

LAY ABSTRACT

TITLE: Pubertal and adult windows of susceptibility to a high animal fat diet in *Trp53-null* mammary tumorigenesis

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A high fat diet from red meat has been shown to be linked to breast cancer development in normal weight women before menopause, but this is not the case for overweight women. A few years ago, we studied this idea in a type of laboratory mice that do not become overweight on a high fat diet. We divided the mice into two groups: one group was fed a diet that was high in fat from red meat, and the other a low fat diet. We then gave each group a chemical that caused the mice to develop breast cancer. In the group fed the high fat diet, we found faster growth of breast cancer compared to the low fat diet group. This finding showed that the mice did not have to gain weight from a high fat diet in order for breast cancer to grow more rapidly. As we looked more deeply, we found that the increase in breast cancer growth only happened when the high fat diet was fed to the mice during puberty. This increase did not happen when the high fat diet was fed to them only as adults.

We built on this research finding and looked at whether a high fat diet would have the same effect in the same type of mice that do not become overweight on a high fat diet, but this time removing an important gene called *Trp53*, which is often abnormal or lost in human breast cancer. Doing the same experiment, we found that a high fat diet fed to the mice that lacked the *Trp53* gene increased the numbers of breast tumors compared to mice fed a low fat diet, and that this happened whether the mice were fed the high fat

diet only during puberty or only during adulthood. However, compared to breast cancers in mice fed a low fat diet, the breast cancers in mice fed a high fat diet only during puberty had: 1) cells that grew faster; 2) a better blood supply; 3) greater numbers of a type of white blood cell that can cause more tumor growth. The breast cancers that occurred when the mice were fed a high fat diet as adults were similar to the tumors in mice fed a high fat diet only during puberty, but they also showed fewer breast cancer cells that were dying. This is important because cell death is an important process in the body that helps keep cancer cells in check. Like our earlier experiment, since the mice that we used do not become overweight on a high fat diet, the fat from the diet seems to be increasing breast tumors rather than weight gain. Importantly, the mice fed a high fat diet only as adults also had increased numbers of a serious type of breast cancer called “triple negative” breast cancer. This means that these mice may be a useful model for researchers studying how triple negative breast cancer occurs in humans.

This work helps shed light on how the breast becomes vulnerable to exposures during puberty and in adulthood that increase the risk of breast cancer later in life. It shows specific effects of a high fat diet in increasing the chances of breast cancer. Since many more people eat a high fat diet than become overweight, these studies give us hints about breast cancer prevention for a broad group of the population. While this study will not be able to be used by doctors right away, these results suggest that avoiding a high fat diet from red meat may help to lower the chances of getting breast cancer in the future. Our studies also show that puberty may be an important time of vulnerability for increasing breast cancer risk in adulthood, and that we might help to reduce that risk by avoiding a high fat diet from red meat during this time.