Panoramic review on mammary carcinomic chemopreventive animal models

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Abstract: **Consequently, animal models are utilised to evaluate the effectiveness of chemopreventive and chemotherapeutic drugs. This is due to the fact that the microenvironment of primary cells that have been cultured and separated from an animal organ or system differs significantly from in vitro systems. To better understand how various cell types and drug or xenobiotic metabolisms interact, animal models are essential. Animal models can be produced chemically or transgenetically to study particular cancer types. There are several tumor-specific animal models available for research on chemopreventive effects. In several chemically produced or transgenic animal models, the effectiveness of chemotherapeutic medications used to treat malignancies such as prostate, skin, liver, and colon, among others, is being studied. In women, breast cancer is the most prevalent type of malignancy. Animal experimentation is a major part of basic and translational breast cancer research. Such breast cancer models should, in theory, be similar to human breast cancer in terms of tumour origin, biological behaviour, pathology, and therapeutic response. This study describes recent developments in several breast cancer experimental animal models and examines their traits, benefits, and future uses. Finally, we suggest future lines of investigation for animal models of breast cancer.**

***Keywords*: Drug development; Metastasis; Animal models; Breast cancer.**

INTRODUCTION

In 2020, there will be 19.3 million new instances of cancer, leading causes of death globally. Over the following 20 years, this number is predicted to rise. Cancer impact may elevate to 28.4 million in the world by 2040. In terms of global incidence, breast cancer comes in first 888place, followed by prostate, lung, and colorectal cancers, according to GLOBOCAN 2020. The malignancies of the breast, prostate, and liver are followed by lung cancer in terms of fatality rates.

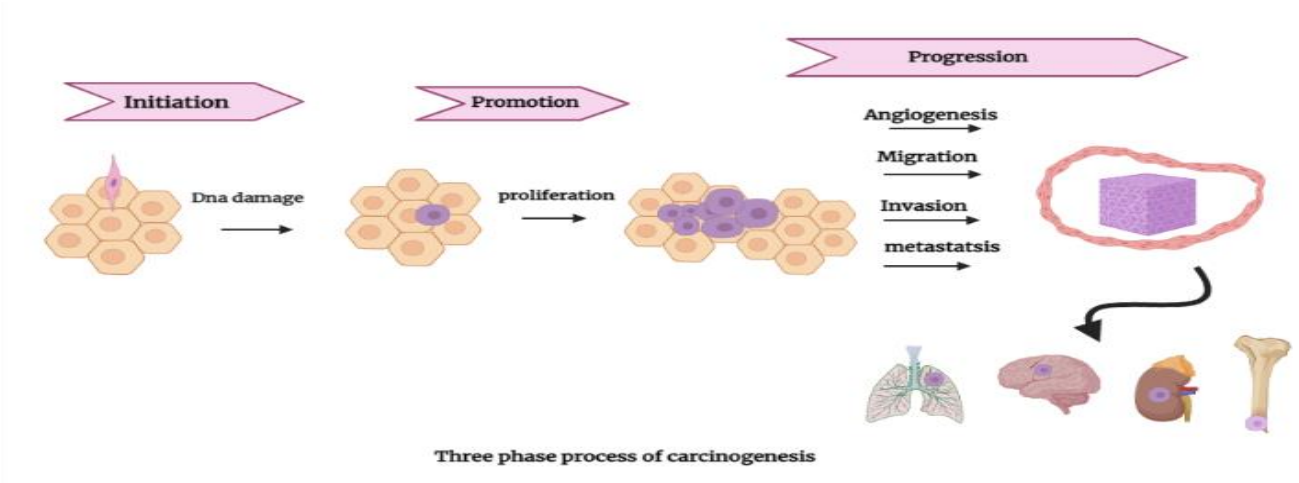
Sporn and associates first used the term "cancer chemoprevention" in 1976. By ingesting dietary or pharmacological compounds that can modulate the process of carcinogenesis, cancer chemo preventive agents help to prevent, inhibit, and reverse cancer. Chemo prevention has advanced Cancer chemotherapy. The preventive medicines for cancer may alter signal transduction by acting as genetic modulators. According to a current definition, they are substances, individually or in combination, that have the ability to change or acts opposite to the expression or certain act of protein target that is responsible for transforming normal cells production.Cancer chemo prevention has become wide field in recent research comparatively short history,then the previous years. The goal of cancer chemoprevention strategies is to use artificial or organic bioactive chemicals to postpone, stop, or reduce the incidence of tumours. Chemopreventive drugs help to prevent the growth of cancer by either preventing the proliferation of the tumor cells.The advantages of employing different dietary ingredients as chemopreventives in cancer therapy have been supported by a number of pre-clinical investigations. It is quite concerning that cancer cases are continuing to increase on a global scale. The necessity for an effective and safer alternative treatment method is justified by the current chemotherapeutic regimen's success rates are lowered by the severe toxicity and chemoresistance associated with traditional chemotherapies. In this context, chemopreventive medications have been demonstrated to be successful in preventing cancer in high-risk populations.

