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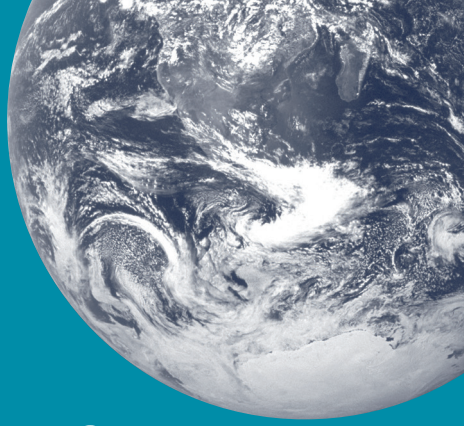

METHODS OF INDUCING BREAST CANCER IN ANIMAL MODELS: A SYSTEMATIC REVIEW

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Abstract – *Objective:* *Breast cancer is the second leading cause of death and the most common cancer in women. With respect to a large number of limitations in human studies, there is the need to develop experimental animal models. The purpose of this study was to investigate the development of breast cancer in laboratory animals.*

Materials and Methods: *This systematic review was conducted based on the PRISMA checklist. Articles were extracted with selected keywords from the PubMed, SID, Springer, Medlib and Since-Direct databases without any language restrictions. 450 articles were identified and after removal of unrelated or repetitive articles, 158 articles were selected.*

Results: *Breast cancer induction models include the use of chemical compounds, transgenic animals, ionizing radiation, and tumor cell transplantation. Tumor chemical compounds usually have advantages such as easy to use and controllable as well as disadvantages such as high toxicity to humans, tissue constraints and tumors in other tissues. The use of ionizing radiation is also dangerous, and its benefits can be accelerated by induction of tumor, low cost and easy to use. Other methods include the transplantation of cultured cells and transgenic animals, in which there are no hazards of prior methods, but there are some disadvantages such as their time and cost.*

Conclusions: *The presented animal models have both advantages and disadvantages. None of them are absolutely ideal while they are chosen according to the purpose of the investigator and the advantages of each method for cancer researches.*

KEYWORDS: *Breast Cancer, Animal Model, Induced Cancer.*

ABBREVIATIONS: *HER2 = Human Epidermal Growth Factor Receptor 2; ATM = Ataxia Telangiectasia Mutated; BRCA1/2 = Breast Cancer genes1/2; EGF = Epidermal Growth Factors; PAH = Polycyclic Aromatic Hydrocarbons; 7-OHM-12-MBA = 7-hydroxymethyl-12 methylbenz(a)anthracene; 7,12-diOHMBA = 7,12-Dihydroxymethylbenz(a)anthracene; BRME-12-MBA = 12- methylbenz(a) anthracenebromide; DMSO = Dimethyl sulfoxide; AhR = Aryl Hydrocarbon Receptor; GEM = Genetically Engineered Mice; Ras = Rat Sarcoma Gene; MMTV = Mouse Mammary Tumor Virus; WAP = Whey Acid Protein; MMTV-LTR = Mammary Tumor Virus Long Terminal Repeat; WNT = Wingless-type ; IGF-II = Insulin-like growth factor 2; Erbb2 = avian Erythroblastosis oncogene B; MT = Metallothionein; B-LG = Bovine β-lactoglobulin; MCF = Michigan Cancer Foundation; CB = Contralateral breast.*

