

# Estrogen's opposing effects on mammary tumors in dogs

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Veterinary oncologist Karin Sorenmo and colleagues cast new light on the complex role of estrogen in canine mammary cancer. The research emerged from Penn Vet's Shelter Canine Mammary Tumor Program, which assists in treating and then finding homes for dogs like Brownie, pictured with former oncology intern, Kiley Daube.

Dogs that are spayed at a young age have a reduced risk of developing mammary tumors, the canine equivalent of breast cancer. Early spaying reduces levels of estrogen production, leading many veterinarians and scientists to cast estrogen in a negative light when it comes to mammary cancer.

But the effects of [estrogen](#) on [cancer risk](#) in dogs aren't straightforward, according to a new study led by researchers from Penn's School of Veterinary Medicine. While it's clear that spaying dogs greatly minimizes their risk of developing [mammary cancer](#), the findings suggest that the practice may increase the risk of more aggressive cancers. And in spayed animals with [mammary tumors](#), the team found that higher serum estrogen levels were actually protective, associated with longer times to metastasis and improved survival times.

"Dogs that remain intact and have their ovaries develop many more mammary tumors than dogs that were spayed, so removing that source of estrogen does have a protective effect," says Karin U. Sorenmo, a veterinary oncologist at Penn Vet and senior author on the study, published in *PLOS ONE*. "Estrogen does seem to drive mammary [cancer](#) development. But what it does for progression to metastasis—that I think is more complicated."

Sorenmo and colleagues have been studying mammary tumors in dogs as a way of improving care and treatment for pets but also to make insights into human breast cancer biology.

"Much of the research we do in veterinary medicine looks at what is done in people and then adapts it," she says. "But dogs are such a great, comprehensive model for cancer. Yes, there are differences in biology between dogs and people, but here those differences may allow us to ask very probing questions about what estrogen is doing in both dogs with mammary cancer and women with breast cancer."

The research used data from two prospective studies, including one involving dogs in the Penn Vet Shelter Canine Mammary Tumor Program, through which shelter dogs with mammary tumors receive treatment, are studied by researchers like Sorenmo, and then find foster or permanent homes.

The team evaluated 159 dogs with mammary cancer, 130 that were spayed as part of the study and 29 that remain intact. In addition to surgically removing the dogs' measurable tumors, the team collected information on serum estrogen levels, [tumor](#) type, disease grade and stage, time to metastasis, and survival time.

Despite estrogen's link with an increased risk of developing mammary tumors, the researchers found that higher serum estrogen levels also seemed to help dogs avoid some of the riskiest aspects of their disease. Unexpectedly, when dogs were spayed at the same time their tumors were removed, those with estrogen receptor-positive tumors that had higher serum estrogen took longer to develop metastatic disease and survived longer than dogs with lower estrogen levels, confirming that these tumors depended on estrogen for progression.

Sorenmo speculates that, in these cases, estrogen's action may be nuanced. "It drives the cancer, but it also seems to control or modulate it, reining it in," she says, because most dogs with high serum estrogen levels had lower-grade and estrogen receptor-positive tumors, rendering them susceptible to hormonal deprivation by spaying.

The protective role of estrogen was also surprisingly pronounced in dogs with estrogen-receptor negative mammary tumors. In these higher-risk cancers, high serum estrogen was associated with delayed or absent metastasis. Complementing these findings and supporting a potential broader, tumor receptor-independent anti-cancer effect driven by estrogen, [dogs](#) with low serum estrogen had a significantly increased risk

for developing other non-mammary aggressive fatal tumors, such as hemangiosarcoma, during their follow-up after mammary tumor surgery.

Some of the findings contradict what has been found in women with breast cancer. For example, higher serum estrogen levels in women following breast cancer therapy have been associated with higher rates of recurrence. But Sorenmo also notes that many cases of breast cancer in women arise just after menopause, when estrogen levels tumble. So there may be a more complex role for estrogen in people's cancer risk as well.

The work points to new possibilities for examining the role of estrogen in cancer initiation and progression. Already, Sorenmo and colleagues, including Penn Vet's Susan Volk and Ellen Puré, are pursuing investigations of how the hormone affects the tumor microenvironment, cells that aren't themselves cancerous but may either stem or encourage a tumor's growth and spread.

"I think this study opens some really complicated questions," Sorenmo says. "If we start dissecting exactly what estrogen is doing, what genes or immune cells it's interacting with, maybe we could harness the power of estrogen to be more clever in our treatment strategies."

**More information:** Karin U. Sorenmo et al, The estrogen effect; clinical and histopathological evidence of dichotomous influences in dogs with spontaneous mammary carcinomas, *PLOS ONE* (2019). [DOI: 10.1371/journal.pone.0224504](https://doi.org/10.1371/journal.pone.0224504)

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