

## Rabbits with mammary carcinomas as a model for comparative pathology and translational science in breast cancer research

Within a breeding colony of rabbits, the American pathologist Harry Greene (1904-1969) observed that mammary carcinomas were restricted to certain families. This is suggestive of a familial predisposition as it occurs in human breast cancer. In rabbits, most invasive carcinomas developed through progression from non-neoplastic cysts over intraductal benign tumors to non-invasive and invasive carcinomas with possible metastasis. Similarly, breast cancer of women may form within precursor lesions.

The recent rise in the diagnostic submission of mammary lesions from pet rabbits is likely caused by increasing popularity of rabbits as pets. Microscopic evaluation reveals that most rabbit mammary tumors represent invasive carcinomas (Fig. 1). These are predominantly diagnosed in middle aged to older does (mean sage: 5.3 years). This is comparable to breast cancer in humans, which mostly occurs in middle aged to older women. Rabbit mammary carcinomas often develop in mammary tissue with multiple cysts or benign tumors, which supports the multistep tumorigenesis observed by Greene.

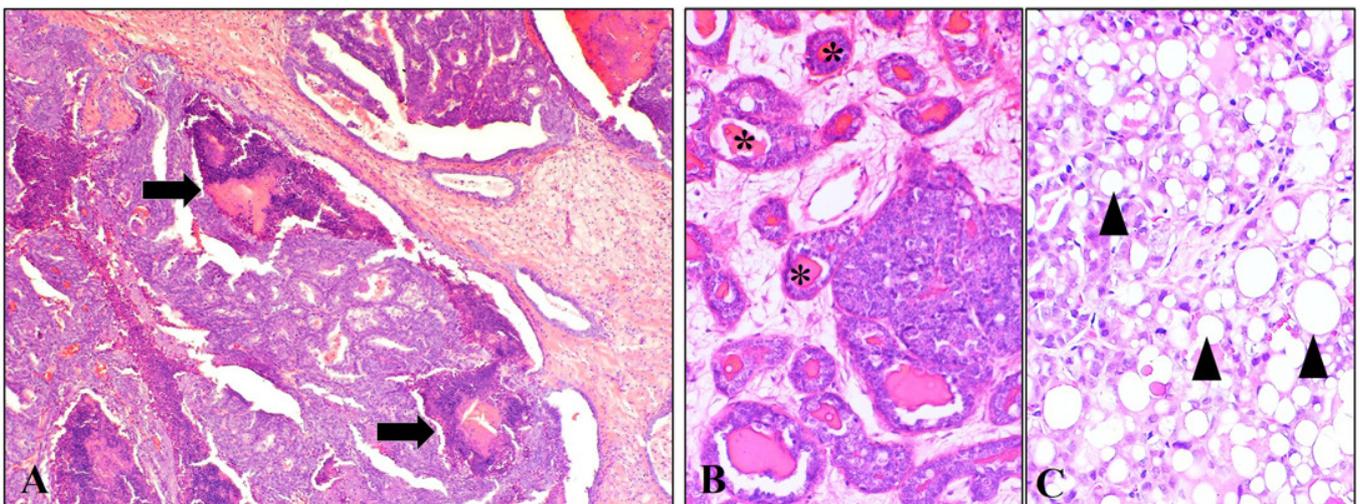


Fig. 1. A. In pet rabbits, the majority of proliferative mammary gland lesions represent invasive carcinomas. The depicted carcinoma contains numerous areas of necrosis (arrows). B and C. Mammary carcinomas of pet rabbits often show secretory activity characterized by extracellular proteinaceous material (asterisks) and lipid vacuoles in tumor cells (arrowheads).

Rabbit mammary complexes and human breast tissue show similar histological features. In rabbits, secretory activity is often detected in the normal mammary gland tissue, and it was observed in more than 65% of rabbit mammary carcinomas (Fig. 1). Evidence for lactational activity includes extracellular proteinaceous material and lipid vacuoles in epithelial and carcinoma cells (Fig. 1), since the rabbit milk has a high protein and lipid content.

In human breast cancer, the estrogen receptor- $\alpha$  and progesterone receptor (ER, PR) status is routinely analyzed, because a positive expression above a threshold indicates a likely response to antihormonal treatment. Hormone receptor negative breast cancer encompasses human epidermal growth factor receptor 2 (HER2) positive carcinomas and carcinomas that are ER, PR and HER2 negative. The latter are named triple negative breast cancer and have a poorer prognosis than hormone receptor positive or HER2 positive subtypes due to only limited targeted treatment options.