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INTRODUCTION

Breast cancer is one of the most common cancers among women, accounting for 25% (1.7 million) of new cases and 15% of cancer deaths[1]. Breast cancer has attracted growing attention among researchers and academic circles in Iran. In this regard, epidemiological studies (38.6%) accounted for the largest share, followed by molecular (29%) and clinical (24.6%) studies[3]. A case study in Tehran, which was conducted with the aim of comparing the malignant and benign breast tumors, found that the most cases were invasive ductal carcinoma (77.4%)[2]. Breast or mammary tissue consists of epithelial and connective (stroma) tissue with hormone sensitivity to estrogen, progesterone, prolactin, and placental lactogen. The secretion of these hormones leads to the proliferation of alveoli. Although the alveoli and alveolar ducts grow and develop during pregnancy, the stroma exhibits no significant growth. Lymphocytes and plasma cells infiltrate the loose connective tissue in the lobules and proliferate over the late stages of pregnancy. After lactation, epithelial cells undergo apoptosis and atrophy, and the resulting dead cells and their debris are cleared by macrophages[4]. In addition to human, breast cancer, has been reported in various species including mice, rats, hamsters, dogs as well as other primates (monkeys), canidae (foxes, tigers), marsupialia (kangaroo), and rodents (wild mice and hedgehogs). However, the reason why some mammals are immune to breast cancer is still unknown[5]. The use of animal models in breast cancer research has a 100-year history. The early pioneers were Strong, Weston, and Bitter[6]. Interestingly, there are biological differences between human and animal breast tumors. For example, rodent mammary tumors comprise less estrogen/progesterone receptors, thereby showing less dependence on these hormones[7]. Such differences are also visible in the metastatic pattern of tumors. Metastasis of breast tumors usually diffuses through the regional lymph nodes in human and mainly affects bone, brain, adrenal gland, and lung, whereas it usually affects the lung tissue through blood in mice[8].

PROBLEM STATEMENT

Breast cancer is the most prevalent cancer among women, accounting for 25.5% of cancer cases. Every 15 minutes, one person dies from breast cancer. Hence, the development of research projects aimed at the diagnosis and treatment of breast cancer is a matter of great concern all around the world. One of the most effective methodological approaches to breast cancer is to create animal models of breast cancer for laboratory experiments. From the models used for developing breast cancer, the researcher chooses the best model for analyzing the cell line and tumor under study. Breast cancer happens when genetic alterations called mutations occur in the genes governing cell growth proliferation. These genes are often divided into three categories, including proto-oncogenes that control cell division and growth, tumor suppressor genes that inhibit cell growth, and DNA repairing genes that repair damages to the cell's genetic material. Those proto-oncogenes that contribute to the development of breast tumors include Neu/HER2, C-myc, and Cyclin D whereas, P53 is a most important tumor suppressor gene, which naturally stops the life cycle of those cells with damaged DNA[9-11] until the DNA is repaired and/or, otherwise, the cell is removed by the apoptotic mechanism. Other breast tumor suppressor genes are ATM, Cystatin, and ARHI. Since 1995, BRCA genes were also introduced as the major susceptibility genes involved in hereditary breast cancer. Mutations in these autosomal genes raise the possibility of hereditary breast cancer, since these genes interfere with DNA repair[12,13]. According to the flowchart in Figure 1, 158 relevant articles were selected and different breast cancer models were compared in this review study. There are similar review studies on various breast tumor models. Nevertheless, the present study conducts a general review of the latest studies on the mentioned models to demonstrate their advantages and disadvantages.

CHEMICALLY INDUCED BREAST CANCER

Carcinogenic chemical compounds are divided into metal compounds (arsenic, lead, and cadmium), hormonal compounds, and chemical compounds. Metals like lead develop different tumors in various ways, such as damaging DNA and preventing its synthesis and repair, forming free radicals, increasing cell proliferation, and inhibiting tumor suppressor factors like P53[14,15]. Increased levels of carcinogenic hormones result in tumorigenic effects[16] in hormone-sensitive tissues, such as testosterone-sensitive prostate[17] and estrogen-sensitive breast. Estrogen receptors (α and β) within the breast cells act differently according to different estrogen levels. The estrogen receptor β inhibits estrogen-induced tumorigenesis through G2 cell-cycle arrest, while the estrogen receptor α induces tumor development in breast cells with increased induction of epidermal growth factors (EGFs) and free radicals[18]. Mense et al[19] used 3 mg dose of estradiol (17 β-estradiol) to induce breast cancer through subcutaneous administration, thereby observing hyperplastic lobules on Day 7 and developed tumors on Day 120. Figure 2 illustrated the mechanism of estrogen synthesis and

