

“New” UROP Proposal

Title of Proposal: Effect of Weight loss on Breast Cancer Growth in Obese Female Mice

STATE THE PROBLEM/TOPIC

According to The World Health Organization, more than 1 billion people world-wide are with obesity (Body mass index above 30). About 650 million adults, 340 million adolescents, and 39 million children, with each of these groups rapidly increasing (Volpi, 2022). Obesity is a great contributor to metabolic syndrome. Which increases your risk of heart disease, stroke, and type 2 diabetes (Mayo Clinic, 2021). Obesity also increases the risk of 13 different types of cancer, one of which being breast cancer. According to the Centers for Disease Control and Prevention (CDC), 240,000 cases of breast cancer are diagnosed in women each year. With about 42,00 women dying every year from this disease (CDC, 2023). We seem to have an understanding about how the risk of breast cancer affects lean individuals, but we know very little on how breast cancer interacts with people that suffer from obesity. Breast cancer patients are regularly told to lose weight at the point of diagnosis and when there is a chance relapse of this disease may occur. The question then becomes; is all weight loss equivalent when considering breast cancer risk, reoccurrence, and severity of this disease? The purpose of this research project is to explore how different weight loss interventions affect breast cancer in female mice. Also, how it affects the clinically relevant parameters of metabolic syndrome. This research allows us to gain knowledge of whether reducing breast cancer risk is merely a question of weight loss, or whether specific mechanisms related to weight loss are implicated. The project's results may prove doctors right that telling individuals with breast cancer that suffer from obesity, it is just a matter of losing that excess weight. With the end goal of this research being breast cancer risk and death reduction.

RELEVANT BACKGROUND/LITERATURE REVIEW

Obesity, defined as having a body mass index above 30 kg/m^2 , increases the risk of metabolic syndrome and 13 types of cancers. Metabolic syndrome is a metabolic disorder that results from the increasing prevalence of obesity. The physiology seems to be largely attributable to insulin resistance with excessive flux of fatty acids implicated (Eckel et al., 2005). The amount of cancer attributable to obesity is 11.9% in men and 13.1% in women (Avgerinos et al., 2019). With these numbers greatly rising. One of these 13 cancers that is attributable to obesity is breast cancer. Breast cancer accounts for 12.5% of all types of cancers diagnosed yearly, making it the most common cancer in the world. Being an individual that suffers from obesity greatly correlates with a higher chance in breast cancer. A meta-analysis shows obesity is associated with a 35% to 40% increased risk of breast cancer recurrence and death and therefore poorer survival outcomes (Goodwin and Jiralerspong, 2016). Obesity promotes chronic low-grade inflammation, particularly in white adipose tissue. The problem being, breast tissue is predominantly composed of white adipose, and developing breast cancer directly interacts with cells and signals from adipose remodeled by obesity (Devericks et al., 2022). Increased levels of estrogens due to excessive aromatization activity of the adipose tissue contributes greatly to the development of breast cancer in the individual (Engin, 2017). The increase of adipose tissue in individuals with obesity produces excess amounts of estrogen, which has been shown to be correlated with the increased risk of breast cancer (Kothari et al., 2020). Semaglutide is a revolutionary weight loss drug. Semaglutide is a glucagon-like peptide-1 receptor agonist that is approved by the US Food and Drug Administration for chronic weight management (Chao et al., 2023). Semaglutide has shown the largest weight loss of any obesity medication to date with reductions of approximately 15% of initial weight at just 68 weeks (Chao et al., 2023). Semaglutide reduces visceral fat and blood lipids and improves glucose metabolism in obese mice (Zhu and Chen, 2023). To our best knowledge, the role of Semaglutide mediated weight loss in relation to breast cancer risk has never been tested. The question then turns to, what happens with breast cancer when the adipose tissue is diminished. The goal of this study is to understand whether losing weight, via Semaglutide, correlates with a decrease in breast cancer. We've gathered large amounts of data on how obesity affects breast cancer, but less research has been done on how to reduce breast cancer in an individual with obesity. This project is trying to bridge that gap in the literature. Furthermore, if all the mice lose weight and the breast cancer diminishes in every mouse, it's a weight loss issue. If all the mice lose weight and the breast cancer doesn't diminish in every mouse, it may be a deeper question of the mechanism chosen to lose the weight. Further research will have to be done at that point.

SPECIFIC ACTIVITIES AND TIMELINE

This study consists of 80 C57BL6J female mice. The mice will be fed a high fat diet (HFD D12492) consisting of 60% fat, 20% protein, and 20% carbohydrate. These mice will be on this diet for 8 weeks during the months of April and May. During these 8 weeks, I will be making sure the mice are progressing in their weight gain by weighing them individually weekly. Alongside weighing, we will monitor food intake. I will prep the food weekly, making the appropriate adjustments to food given if they are not putting on the optimal weight per week. After these 8 weeks, we will perform a body composition on each mouse to make sure they meet the requirements for obesity. Getting their fat mass and lean muscle mass through a Dexa-scan. Following the body composition, the mice will go on a 4-week weight loss intervention during the month of June. 5 nmol/kg of Semaglutide will be injected into these mice each day over this 4-week period. Following the weight loss intervention, another round of body composition data collection will be done. Alongside the body composition, blood will be collected from the mice to establish clinically relevant parameters of metabolic syndrome.

After these 3 months, breast cancer cell line E0771 will be injected into the mice. Over the proceeding 3 weeks in July, monitoring of the tumors will take place to make sure everything is how it should be. After the 3 weeks have passed, the mice will be sacked. Then we will analyze the tumors in each of the mice, to see the effects the breast cancer had.

Timeline -

- April-May: 8-week HFD, prepping food, weighing mice, making sure mice are progressing
- First body composition
- June: Daily Semaglutide injections for the entire month
- Second body composition and blood collection
- Breast cancer cell line E0771 injection
- July: Monitoring of breast cancer tumor (3 weeks)
- Sack mice
- Analyze the tumors of each of the mice

RELATIONSHIP OF WORK TO THE EXPERTISE OF THE MENTOR

My research advisor is Dr. XXX, an Assistant Professor at The University of Utah in the Nutrition & Integrative Physiology department. She leads the Dr. XXX Lab, exploring the dynamic relationship between nutrition and the circadian clock in health and disease to develop new therapeutic strategies to increase health span and well-being across lifespan in humans. Dr. XXX is greatly interested in studying how weight loss interventions can mitigate the risk of disease, with regards to the better overall health of people. My research proposal and Dr. XXX's vast knowledge of this area of study directly correlates to the goal of my proposal.

PROPOSAL: RELATIONSHIP OF THE WORK TO YOUR FUTURE GOALS

I am currently a sophomore at The University of Utah with the goals of obtaining a Bachelor of Science in Biology. Once I have built some knowledge in the field of science, I want to go to medical school and hopefully be lucky enough to one day become a doctor. Ever since I can remember I've been fascinated with the idea of maximizing your biological performance, through exercise, diet, sleep, etc. This being especially regarding performance in sports. I was lucky enough to be able to join Dr. XXX lab and gain the knowledge that nutrition has a far greater reach than that of just athletic performance but can provide longevity and health benefits I didn't know were achievable. Participating in an incredible program like UROP would allow me to gather an even deeper understanding of how nutrition and weight loss interventions can impact the lives of millions of people across the world. Especially the individuals that have been diagnosed with breast cancer. Leading to one day, me being able to help these individuals understand the best mechanism to prolong their health.

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