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ANIMAL MODEL IN BREAST CANCER RESEARCH

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History

Breast cancer is an abnormal cell growth that can occur in mammals, and it is the most common cancer that leads to fatality in women. Since humans shared a common cell growth system with other mammals, animals such as rodents, canines, primates, and porcines were usually used for breast cancer experimental models. It had been started in the 1930s when this animal was used to study endocrinology. The animal models were designed according to the requirements of the studies and can be divided into four categories as shown in Table 1.

Spontaneous breast cancer tumors have been frequently observed in rodents, and usually inbred mice are used for these cancer studies. TA2 inbred mice that were bred in Tianjin Medical University exhibited a stable genetic phenotype and were able to develop spontaneous breast cancer similar to human basal breast cancer in terms of biology, morphology, and phenotypes (Sun et al, 2008). In addition to this, spontaneous breast cancer can also be studied using canines, felines, and primates as they can mimic human lifestyles and environmental effects for immune system studies. The disadvantages of spontaneous breast cancer animal models include low incidence rates, long latency, lengthy experimental periods, and non-synchronization.

For induced breast cancer models, the researcher can artificially increase the incidence and acceleration of tumorigenesis via chemical, physical, and biological carcinogens through oral administration, injection, and whole-body treatment (Su et al, 2010). Most chemically induced breast tumors are adenomas and type B adenocarcinomas and these cancers are hormonally dependent. Breast cancer can also be induced by physical approaches such as ionizing radiation from X-ray or neutron radiation. This method will induce hormone-dependent adenocarcinomas or fibroadenomas. Meanwhile, for the biologically induced breast cancer model, the researchers mainly relied on lentiviruses to overexpress oncogenes or silence the tumor suppressor genes in the animal. The advantages of this model include relatively high incidence rates, short latencies, and more reliable results compared to spontaneous breast cancer models. However, the disadvantages of induced models are low efficiencies, long incubation times, different incidence times, and different pathological characteristics.

Transplanted models involve the transplantation of spontaneous or induced breast cancer tissues or cells into experimental animals. It can be divided into allograft and xenograft (requiring immunodeficient mice). The cancer tissues will be transported via orthotopic and ectopic transplantations.

Even though transplantation can generate a better pathological microenvironment for breast cancer, fewer cancer cells can be injected, and the procedure itself is technically challenging.

Table 1: Categories of animal models for breast cancer studies (Source: Li Zeng et al, 2020).

Model	Interactions	Method
Spontaneous		No treatment
Induced	Chemical Physical Biological	DMBA or MNU Radiation Lentivirus Infection
Transplantation	Homeotransplantation	Spontaneous or induced breast cancer cells transplanted into the same strain.
	Heterograft	Human breast cancer cells or patient tumor tissues are transplanted into immunodeficient animals.
Genetic Engineering Mouse Model	Transgenic Knockout	Oncogene activation tumor suppressor gene inactivation

Genetic Engineering Mouse Model or GEMM are created using transgenic technology. The animal's genetic will be altered to suit the requirement to grow mammary tumors cell rapidly, can be hormone activated, and can help to mimic a large range of breast cancer spectrum whether for *in situ* cancer or metastasis cancer. The advantages of GEMM are the animal's immune function is usually intact and the genetic alteration is similar to breast cancer patients, making it suitable for etiological and preventive studies. However, there are several disadvantages of GEMMs: the breast tumors developed from GEEMs are different from human breast tumors in histology, they are expensive and time consuming, and gene editing occurs in almost all mammary ductal epithelial cells which does not reflect the actual situation of cancer initiation.

Animal for breast cancer model

The animals that are usually used as a model for breast cancer studies can be divided into two categories: non-mammals and mammals.

Non-mammal animals such as *Caenorhabditis elegans*, Drosophila, zebrafish, and chicken are frequently used to mimic breast cell growth and metastasis. It becomes more favourable for toxicity studies since these animals have shorter reproductive cycles. For example, Mercatali et al (2016) injected the primary cultured bone metastases cells from human breast cancer into zebrafish embryos to study their metastatic potential. However, there are disadvantages to these animals: they are very different from humans, lack genetic diversity, and have a different physiological structure. Figure 1 shows mature zebra fish.