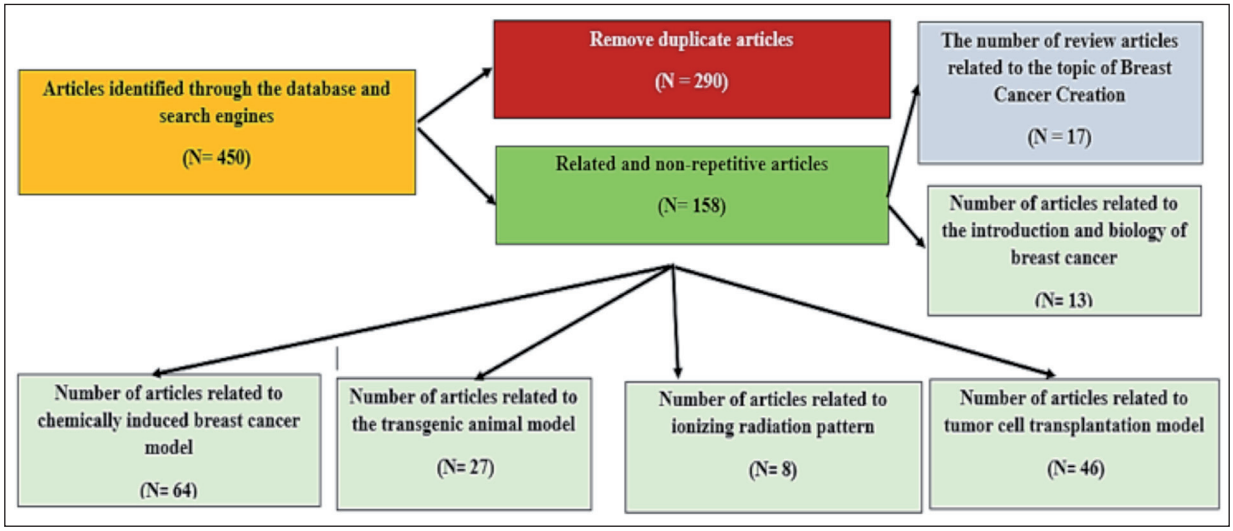


Fig. 1. The flowchart of the process of extracting information from the included articles. According to the flowchart, 450 papers from from the Pubmed, SID, Springer, Medlib and SinceDirect databases and search engines were gathered in this study. After removing repetitive articles, articles related to a variety of animal models of breast tumor induction were presented in the form of 158 articles. Of the 158 papers in the study, there were 17 review articles and the rest of the original articles. 64 articles for the use of chemical compounds, 27 articles for transgenic mice, 46 papers for tumors created by breast cancer stem cells culture and their transplantation, and finally 8 papers for the use of ionizing radiation for induction of breast tumors.

the process of growth stimulation by this hormone. Chemical compounds used to induce tumor tissues require characteristics such as strong tumorigenicity, specific target tissue, long half-life, availability, and bioprocess ability. One of the methods used to induce tumor in breast tissue is the application of chemical compounds. Table 1 summarized four chemical compounds most commonly used for this purpose.

This compound belongs to the family of polycyclic aromatic hydrocarbons (PAHs), which is used in experiments as promutagen, procarcinogen, and teratogen[65]. Hepatic metabolism is dependent on cytochrome P450-linked mono-oxygenase systems, through which its metabolites are transferred to the target tissues. Skin tumors were reported with low doses due to epidermal biotransformation[66].

