

Feline Postvaccinal Sarcoma: A 2007 Update

The Essentials

The only proven cause is prior administration of a traditional adjuvanted, killed vaccine (rabies, feline leukemia).

The risk of tumor development is about 1 in 5000 vaccinations.

The interval between vaccination and tumor detection varies from 6 weeks to at least 13 years... making it almost impossible to determine exactly which vaccine was responsible.

The risk of postoperative recurrence and worsening invasion is very high; the metastatic risk is very low, although it probably increases gradually with time in those cats kept alive with aggressive surgical and radiation protocols.

Vaccinating at sites amenable to amputation will greatly reduce the case fatality rate; vaccinating less frequently should reduce overall prevalence, and vaccinating only with non-adjuvanted vaccines should completely eliminate the disease once the current generation of traditionally-vaccinated cats has disappeared.

What is it?

Feline postvaccinal sarcoma is a locally invasive spindle cell sarcoma occurring at sites of previous vaccination in cats. There is no known breed predilection. Most of the tumors are histologically classified as fibrosarcomas, but other stromal sarcomas like osteosarcoma, chondrosarcoma, or rhabdomyosarcoma can also occur. The interval between vaccination and development of tumor is as short as 6 weeks or as long as 13 years. These tumors are extremely invasive and are difficult to cure even with aggressive surgical excision.

How frequent is it?

The prevalence varies widely from region to region, presumably depending on many variables that include vaccine practices and products, genetic composition of the feline population, and sensitivity of detection. The overall prevalence is estimated at between 1 and 10 per 10,000 vaccinations. Canadian data, derived from our Histovet database, are presented in Figure 1 and Table 1. This data reflects primarily the prevalence in Ontario, Quebec, and Atlantic Canada.

How does it develop?

Feline postvaccinal sarcoma is the only proven example of cancer arising at a site of previous "drug" administration in any species. The syndrome was first described in 1991, but cases had been seen in the northeastern United States since about 1987. The first Canadian cases were seen in 1994. At least in the United States, the appearance of postvaccinal sarcomas was linked to three historical events: legislation making rabies vaccination of cats mandatory, introduction of high-potency killed rabies vaccine replacing the modified live products, and introduction of killed feline leukemia vaccines.

Analysis of the microscopic lesions, epidemiologic evidence, and what we know about cancer biology suggests that these tumors arise by malignant transformation of the fibroblastic population found within the wall of a postvaccinal granuloma. The development of at least some degree of localized chronic granulomatous inflammation (usually termed postvaccinal panniculitis) is essential for the efficacy of adjuvant-potentiated killed vaccines. Every single vaccine administration induces this reaction to some degree. Part of the histologic lesion is a wall of intermingled macrophages and fibroblasts around the vaccine deposit. It is within that wall that we can sometimes see the stepwise evolution of fibroblastic malignancy. The risk of cancer development is additive: the more vaccines are given to an individual, the higher is the risk of cancer development. This is probably the reason for the rising prevalence with age: most cases occur in cats over 10 years of age (Figure 2).

The actual malignant transformation is undoubtedly a very complex event, but one of the steps is the accidental activation of the *cis* oncogene that codes for the potent fibroblast-stimulating cytokine known as platelet-derived growth factor (PDGF). PDGF is a normal part of the wound healing process, but in cats with postvaccinal sarcoma its production appears to be continuous and unregulated, suggesting that postvaccinal sarcoma is a manifestation of improperly "downregulated" wound healing. As far as we can determine, there is no role for any accidental contamination of the vaccines with oncogenic virus in the pathogenesis of this disease. There is some evidence that individual cat genetic predisposition may be important, based on fairly scant evidence of increased prevalence in closely-related cats, and the development of multiple independent tumors at different locations in the same cat. There is also unexplained geographic variation in prevalence, again pointing to the possibility of geographic "clustering" of genetically-related susceptible individuals. In Canada, the Atlantic provinces have a substantially higher prevalence, with Newfoundland being the highest of all. The speculation that this may reflect a sequestered genetic population has not been tested.

What products have been incriminated?

It appears that any killed vaccine containing adjuvant is capable of inducing this reaction. Most reports implicate killed rabies vaccine and feline leukemia vaccine as the main culprits, but analysis is complicated by the recognition that the vaccine that caused the tumor may be one given 5, 7 or 10 years earlier! There are scattered anecdotal reports of other long-acting products like lufenuron, long-acting penicillin, methylprednisolone, or even microchips triggering the development of similar sarcomas. The credibility of such claims is hard to evaluate because in none of those reports were the authors able to rule out the possibility of previous vaccination in that same location.