Diminishing the promotion phase, where the starting cells grow and become a tumour, or preventing the onset of carcinogenesis, cancer chemoprevention suppresses, prevents, or delays tumorigenesis. Blocking agents are substances that prevent the initiation stage from occurring, and suppressing agents are substances that prevent the promotion stage from occurring. Reactive oxygen species (ROS) concentrations are decreased, pathways for genomic repair are activated, and pro-carcinogens are not metabolically activated into carcinogens as a result of blocking agents. Initiation blockers can prevent tumours in addition to preventing DNA damage by controlling epigenetic modifications such the hypermethylation of tumour suppressor genes. By suppressing the immune system, suppressive agents may achieve their chemopreventive efficacy.

The first stage in the development of cancer is initiation. The compounds known as initiators are those that, despite frequently not reacting with DNA, are changed by the body's enzymes that metabolise drugs and are then capable of causing DNA modifications (mutations), frequently following a covalent bond. A lot of initiators are specialised to certain species or tissue types. Since initiation is irreversible, a cell is susceptible to promotion once it has been impacted by an initiator. Any daughter cells produced from the division of the mutant cell will likewise have the mutation because initiation results in a permanent genetic alteration.The quantity of tumour cells formed and the initiator dose are inversely correlated, meaning that the greater the exposure, the greater the risk of carcinogenesis.

On cells that have already undergone an initiator mutation, promotion is the next phase that takes place.The substances known as "promoters" encourage cell division and the production of numerous daughter cells that have the initiator's mutation. Only when the organism has previously been exposed to an initiator do promoters take effect. Promoters influence intracellular pathways that boost cell proliferation, but unlike initiators, they rarely bind covalently to DNA or macromolecules inside the cell. Instead, they

frequently connect to receptors on the cell surface.There are two kinds of promoters: specific promoters that engage with receptors on or in target cells, and nonspecific promoters that modify gene expression without interacting with a recognised receptor. The third step progression describes how a benign tumour sequentially changes into a neoplasm and then into malignancy. Since most advanced malignancies have aneuploidy with the incorrect number of chromosomes, progression is linked to karyotypic alterations. Due to ongoing mutations or genetic instability, this karyotypic shift is accompanied by accelerated growth, invasiveness, metastasis, and changes in biochemistry and morphology.Once this phase is activated, progression cannot be stopped.so the initiation process should be stopped .