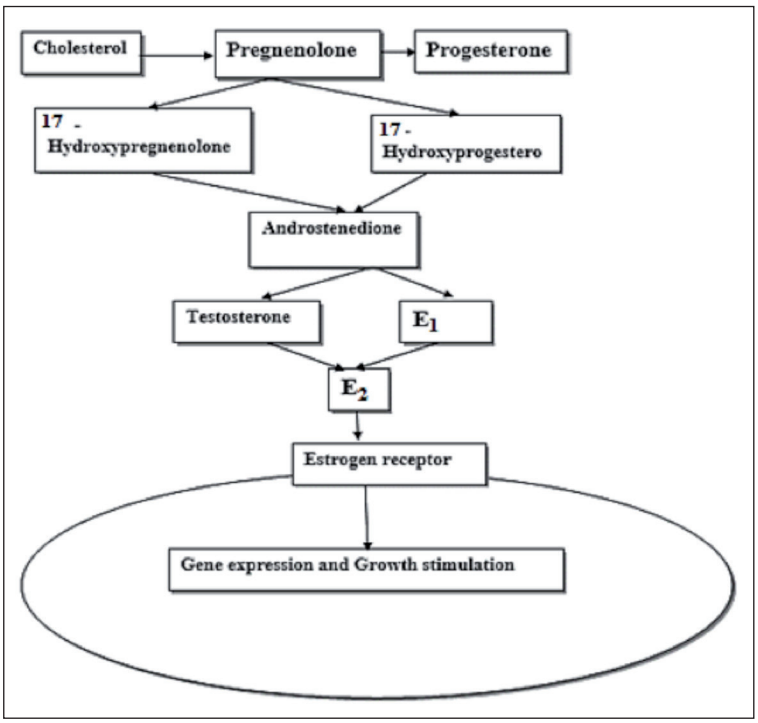
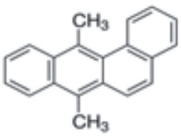
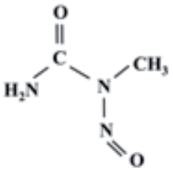


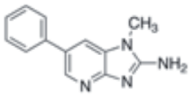
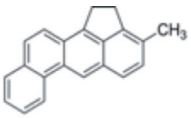
Fig. 2. Estrogen synthesis and growth stimulation. In this figure, how to convert cholesterol as a precursor (pregnenolon) to estrogen, and ultimately its effect on gene expression and stimulation of growth in estrogen receptor (breast) cells is shown. Estrogen can be used to induce tumors of the breast to increase tumor induction.

TABLE 1. Compounds used to induce breast tumors

Tumor inducer	Animal	Dose	Drug administration	Administration method	The duration of tumor formation	Reference
DMBA[1] 	Rat	5 mg/100 g BW in 1 ml almond oil	SD	IG	After 20 days	20
	Rat	20 mg in 1 ml corn oil	SD	IG	After 6 weeks	21
	Rat	15 mg in sesame oil	SD	IG	After 120 days	22
	Rat	65 mg/kg in sesame oil	SD	IG	1×1×1 mm after 54 days	23
	Rat	15 mg in sesame oil	SD	IG	After 74 days	24
	Rat	60 mg/kg in sesame oil	SD	IG	After 5 weeks	25
	Rat	75 mg/kg BW in 1 ml sesame oil	SD	IG	After 18 weeks	26
	Rat	50 mg/kg BW in olive oil (2 ml/kg BW)	SD	IG	After 40 weeks	27
	Rat	10 mg per rat in corn oil	SD	IG	—	28
	Rat	80 micrograms per gram BW in olive oil	SD	IG	After 4 months in 70% of rats	29
	Rat	12 mg per rat in sesame oil	SD	IG	After 100 days	30
	Rat	20 mg per rat in 1 ml corn oil	SD	IG	After 2 months	31
	Rat	5 mg per rat in 1 ml sesame oil	SD	IG	After 3 months	32
	Rat	25 mg in 0.5 ml sunflower oil and 0.5 ml saline per rat	SD	SC in mammary glands	After 90 days	33
	Rat	20 mg in 1 ml sesame oil	SD	IG	After 40 days	34
	Rat	65 mg/kg in olive oil	SD	IG	After 24 weeks	35
	Rat	5 mg per rat	SD	IG	Tumors after 20 weeks	36
	Mouse	1 mg in 0.1 ml corn oil	1 week	IG	After 20 weeks in 68% of the mice	37
	Knockout mouse	1 mg in 100 µl of corn oil	In Weeks 9, 10, 12 and 13	IG	In Week 34 and	38
	BALB/c 53 and P Hemizygous Mice	1 mg/kg in flaxen oil on a weekly basis	6 weeks	IG	After 3-7 weeks	39
	SENCAR mice	1 mg/kg on a weekly basis	For six weeks	IG	After 15 weeks	40
NMU[2] 	Rat	35 mg/kg	SD	IP	After 4 weeks	41
	Rat	50 mg/kg in 9% saline	SD	Jugular, IV	After two weeks and separation of the tumors 99 days later	42
	Rat	50 mg/kg in saline at with a dose of 20 mg/ml and adding 3% acetic acid	SD	Jugular, IV	After 6 months	43
	Rat	50 mg/kg	SD	IP	After 94 days	44
	Rat	5 mg per 100 g body weight	SD	IV		45
	Rats	5 mg/kg	3 doses on Days 0, 14, and 28	IC	After 7 months	46
	Rat	50 mg/kg	SD	IC	After 141 days	47
	Rat	37.5 mg/kg	SD	IC	After 31 weeks	48
	Rat	25 mg/kg	SD	IC	After 5 months	49
	Rat	5 mg per 100 g of BW in saline	SD	IC	After 20 weeks	50

