

## LAY ABSTRACT

TITLE: Pubertally Initiated High-Fat Diet Promotes Mammary Tumorigenesis in Obesity-Prone FVB Mice Similarly to Obesity-Resistant BALB/c Mice

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AUTHORS: Yirong Zhu<sup>\*, †</sup>, Mark D. Aupperlee<sup>†, ‡</sup>, Sandra Z. Haslam<sup>†, ‡, ¶</sup> and Richard C. Schwartz<sup>†, §, ¶</sup>

INSTITUTIONS: <sup>\*</sup>Cell and Molecular Biology Program, Michigan State University, East Lansing, MI; <sup>†</sup>Breast Cancer and the Environment Research Program, Michigan State University, East Lansing, MI; <sup>‡</sup>Department of Physiology, Michigan State University, East Lansing, MI; <sup>§</sup>Department of Microbiology and Molecular Genetics, Michigan State University, East Lansing, MI

<sup>¶</sup>Corresponding authors

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There is concern that red meat may be a risk factor for breast cancer. Previous research from this same laboratory shows that mice who were fed a high fat diet from red meat and were given a chemical that causes cancer were more likely to develop breast cancer. These studies were done in mice that did not become overweight, even when fed a high fat diet. The mice in these studies were chosen because researchers wanted to study the effects of diet, but not weight gain or obesity, on breast cancer risk. While this study showed that high fat diet did increase risk of breast cancer among mice exposed to chemicals that cause cancer, several questions were still unanswered. This study asked the question: if you fed a high fat diet from red meat during puberty to mice that gain weight, do they also develop breast cancer? This research also asked the question about when the breast cancer would occur. Researchers wanted to see if the mice got breast cancer before or after the mice gained weight. This allowed them to see if the cancer was caused by eating a high fat diet or from being overweight from a high fat diet. A final question was what type of cancer did the mice get? Results showed that the new mice did get breast cancer. It was also found that the mice got breast cancer before they become overweight. Finally, the mice were more likely to get triple negative breast cancer, an aggressive type of breast cancer that is difficult to treat. There was also an increase in cells that are known to promote cancer risk. Results of these studies suggest that diets high in saturated fat found in red meat can increase risk of breast cancer, even if mice are not overweight. These studies have important implications for breast cancer prevention in a broad segment of the population who consume diets high in saturated fats from red meat, including those who may not be overweight.

## ADVOCACY ABSTRACT

A high fat diet from red meat has been implicated as a risk factor for breast cancer in normal, but not overweight, women before menopause. In earlier studies, we showed that a high fat diet from red meat promoted the occurrence of breast cancer in mice that had been treated with a chemical carcinogen and do not become overweight on this diet. We also found that a high fat diet promoted the occurrence of breast cancer in mice that lack a gene called p53 in their mammary glands, again in mice that do not become overweight.

This paper looked at the effects of a high fat diet from red meat initiated during puberty in mice that had been treated with a chemical carcinogen, but in a mouse strain that gains weight on a high fat diet. High fat diet from red meat promoted breast cancer in these mice similarly to the mice that do not gain weight. The breast cancers occurred before these mice became obese, indicating the role of the high fat diet rather than the resulting obesity in promoting breast cancer. Also similar to the mice that did not gain weight, these mice had an increased numbers of a type of triple negative breast cancer. The tumors from mice fed a high fat diet also had increased “M2 macrophages”, a type of white blood cell that can promote the growth of tumors.

This work addresses the specific effects of a high fat diet in increasing susceptibility to breast cancer. Importantly, since many more people eat a high fat diet than become overweight, these studies have important implications for breast cancer prevention in a broad segment of the population. While the results of this study will not have immediate clinical application, the results of this study suggest that the avoidance of a high fat diet from red meat may be beneficial in lowering breast cancer risk, while clearly having no deleterious consequences. Importantly, the mice that were fed a high fat diet from red meat had increased numbers of a type of triple negative breast cancer. This type of breast cancer is aggressive and more difficult to treat, and studies in humans have associated it with premenopausal obesity. This means that these mice may be a useful model for studying how triple negative breast cancer occurs in humans. Furthermore, the increase in the number of tumor promoting macrophages that we have seen across several cancer models may indicate that a similar effect of high fat diet on immune function may contribute to epidemiological findings of increased breast cancer risk in young, premenopausal, normal weight women who consume a diet high in saturated animal fat.