Three phase process of carcinogenesis

CANCER CHEMOPREVENTIVE AGENT CLASSIFICATION BASED ON CELLULAR MECHANISM OF ACTION

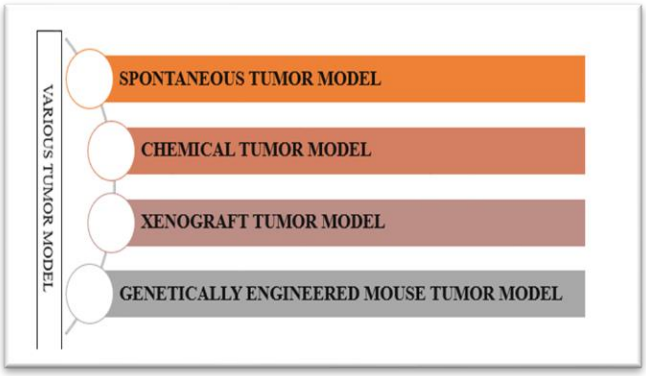
According to studies, there may be more than one mechanism contributing to any chemo preventive agent's protective effects. Since most of these have essentially no side effects, using chemo preventive medicines originating from nature on humans is advantageous. The following widely established mechanisms can be used to explain how different chemo preventive drugs work. Since the late 1960s and early 1970s, there has been a decline in cancer mortality due to the adoption of several chemo preventative medications. Based on ecological and correlation studies, it was immediately obvious that these medications had anti-cancer capabilities. Chemoprevention occurs at the cellular, molecular, and systemic levels. The anticancer benefits of cancer chemotherapy preventive medications have been explained by a number of various mechanisms, according to a review of the literature. The following classes are (a) Anti-oxidant (b) Phase I enzyme inducer (c) Phase II enzyme inducer (d) Immunomodulatory (e) hormone modulation , (f) Antibacterial and Antiviral, (g) Apoptosis, (h) the anti-angiogenesis I the induction of cell differentiation, (j) Molecular assemblage with carcinogen, (k) Cell cycle arrest , (l) A test agent's ability to change any of these molecular processes can lead to chemo preventive activity.

ANIMAL MODEL FOR TUMOR

Animal models have had a tremendous impact on the development of basic and translational breast cancer research in humans throughout history. This review provides numerous experimental animal models of breast cancer and explores their characteristics, advantages, and potential applications. It starts with the selection of the animals and continues with the creation of various animal models. Finally, we suggest future lines of investigation for animal models of breast cancer.

This review introduces and assesses a range of experimental animal models of cancer, from the selection of animals to the creation of distinct animal models. characteristics, advantages, disadvantages, and potential applications. We conclude by suggesting future research directions for cancer animal models

VARIOUS ANIMAL MODEL FOR CANCER



SPONTANEOUS TUMOR MODEL

The evaluation of chemopreventive medicines and the study of spontaneous tumours both involve early animal models of cancer. Due to unique genetic backgrounds, many animal species are more or less susceptible to developing spontaneous tumours. The main benefits of spontaneous tumour models are that tumours form naturally and may depict the genesis and evolution of cancers. However, the prevalence of spontaneous tumours is typically low, and they typically develop over a considerably longer period of time than in other tumour models.

Additionally, spontaneous tumours can form at multiple organs rather than just one. These drawbacks generally preclude the use of spontaneous tumour models in routine assessments of the effectiveness of preventative measures.

For breast cancer

Natural spontaneous cancers develop in populations of experimental animals. The fact that the experimental animals have not had any artificial treatment and are therefore equivalent to people in terms of aetiology is the most significant trait of spontaneous breast cancer.

Breast tumours that form on their own are common in rodents. The incidence and frequency of these tumours might differ greatly among many mouse strains (C3H, A, CBA/J, and TA2), even though inbred mice are frequently used in investigations on spontaneous breast cancer. Tumor development lasted 329.8195.3 days. They found that 25% (89/398) of female breeding mice had breast cancer over a period of 329.8195 days in outbred mice. 25% (89/398) of female breeding mice in a study utilising Kunming outbred mice developed breast tumours, with an average carcinogenesis time of 13.5 months.