Continued

TABLE 1 *CONTINUED*. Compounds used to induce breast tumors

Tumor inducer	*Animal*	*Dose*	*Drug administration*	*Administration method*	*The duration of tumor formation*	*Reference*
PhIP[3] 	Rat	150 mg/kg in 7.5 ml corn oil	4 days	Oral	After 1 year	51
	F344 rat	0.02% of basal diet	-	Oral	After 52 weeks	52
	Rat	100 mg/kg in corn oil with diet for 4 weeks	Along	IG	After 42 weeks	53
	F344 rat	4% of basal diet	52 weeks	Oral drug delivery	After 52 weeks in 47% of female rats and colon tumors in 55% of male rats	54
	Rat	75 mg/kg	4 times on a weekly basis for 2 weeks	Oral along with diet	After 20 weeks	55
	Rat	75 mg/kg in 5 ml corn oil	On a daily basis for 10 days	Oral	After 25 weeks	56
	F344 rat	Along with the diet with a dose of 400 PPM	52 weeks	Oral	After 32 weeks	57
	Rat	100 mg/kg	SD	IG	After 40 weeks	58
	Rat	100 mg/kg in sesame oil, + 1% DMSO (5 ml/kg)	5-8 days in a row	Oral	After 25 weeks	59
		75 mg/kg in 5 ml corn oil	days in 5 a row	Oral	After 42 weeks	
	Rat	75 mg/kg	10 days	Oral	After 6 weeks	60
	Rat	85 mg/kg in 0.1 ml corn oil	8 doses in 11 days	IG	After 24 weeks	61
MC[4] 	Rat	10 mg in 1 ml sesame oil	20 days	IG	After 20-25 days	62
	Mice	80 µg/g, a total of 150 µg	SD	IG	After 7 months	63
	Rat	10 mg/kg	3-6 times on a weekly basis for 7 weeks	IG	After 44-52 days	64

7, 12-Dimethylbenz(a)anthracene, SD: single dose, IG: Intragastric, BW: body weight, IC: Intra-caudate, IV: intravenous. [1]: 7,12-Dimethylbenz(a)anthracene, [2]: N-methyl-N-nitrosourea, [3]: 2-Amino-1-methyl-6-phenylimidazo[4,5-B]pyridine, [4]: Methylcholanthrene.
This compound belongs to the family of polycyclic aromatic hydrocarbons (PAHs), which is used in experiments as promutagen, procarcinogen, and teratogen (65). Hepatic

The main metabolites produced by this combination for tumorigenic breast tissue are 7-hydroxy methyl, 7-OHM-12-MBA, and 7,12-diOHMBA that can form epoxide derivatives. A study on the bromine derivatives of this compound (BRME-12-MBA, 7-BRMBA) included examining the effects of link with DNA[65]. This compound disrupts DNA repair through depurination, thereby inducing cell death pathways and tumor development in tissues[67]. Figure 3 shows the tumorigenic effect of the metabolites of this chemical compound on DNA.