What is the interval between vaccination and detection of neoplasia?

The interval varies from a few months to 13 years. It is important to realize that the tumor is not necessarily the result of the most recent vaccination, making it difficult to pinpoint the true villain. We do not know the minimal interval between vaccination and tumor development. Theoretically it should be at least several months, and in most cases it will be several years.

What is its usual behavior?

These tumors develop slowly at sites of pre-existent postvaccinal granulomatous panniculitis. The tumor grows with invasive peripheral tentacles, so the extent of the tumor is extremely difficult to determine even with microscopic examination. It seems very clear that the neoplastic transformation occurs even in subcutaneous tissue well beyond the limit of the palpable or visible nodule. Following "routine" excision (margins of less than three centimeters), the prevalence of recurrence is in excess of 90 percent, almost all within the first six months. The mean tumor-free interval following such routine excision in one study of 61 cats was 79 days. In contrast, the tumor-free interval following radical excision (in particular, limb amputation) was 325 days. In a study of 82 cats with postvaccinal sarcomas excised with 5 cm margins and/or at least two muscle planes, the surgical cure rate was claimed to be 90%. The problem, of course, is that very few of these tumors occur in regions in which 5 cm margins are going to be possible without amputation.

Combining aggressive surgery with radiation therapy is claimed to increase survival duration and approximately double the probability of cure. At the present time, adjunct chemotherapy has not been proven to be beneficial. The cost for the complete "optimal" surgical/radiation protocol is \$5000-10,000!

Under most circumstances, the risk of metastatic disease is essentially irrelevant because of our inability to adequately control the locally invasive, recurring disease. The prevalence of detected metastatic disease at the time the cat is initially diagnosed with postvaccinal sarcoma is less than 5 percent. That number appears to rise with increasing survival times in cats that are aggressively treated, with estimates in the region of 25 percent. Metastatic disease is rarely the reason for euthanasia.

What should I do with a lump suspected of being a postvaccinal sarcoma?

Since the best chance for long-term survival comes from aggressive initial excision and radiation therapy, this is one type of skin tumor that should be sampled with a core biopsy prior to excisional surgery. If it is diagnosed as postvaccinal sarcoma, you should then recommend radical surgery. Alternatively, if the histologic diagnosis is of some other type of neoplasm or just postvaccinal granuloma, then your excision can be much less traumatic and disfiguring. *Cytologic assessment is unreliable and should not form the basis for your decision.*

What is the future?

The emergence of this syndrome has been a powerful stimulus for veterinarians and vaccine companies to re-evaluate not only the composition of the vaccines, but also our current recommendations for the range and frequency of vaccination. Although even the maximum estimated prevalence of postvaccinal sarcoma (10 in 10,000 vaccinations) is much lower than the risk of infectious disease if we were to stop vaccinating, this disease breaks the cardinal medical

rule of "Do No Harm". There has been considerable criticism of traditional vaccination protocols, and tremendous pressure to reduce the frequency of vaccination, reduce the number of diseases for which we vaccinate, and use safer products that do not routinely induce the postvaccinal granulomas that represent the fertile soil for eventual neoplastic transformation. The problem in altering current vaccine protocols is that we have virtually no data about the duration of effective immunity from the current vaccines. One cannot extrapolate from product to product or from disease to disease. For some, like feline panleucopenia, immunity probably persists for years. For others, like the upper respiratory viruses, the duration of immunity probably resembles that following natural infection: transient and fragile. The consensus seems to be that we should reduce the range of diseases for which we vaccinate to those that represent a substantial risk for that individual patient. The solitary cat that is exclusively indoors, for example, should receive a very different vaccination protocol from the neighborhood tramp in a multi-cat household! There is no evidence that changing the site of vaccination, using single-antigen vaccines, dividing the dosage, or any other such recommendation has any effect on the risk of developing a postvaccinal sarcoma.

New vaccine technology holds great promise, in that there are now non-adjuvanted DNA-based vaccines that are safe, effective, and cause essentially no tissue injury at the site of administration. At least theoretically, these should not cause sarcomas. Old habits die hard, and the penetration of these products into the marketplace has been relatively slow. Given the long lag time between vaccine administration and tumor detection, we will continue to see postvaccinal sarcomas for at least the next 10 years even if we were to stop vaccinating altogether!

Nonetheless, the reduction in how frequently we vaccinate and, perhaps, what products we use does seem to be having a positive effect. As seen in figures 1-2, the prevalence is slowly falling and the age of affected cats is rising. This probably reflects disease caused by the "sins of our past" with older cats getting tumors from vaccinations done several-to-many years earlier.