STRAIN	DURATION	POTENCY
C3H	6-10 months	Breeding Female mice:95%; Virgin mice:88% ; Male mice :<1%
BALB/C	12 months	Female mice 5% Virgin mice :1%
SHN	6.6 -8.7 months	Breeding rats :97.2%
TA2	329.81 days	84.1 %
Kunming	13.5 months	25%

CHEMICAL TUMOR MODEL

To better understand this, many hormone- or chemical-induced tumour models have been developed.Understanding human cancer and to offer in vivo testing platforms for novel preventive and therapeutic approaches. Hormones like oestrogens and androgens have been used alone or in combination with chemical carcinogens to simulate human cancer and tumour formation. The use of hormones in the creation of tumour models is helpful because it has been discovered that oestrogens and androgens are risk factors for hormone-dependent malignancies, such as breast and prostate cancer. a number of progressive processes, such as initiation, stimulation, development, and metastasis, are used to build tumours.

However, these tumour models come with a number of built-in drawbacks. Although various chemical carcinogens are utilised to create tumour models, there is human evidence to support the claim that these substances are one of the risk factors.It is necessary

to utilise hormones and chemical carcinogens at high doses and/or over an extended period of time. Carcinogens in chemicals are harmful and can harm anyone who come in contact with them.
Multiple organ tumours that are not organ-specific are present. Due to these drawbacks and the creation of new, more suitable tumour models, these tumour models are now less frequently used in studies on cancer prevention which makes the chemically-induced tumour model a desirable one..

For breast cancer

DMBA, 3,4-benzopyrene, 3-methylcholanthrène (MCA), 1,2,5,6-dibenzanthracene, and urethane have all been used to create breast cancer in mice. The most common types of breast cancer in chemically created mice are adenomas and type B adenocarcinomas. According to Fabris et al. (2014), progesterone or medroxyprogesterone acetate (MPA) and DMBA together can decrease the breast cancer incubation time to three months and increase the incidence of the disease. They gave female (BALB/cDBA/2) F1 mice an incubation period of seven months before administering DMBA to cause breast tumours. Continuously administered MPA to BALB/c mice for a year, causing mammary ductal carcinoma in 79% of the animals. Breast cancer is frequently brought on by the use of the drugs DMBA, MNU, MCA, 2-acetylamino-fluorene, 3,4-benzopyrene, ethylnitrosourea, and butylnitrosourea.commonly DMBA and NMU are the basic reason for causing cancer in rats.
According to Russo & Russo (1996), hormones are primarily responsible for cancer. The most popular technique for inducing mammary carcinoma by injecting DMBA or NMU to Sprague-Dawley (SD) or Fischer 344 rats, typically intravenously, subcutaneously, or intragasturally . Preliminary methods of rat tumours generated by NMU resemble ER-positive low-grade human breast cancer. After giving 20 mg of DMBA through gavage injection to 47-day-old SD rats, Barros et al. (2004) found that the incubation period for tumour induction ranged from 8 to 13 weeks, and the incidence of breast tumours was about 100% at 13 weeks.

STRAIN	DAYS	INDUCING AGENT	INDUCING DOSE	ADMINISTRATION ROUTE
SD	47 50	DMBA NMU	20mg/kg 50mg/kg	ig iv
NSD	50	DMBA NMU	5mg/kg 50mg/kg	Ip iv
BUF/N	50	NMU	50mg/kg	iv
F344	50	NMU	50mg/kg	iv