DOSE AND ADMINISTRATION METHOD

The tumorigenic dose of this compound is 50-80 mg/kg (20-30 mg per rat) (Table 1), which is commonly used as single-dose through gavage, intraperitoneal, subcutaneous, and intravenous administration. Barros et al[68] intramuscularly administered a dose of 20 mg/kg in 1 ml oil for inducing breast tumors. After 8 weeks, 80% of the rats exhibited three tumors on average. In week 13, tumors were developed in all the rats, with an average of five tumors per animal. Lai et al[27] used a 50 mg/kg dose for this purpose after dissolving it in olive oil and achieving a 2 ml/kg dose for gavage administration in rats. After 40 weeks, the average number of tumors in the rat groups was 1.1-3.7 and the tumor volume was 37.7-14.7 cm^3. A dose of 8 mg/kg was used intravenously to induce tumors, suggesting that the use of this approach requires a lower amount of DMBA[69]. Doses and various routes for inducing breast tumors have been used by this compound, some of which are listed in Table 1.

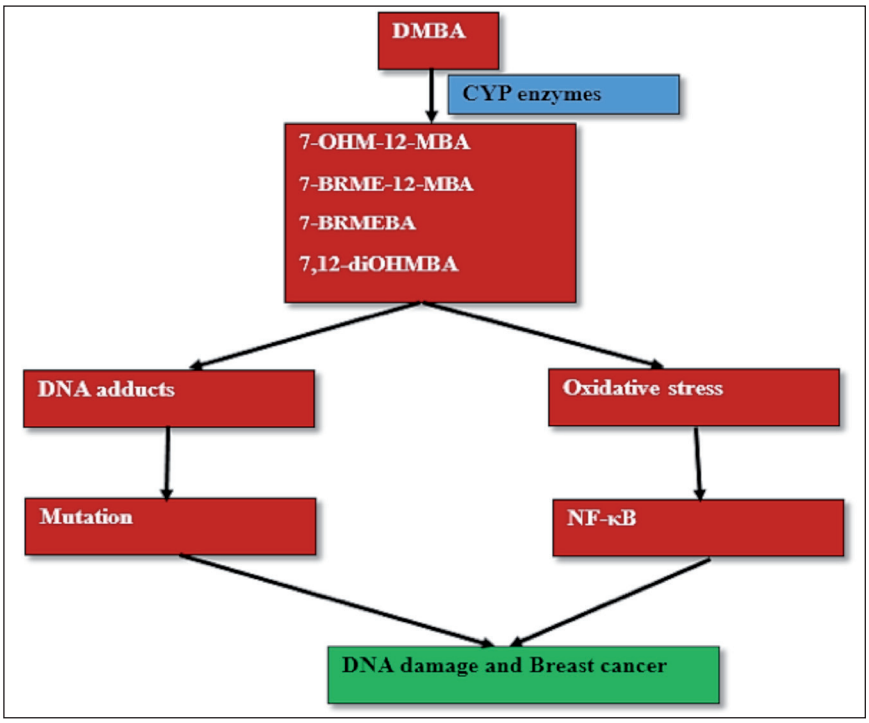


Fig. 3. Tumorigenic effect of 7,12- Dimethylbenz (a) anthracene. This figure depicts the metabolism of DMBA, which has been transformed into liver enzymes by cytochromes P450 system. These compounds, by their effect on DNA and produce free radicals, causing mutations and NF-κB that eventually result in the cell's genetic material They undergo changes and cells are redirected to tumor.

