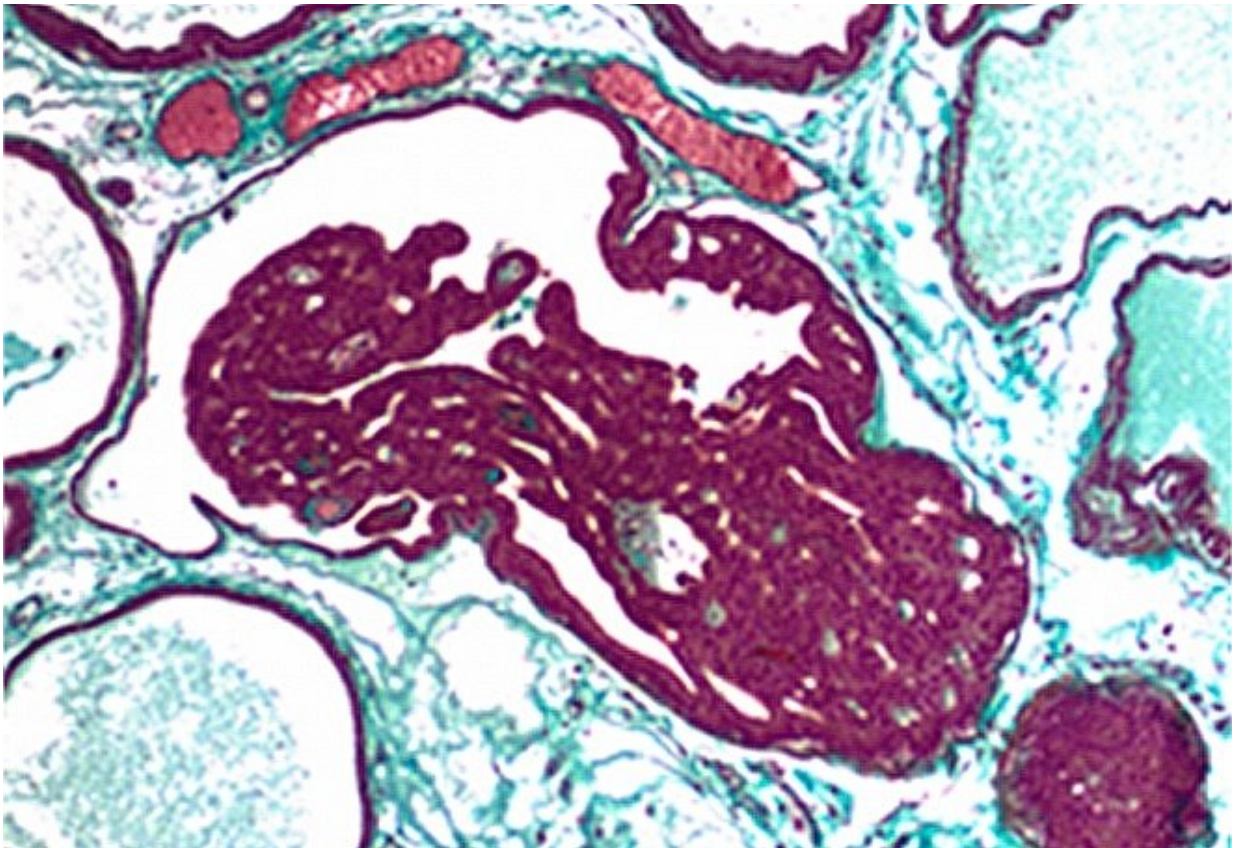


Low-protein diet during pregnancy increases prostate cancer risk in offspring

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Experiments with rats show that intrauterine protein restriction induces sex hormone imbalance, which appears to favor development of cancer in old age .
Credit: FAPESP

The offspring of females fed a low-protein diet during pregnancy and

lactation are significantly more likely to develop prostate cancer as they age. This is the main finding of a study performed with rats at São Paulo State University's Bioscience Institute (IBB-UNESP) in Botucatu, Brazil. The results of the study, which was supported by the São Paulo Research Foundation (FAPESP), have been published in *The Journals of Gerontology: Series A*.

"Our previous research showed that intrauterine exposure to a low-protein diet impairs prostate development. Our latest published study proves that this effect observed postnatally increases the incidence of prostate disease when the individuals concerned are older," said Luis Antonio Justulin Junior, a professor at IBB-UNESP and principal investigator for the study.

