic complications alone highlight the urgent need to tackle growing obesity rates, the rising incidence of obesity-related cancers and mortality is also a dangerous trend that will require considerable effort for healthcare systems to control.

Though obesity can be found in all sectors of society, epidemiological studies reveal that there is an uneven distribution of obesity and related complications across the developed world. Depending largely on socioeconomic factors, populations that experience higher rates of obesity and obesity-related cancer in the developed world include African Americans and Hispanics in the US, as well as South Asians. These inequalities observed across sub-populations indicate that there is a dire need for wider education and research into the links between obesity and related malignancies in these vulnerable populations.

INFLAMMATION – A LINK BETWEEN OBESITY AND CANCER

To help address the problem, researchers at Boston University School of Medicine, USA, are conducting detailed investigations into cancer risks in obesity. Of particular interest to them is the fact that roughly one-quarter of the obese population show few apparent metabolic complications. This so-called healthy obesity is an indication that fat accumulation alone is not sufficient to cause metabolic complications, such as type 2 diabetes, or malignancies such as breast cancer. "Some clinicians declare that relatively healthy obesity is a misleading myth, that all humans who are obese are on a relentless decline towards

early mortality, but this view does not explain the (albeit rare) high BMI adults who seem to be stubbornly protected from diabetes and cardiovascular disease," explains Associate Professor Dr Gerald Denis, who heads up the research group.

As demonstrated by this relatively healthy sector of the obese population, factors other than fat (adipose tissue) deposition may be important for the development of metabolic disorders in obesity. Furthermore, obesity-related cancers often arise in or near adipose tissue, suggesting that certain characteristics of fat may promote the growth of tumours such as breast cancer. One characteristic of great interest to the Boston researchers is inflammation in adipose tissue and bloodstream. "All breast cancers are surrounded by fat, and we have robust evidence that the metabolism and inflammatory properties of that fat strongly influence tumour progression," Denis elaborates. Insulin-resistant obesity is strongly linked with chronic inflammation, both local and systemic, a condition arising from adipose tissue invasion with the immune system's white blood cells such as T cells, B cells and macrophages. One key feature of this inflammation is that activated white blood cells secrete pro-inflammatory cytokines in the adipose tissue and blood circulation, wreaking havoc with insulin-sensitive glucose-uptake mechanisms and worsening metabolic complications in the patient.

In their search for a potential link between the development of insulin-resistant obesity, inflammation and the development of obesity-related cancer, the Boston researchers investigated proteins known as Bromodomain and ExtraTerminal domain-containing transcriptional co-regulators (BET proteins). By controlling the access of transcription machinery to genetic coding in the cell, BET proteins regulate the expression of different critical genes, such as cell cycle-regulators, that are deeply implicated in cancer development. In a surprising study, the group also discovered that a mouse model expressing reduced amounts of a certain BET protein

UNCOUPLING OBESITY FROM BREAST CANCER IN AFRICAN AMERICAN WOMEN

OBJECTIVES

- To identify treatment options and prevention strategies for at-risk populations
- To understand the relationship between sex and socioeconomic status and risk of cancer

KEY COLLABORATORS

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DR GERALD V DENIS, a Canadian molecular biologist, was the first to describe functions for proteins of the Bromodomain and ExtraTerminal domain (BET) family. These factors (BRD2, BRD3 and BRD4) are essential transcriptional co-regulators that control human gene expression and play a role in obesity, inflammation and cancer.

named Brd2 also displayed a 'healthy' obesity without inflammation and other metabolic complications, similar to one-quarter of obese humans. This insight had three important implications. Firstly, BET proteins offer strong mechanistic links between obesity, inflammation and cancer. Secondly, this link could be exploited with novel BET-targeted anti-cancer drugs. Thirdly, understanding metabolic and inflammatory characteristics of obese patients could help to improve cancer risk assessment and diagnosis, perhaps even providing mechanisms for explaining the different cancer risks across human sub populations.

POPULATIONS AT RISK

In spite of recent progress to unravel the biology that underlies interactions between obesity and cancer, obesity remains a multifactorial condition with both biological and non-biological causes. This complexity complicates the interpretation of stratified risk for obesity-related diseases in different ethnic groups. For example, African-American women in the US exhibit a higher risk of obesity than US Caucasian women and are more likely to suffer related complications such as type 2 diabetes and breast cancer. The reasons for this trend are numerous and complex. However, one important factor is socioeconomic status, as Denis elucidates: "Obesity is strongly associated with income; it generally takes significant money to consume a healthy diet and purchase a gym membership. Furthermore, many cities harbour 'food deserts': neighbourhoods that lack supermarkets with fresh vegetables and fruits". Because many African-American families reside in more deprived food desert neighbourhoods, it may be harder for these women to maintain a healthy lifestyle in comparison to other sub-populations.

Though socioeconomic status may predict a large proportion of obesity-related cancer risk, biological factors are also crucial. One example can be seen in South Asians, whose increased tendency to deposit adipose tissue within internal organs compared to Caucasians contributes more easily to obesity-related complications and cancer despite relatively low BMI. The interacting web of factors involved in obesity, inflammation and cancer demands that researchers update and refine existing preventative strategies to address ethnicities with higher cancer risk.

Obesity remains a complex, multifactorial disease with both biological and non-biological causes

TIME TO GET PERSONAL

As research into obesity continues, multiple opportunities are emerging. The Boston researchers are now using our deeper knowledge of the interplay between obesity, inflammation and cancer to develop new tools that will improve cancer screening for at-risk populations. One intriguing avenue of research for the group is to compare blood inflammatory profiles across different populations. "We do not yet know if the inflammatory profiles of South Asian and Caucasian women highly overlap with African-American women, but we will find out soon. This advance will be very important from the perspective of 'personalised medicine' and development of more highly tailored recommendations," Denis reveals.

In conclusion, while obesity is a condition that is often accompanied with a convoluted mixture of causes and modifying factors, innovative research into this disease and its relationships with metabolic disorders and cancer risk is already helping to improve our knowledge and management of the obesity epidemic, enabling greater focus on the most vulnerable sectors of the population worldwide.

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