MODEL FOR XENOGRAFT TUMORS

Particular cell types produced from relevant animal models and human cancers exhibit distinctive molecular and histological characteristics linked to the growth and spread of human cancer. Those cancerous cells can be very useful in defining the molecular pathways that determine development and progression as well as in creating preventive and therapeutic regimens that specifically target particular molecular targets. Particularly, xenograft tumour models made from human cancer cells accurately reflect the characteristics of human illness. Murine cell-derived transplantable tumour models and the specific human cancer they aim to represent may exhibit a great deal of genetic, histological, and biological similarities.
Typically, studies on secondary cancer prevention and, more particularly, cancer therapies, use xenograft tumour models, in which tumour cells are transplanted in mice subcutaneously or orthotopically (by injecting the tumour cells into the tissue or organ of their origin).
The convenience, speed, and affordability of subcutaneously transplantable tumour models make them advantageous. Additionally, tumour size measurements can be used to determine whether a tested drug has any anticancer effect. Subcutaneous tumour models, however, lack the stromal-epithelial connections and paracrine growth factor activity that influence tumour growth and metastatic spread. Even though injecting cells suspended in Matrigel can improve some tumours' subcutaneous growth, some malignancies are difficult to grow in this way..
The ideal place to evaluate the biological potential of tumour cells is in the organ orthotopic to the tumour cells. According to studies, different environments have different potential for the formation of tumour cells. Despite the fact that many human cancer cells are transplantable, how invasive and metastatic they can become depends on both their inherent traits and the host environment at the inoculation site. Orthotopic implantation frequently boosts tumorigenic or metastatic potential, claim Sato et al. (1997). Because it replicates stromal-epithelial cell interactions, the presence of endogenous factors (growth factors, angiogenic factors, etc.), the preservation of the tumor's original histological features, and the presence of extracellular matrix molecules and receptors, the orthotopic tumour model is more clinically relevant than the subcutaneous tumour model.

For breast tumor

Because of their prolonged in vitro development, human breast cancer cell lines are distinct from primary tumours in terms of their genetic abnormalities, gene expression patterns, pathological characteristics, treatment responses, and tumour microenvironments.. As they are directly produced from human tumour specimens and have never been cultivated in vitro, patient-derived xenograft (PDX) models are gaining popularity. In terms of genetic anomalies, expression of gene, clinical characteristics, potential for metastasis, and therapeutic responsiveness, these xenografts are highly similar to patients (DeRose et al., 2011). To find biomarkers for individualised drug selection and get around CDX transplantation's as an drawbacks in clinical therapy,Nowadays,PDX models have been used since a lot of institutions create their own PDX model libraries.

Because they can predict clinical results, PDX models are used in preclinical drug review, biomarker identification, biological research, and individualised medicine . Making PDX models is also costly, difficult, and time-consuming because NSG mice and humanised matrix components are typically needed. Patient-derived organoids, or PDOs, are created from primary human cancers and grown in a lab setting while retaining the diversity and intricate histological architecture of tumour tissue. PDOs are suitable for large-scale anti-tumor drug screening because they can deal with the expensive and time-consuming setup cycle of PDX models. An established genetic model of BRCA1 and BRCA2 breast cancer was effectively integrated with organoid culture technology by Duarte et al. (2018) to produce a three-dimensional cancer organoid.

GENETICALLY ENGINEERED MOUSE MODEL

GEMMs were originally applied to evaluate carcinogenicity more than 20 years ago. The European Commission currently feels that the mouse looks to be a widely accepted animal for genetic modification to investigate the most cutting-edge pharmacological approaches for treating a variety of ailments, some of which are listed below..

First, the mouse genome and the human genome share 99 percent of the same genes. Due to two considerations, including the availability of an excellent molecular toolset and the fact that their small size encourages high-throughput/large-scale research, it is a cost-effective model. Transgenic modified mice could offer excellent preclinical safety testing and screening platforms for lead optimization and identification. The thorough phenotyping of GEMMs can help us understand how functional and optimising genes work. We can learn more about the relationship between genes and human disease and health because to the thorough phenotyping offered by GEMMs. Determining the dosage, method, or process for advanced treatment is one circumstance where using GEMM in clinical research has demonstrated success..