Figure 1: Zebra fish.
(Source:
https://www.understandinganimalresearch
.org.uk/news/why-zebrafish)

As compared with non-mammalian animals, mammals are more similar to humans. Rodents, mice, and tree shrews are usually used as animal models because they are similar in terms of anatomy, physiology and genetics compared to non-mammalian. Additionally, there are many inbred strains of mice and rodents available, thus making the study of breast cancer more diverse. However, there are several drawbacks to the animal model using rodents and mice, as those two mammals have a higher tolerance for drugs compared to human.

Feline breast cancer model

In utero implantation of mammary cancer cells in a cat's fetal tissue produced tumor that was able to metastasize after 6 to 10 weeks. The tumor is usually radio- and chemo-resistant. An example of a tumor in a feline is shown in Figure 2.

Canine breast cancer model

Similar to feline, canines' mammary tumors occur spontaneously, are hormone dependant and show dysregulated expression for the gene of breast tumors identical to human breast cancer, especially when it comes to its histological and molecular characteristics. Figure 3 shows an example of breast cancer in canine.

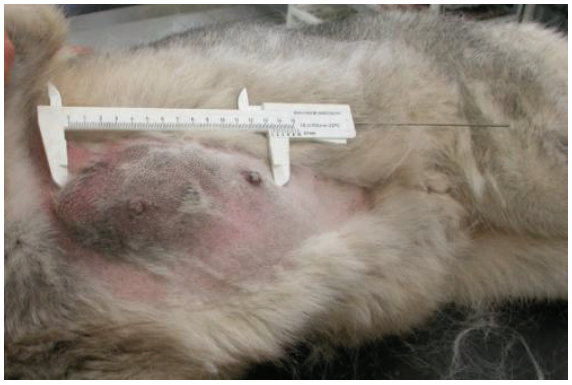

Figure 3: Dog with a mammary tumor. (Source: Veronica Kristiansen,2013)

Porcine breast cancer model

Porcine model is usually used to study the pharmacokinetics of breast cancer drug before they are introduced to human trials. This is because the pig has the most similarity to human with respect of drug reactions. However, there are disadvantages of using large animal cancer models as it involved high cost, space, special tools, and maturation time. For this reason, most researchers preferred using small mammals like rodents for their research.

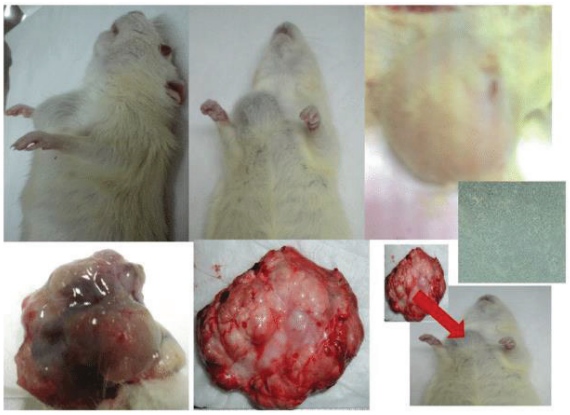

Figure 4: Breast cancer tissue extracted from rats (Source: Al-Saeedi, 2014)

Rodents breast cancer model

Rats have been considered a suitable animal model to study breast cancer due to their similarity to human mammary cancer in terms of histology, immunocytochemical markers, and biological behaviour of tumors. Long-term studies have shown that some rats can develop breast tumors spontaneously, making it easier to mimic the growth of breast cancer in a shorter time. Figure 4 shows the breast cancer tissue growth that was extracted from rats.