Want further information?

Probably the single most comprehensive review of vaccine-associated feline sarcomas is a report of the Vaccine-Associated Feline Sarcoma Task Force published in June 2005. It is in a very readable "question and answer" format, and reflects a roundtable discussion by a very experienced and opinionated panel of experts. You can find it at <http://www.histovet.com/PDFs/FelineSarcomaRoundtable.pdf>

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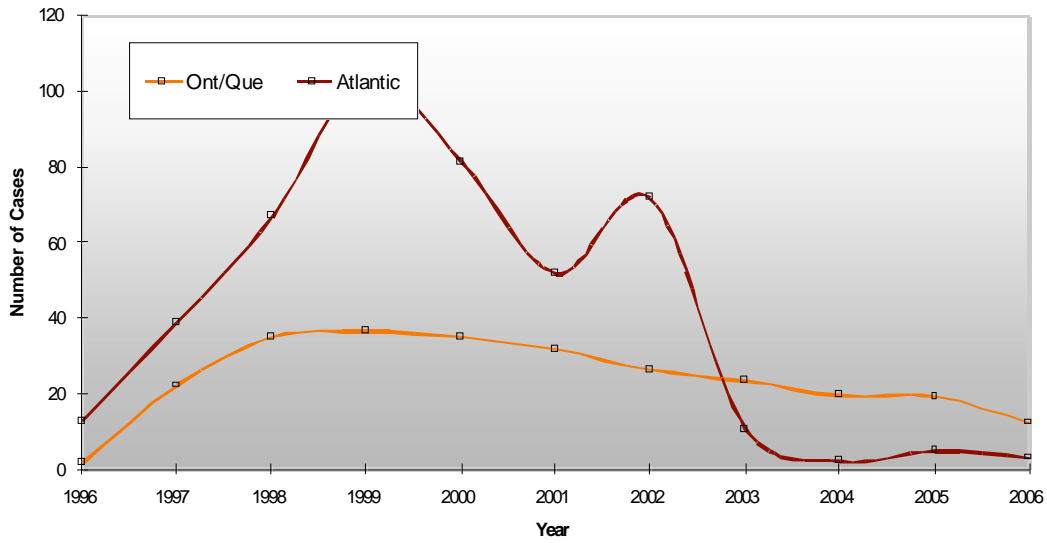


Figure 1. Geographic Distribution of Feline Postvaccinal Sarcomas (cases per 1000 submissions).

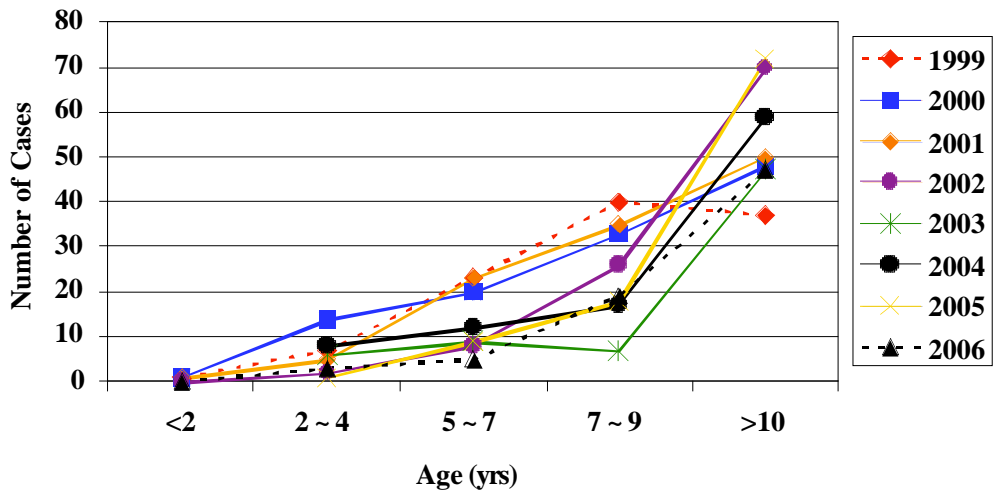


Figure 2. Age Demographics of Feline Postvaccinal Sarcomas

Table 1. Annual Prevalence (1996-2007)

Year	Total Feline Biopsies	Total Postvaccinal Sarcomas*
1996	1741	4
1997	2222	50
1998	2747	108
1999	3006	122
2000	3333	124
2001	3589	114
2002	3709	110
2003	3802	69
2004	4100	96
2005	4192	120
2006	3936	76
2007	4250	102

*Source: Histovet Surgical Pathology.