For breast tumor

Mammary cancer Through the use of transgenic technology, GEMMs are created. Transgenic mice are often produced using tissue-specific promoters to carry out transgene expression. Then numerous copies of oncogenes are randomly fused into the mouse genome. The two main promoters used in transgenic animal models of breast cancer are whey acidic protein (WAP) and mouse mammary tumour virus long terminal repeat (MMTV-LTR). The MMTV virus is a significant contributor to breast cancer in mice. The MMTV promoter causes transgenic expression in ducts and alveolar cells at all stages of mammary gland development. The hormone-activated MMTV promoter is significantly more active during pregnancy. This promoter's shortcomings include leaking and uneven mosaic pattern activation.

The WAP promoter in the breast is only functional in the middle of pregnancy. Lactogenic hormones activate it in mice breast tumours, and it selectively increases transgene expression in alveolar cells during small alveolar development. Both promoters can be used to achieve selective expression of foreign genes in breast epithelial cells, preventing the growth of tumours in other organs. The phenotype presented by WAP and MMTV transgenes may differ depending on each mouse's stage of embryogenesis. Two more, less common promoters are the metallothionein (MT) promoter and the C3(1) promoter (5' surrounding region of the C(3)1 component of the rat prostate steroid binding protein).

CELL LINE	ORIGIN	TRANSPLANTATION	MOUSE STRAIN	LATENCY	METASTASIS SITE
1.BT20	Breast	Subcutaneous	Nude mice	3 week	
2.BT474	Breast	Left ventricle	Nude mice		Bone
3MCF-7	Pleural effusion	Mammary gland fat pad	Ovariectomized female athymic nude mice	1 week	Lung ,Liver
4.MDA-MB-231	Pleural effusion	Mammary gland fat pad	Immunodeficient mice	5-9 week	Lung ,Liver
5.MDA-MB-453	Pleural effusion	Mammary gland fat pad	NOD/SCID	4 week	Bone
6.MDA-MB-435	Pleural effusion	Mammary gland fat pad	Ncr Nu/Nu Nude mice		Lung
7.SUM149	breast	Mammary gland fat pad	NOD/SCID	6-8 week	lung

FUTURE DIRECTIONS FOR RESEARCH

The models shown here demonstrate that a variety of parameters must be taken into account when determining whether a mouse model of cancer may be used to study human cancer. Although laboratory animals differ from people in several ways that might affect how they react to risky exposure and chemopreventive drugs, these models have significant genetic, genomic, physiological, biochemical, and metabolic parallels to humans. An important method for finding chemopreventive drugs has been and will continue to be the use of animal models with specific phenotypic traits. However, it is noteworthy that no model available today can fully capture all aspects of cancer genesis and progression. The development of the genetically altered animal models is based on the alteration of genes involved in the latter stages of carcinogenesis. In a similar vein, syngeneic and orthotopic xenograft models are more suited as cancer progression models than cancer initiation or promotion models. Future research should prioritise the creation of animal models that accurately depict the early phases of tumorigenesis and carcinogenesis as our understanding of the pathways relating to cancer start and promotion advances. Future studies on nutritional cancer prevention should also address the synergistic effects of several dietary components. Future directions for nutritional cancer research are outlined in this section.

DISCUSSION

Based on our understanding of the molecular pathways that are essential for the early development of carcinogenesis, one of the research goals should be the continued creation of clinically relevant animal models that replicate the cancer initiation and promotion processes. One of the animal models to be developed could include one in which carcinogenesis is derived from an epigenetic modification, for instance, as epigenetic alterations are thought to play a crucial role in early carcinogenesis. Animal genetic engineering should be a major factor in the creation of this kind of model .It is frequently studied if numerous gene changes contribute to tumorigenesis or carcinogenesis. Although the development of the genetically altered mice models used today only requires the change of one gene, it may be more appropriate to modify numerous genes. As a result, numerous genes should be altered to create a different kind of animal model that must be created. Breeding genetically altered creatures together could be a practical method for creating animal models with several genetic changes..

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