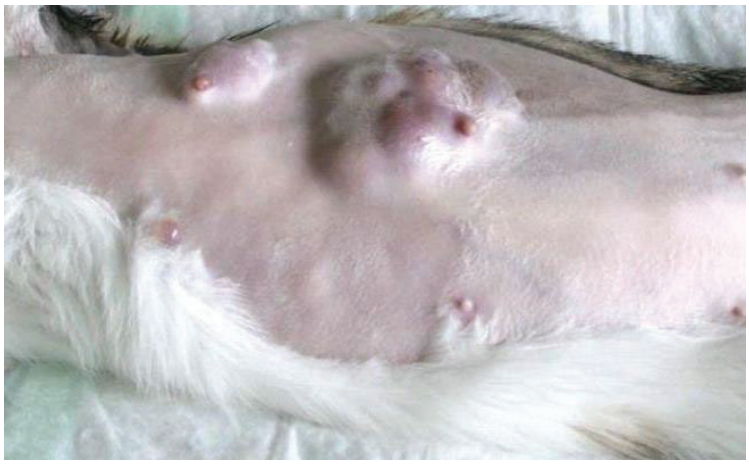

Figure 2: Breast cancer in female cat. (Source: L. Soltes, 2011)

Animal ethic

To protect the animal's well-being, several guidelines need to be followed, and the researcher needs to have a proper qualification and have attended a validated course for animal handling in research. Those guidelines are:

1. Respect for animal dignity: The researchers must have respect for animals worth, regardless of their utility value, and must provide care that is adapted to the needs of each laboratory animal.

2. Responsibility for considering other options: The researchers are responsible for studying whether there are alternatives to experiment on animals. Alternative options must be prioritized if the same knowledge can be acquired without using laboratory animals.

3. The principle of proportionality (responsibility for considering and balancing suffering and benefits): The researchers must consider the risk that laboratory animals experience pain and other suffering. The possible benefits of the study must be considered, substantiated, and specified in both short and long terms. Suffering can only be caused to animals if this is counterbalanced by a substantial and probable benefit for animals, people, or the environment. The research institutions should provide training on suitable models and the researchers are responsible for using such methods of analysis when planning experiments on animals.

4. Responsibility for considering reducing the number of animals (reduce): The researcher is responsible for considering whether it is possible to efficiently plan for the usage of animals in their research and must only include the number necessary to maintain the scientific quality of the experiment.

5. Responsibility for minimizing the risk of suffering and improving animal welfare (refine): The researcher must minimize the risk of suffering and provide good animal welfare. This includes before, during, and after the experiment, such as trapping, labelling, breeding, transportation, stabling, and euthanizing.

6. Responsibility for maintaining biological diversity: The researcher is responsible for ensuring that the use of laboratory animals does not endanger biological diversity by considering the consequences for the stock and the ecosystem. The use of endangered and vulnerable species must be reduced to an absolute minimum.

7. Responsibility when intervening in a habitat: The researcher is responsible for reducing disruption and any impact on the natural behaviour of individual animals, including those that are not the direct subject of research.

8. Responsibility for openness and the sharing of data and materials: The researcher is responsible for ensuring that there is transparency about research findings and facilitating the sharing of data and material from experiments on animals. This is to avoid the unnecessary repetition of experiments. Transparency is also important to ensure that the public is informed about the findings of the research.

9. Requirement for expertise on animals: The researcher and other experts who handle live animals must have adequately updated and documented their finding to ensure the well-being of the animal.

10. Requirement of due care: The researcher must update their knowledge regarding the current rules and regulations for animal handling by attending the workshop and seminar on these matters.

Figure 5 shows the author being certified by the Faculty of Pharmacy, UiTM, after attending 2-day workshop on handling Laboratory rodents.

Figure 5: The author had been certified by Associate Professor Dato' Dr. S. Vellayan on her completion of the workshop for animal handling. (Source: Author's personal collection)

In the future, the usage of artificial intelligent, or A.I had the higher potential to further minimize the usage of animals in research as they can mimic the interaction between drugs and animal cells, thus reducing the usage of animals for cancer studies. One must be responsible when using the animal for study, and it also has a life that needs to be appreciated.