The model used in Justulin's laboratory consists of feeding pregnant females a diet with only 6 percent protein. Laboratory rats are normally fed a diet that contains between 17 percent and 23 percent protein.

"Data in the literature show 12 percent to be the minimum protein content needed for rats to carry a pregnancy to term without problems," Justulin said.

The pregnant rats included in the study were divided into three groups. The control group was fed the standard diet with at least 17 percent protein during pregnancy and a 21-day lactation period. After weaning, the offspring were also fed the standard diet. No cases of [prostate cancer](#) were found in these offspring 540 days after birth, when rats were considered old.

The second group of females were fed the 6 percent protein diet only during pregnancy. After giving birth, they were fed the [standard diet](#), as were their weaned offspring. In the assessment performed 540 days after birth, 33 percent of their male offspring had developed prostate cancer.

The third group was fed the low-protein diet throughout pregnancy and lactation, and 50 percent of their offspring developed prostate cancer.

"We performed a histopathological analysis on these animals' prostates, and in all three groups, we found preneoplastic alterations capable of interfering with glandular function, such as hyperplasia, epithelial atrophy and intraepithelial neoplasia; the latter has the potential to become carcinoma, according to data in the scientific literature," said the FAPESP-supported researcher. "However, cancer was found only in the animals exposed to the low-protein diet in their intrauterine life."

Hormone imbalance

The previous study, [published](#) in 2017 in *General and Comparative Endocrinology*, described some of the impairments caused in offspring by a maternal low-protein diet.

The analysis performed on the 10th and 20th days after birth showed that compared with prostates in the offspring of females fed the normal diet, those in the offspring of females fed the low-protein diet were smaller and had fewer differentiated epithelial cells, which is considered a sign of retarded development. The prostate also displayed functional impairment, secreting and storing less prostate fluid.

It is worth recalling that the function of the prostate is to produce the fluid that protects and nourishes sperm in semen, making it more dilute. "Generally speaking, these animals had [low birth weight](#), less developed organs, and altered [hormone levels](#)," Justulin said. "However, around the twenty-first day after birth, we began to see accelerated growth to try to make up for the deficit."

In a recently published study, researchers collected blood from male pups on postnatal days 21 and 540. They found an imbalance between

female and male hormone levels between the offspring of mothers fed a low-protein diet and the [offspring](#) of the control group.

While control males had 15 picograms (pg) of estrogen on PND 21, males born to rats fed the low-protein diet during pregnancy and lactation had 20 pg. On PND 540, the difference was even greater: 14 pg versus 35 pg, respectively.

Moreover, on PND 540, increased female hormone levels were associated with a decrease in the level of testosterone, the main male hormone. Control mice had 5 nanograms (ng), while those from the low-protein diet group had only 0.8 ng.

According to Justulin, no decrease in testosterone was observed in the low-protein diet group on PND 21 because this is the stage at which rat pups are growing the fastest.

"Our prior research showed that pups exposed to an intrauterine low-protein diet were born small but that as young adults they no longer displayed differences compared with controls in terms of size, prostate volume or hormone levels," said the FAPESP research project coordinator. "In our new study, the differences reappeared as they aged. It's as if aging were a second insult to the organism, considering that the first was the low-protein diet in the initial stage of development."

Researchers are now testing the hypothesis that exposure to altered hormone levels in old age favors carcinogenesis (tumor formation).

"We observed this in the prostate, but other studies show low birth weight induced by maternal undernourishment is correlated with altered insulin levels and increased incidence of metabolic syndrome and heart disease," Justulin said.

The research group at IBB-UNESP is currently investigating sex hormone synthesis pathways with the aim of understanding how a low-protein diet affects the estrogen-testosterone balance. They also want to demonstrate the mechanism through which [hormone imbalance](#) can favor the development of prostate cancer.

Preliminary results of this research point to dysregulated messenger RNAs and microRNAs in the restricted-[diet](#) animals on postnatal day 21.

"We found several messenger RNAs and microRNAs that were dysregulated in both pups at 21 days and 540-day-old animals with cancer," Justulin said. "What's interesting is that some of these molecules are also altered in human patients with [prostate](#) tumors, according to our analysis of public genome databases with the aid of bioinformatics tools."

More information: Sergio A A Santos et al, Maternal Low-Protein Diet Impairs Prostate Growth in Young Rat Offspring and Induces Prostate Carcinogenesis With Aging, *The Journals of Gerontology: Series A* (2018). [DOI: 10.1093/gerona/gly118](https://doi.org/10.1093/gerona/gly118)

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