Immunohistochemistry reveals that more than 60% of pet rabbit mammary carcinomas do not express ER and PR, whereas these receptors are present in secretory epithelial cells of the adjacent non-neoplastic mammary tissue. Rabbit mammary carcinomas show a statistically significant association between a lower ER or PR expression and a higher tumor cell proliferation.

These findings indicate that the hormone receptor status has prognostic significance in pet rabbits, and that pet rabbits may represent a suitable animal model for hormone receptor negative human breast cancer.

Rabbits are widely used in translational research as animal models for human diseases (Fig. 2). Their physiological functions and organ structures are more related to primates than those of rodents. Further, rabbits have a tame behavior. Their life expectancy averages 9 to 13 years and would permit follow-up studies. Housing and feeding requirements can easily be met, and numerous offsprings can be obtained within a short period of time. Adult pet rabbits often develop obesity that is a frequent life-style associated disorder in humans.

*Value of pet rabbits as an animal model for human breast cancer*

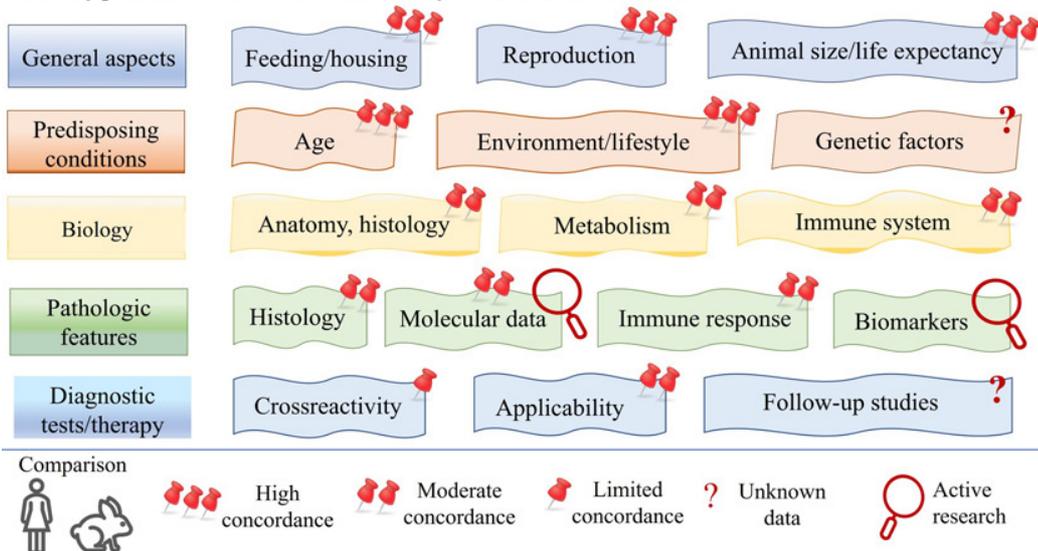


Fig. 2. Shown are the general requirements for animal models of human diseases. Pet rabbits are widely used in translational research, since they partially to completely fulfil numerous of the listed criteria. In humans and rabbits, non-neoplastic mammary tissue and carcinomas show very similar histological features. Comparative pathological studies are ongoing. Already available molecular data suggest that pet rabbits with mammary carcinomas may represent animal models for hormone receptor negative human breast cancer.

The described data contribute to the one-health one-medicine concept, which is based on comparative pathophysiological investigations and aims to improve medical care for humans and animals that share the same environment and develop similar diseases. An important prerequisite for such studies is the use of cross-reactive diagnostic tests as well as standardized procedures (Fig. 2). So far, the only treatment for rabbit mammary carcinomas is surgical excision, which may not be feasible in debilitated animals. Comparative pathological investigations aim to identify novel treatment strategies for certain types of human breast cancer on the one hand and to reveal prognostic markers and additional treatments for rabbits with mammary carcinomas on the other hand. Regarding the latter, possible differences in drug tolerance and metabolism need to be investigated as well.

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## **Publication**

[A review on mammary tumors in rabbits: translation of pathology into medical care](#)

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