N-METHYL-N-NITROSOUREA (NMU)

This compound directly causes DNA alkylation and disrupts its synthesis and repair. It exhibits a tumorigenic, teratogenic, and mutagenic potential depending on age, dose, frequency, and administration method. It was reported that the age of 4-7 weeks is the most sensitive and susceptible period to development of ER^+/PR^+ tumors with intraperitoneal injection in rats[70]. Cells undergo apoptosis after DNA alteration through alkylation (methylation)[71]. Figure 4 depicts the effective mechanism of the family of nitrosourea compounds. The tumorigenic dose of this compound was reported to range

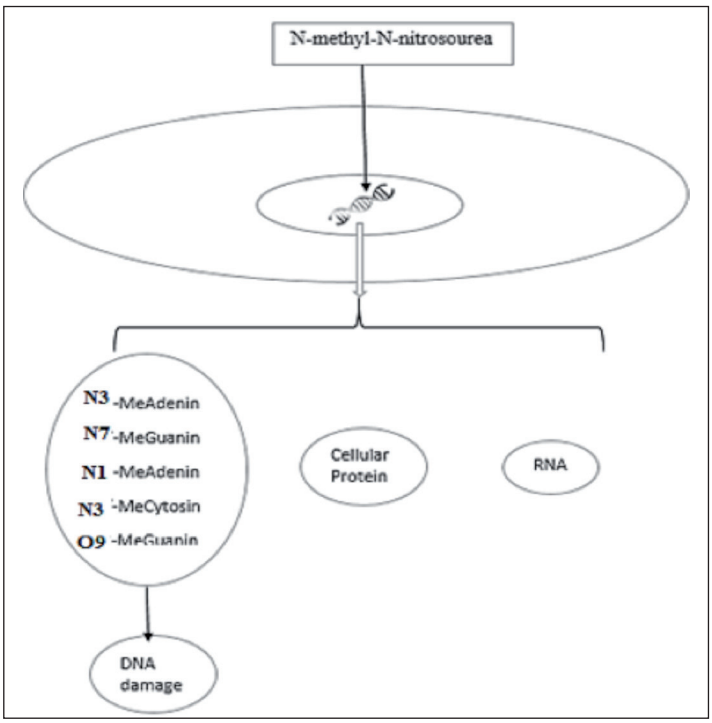


Fig. 4. The effects of NMU on cells. NMU causes DNA methylation and effects on cellular proteins, and ultimately the cell goes to tumor.

50-70 mg/kg by several studies as single or double doses on a weekly basis through gavage, intraperitoneal, subcutaneous, and intravenous administration. Tsubura et al[70] examined its tumorigenic effects in different tissues and animals. This study included tumor induction in the gastrointestinal tract of monkeys, pig stomach, dog brain, neural tissue, and blood vessels of rabbits, lymphatic tissues, stomach, blood vessels, kidneys, respiratory system, and rodent skin. The tumorigenicity of this compound was also studied in various tissues including colon[72] and prostate[73] tissues.

TUMORIGENICITY OF 2-AMINO-1-METHYL-6-PHENYLIMIDAZO [4,5-B]PYRIDINE (PHIP)

This compound is found in fried food, especially meat and fish, and in cigarette smoke as carcinogens affecting mammary, colon, and prostate tissues[74,75]. It is a heterocyclic amine, which includes gray crystals soluble in methanol and dimethyl sulfoxide (DMSO). It is also known as a mutagenic and carcinogenic compound that directly affects DNA. The experimental dose is 80-100 mg/kg administered through gavage usually 4 times a week for 2 weeks. However, this dose was used differently by different studies in terms of administration frequency[75,76].

3-METHYLCHOLANTHRENE

This is a polycyclic aromatic hydrocarbon with high carcinogenic potential. It acts as an agonist of the aryl hydrocarbon receptor (AhR) and induces estrogen activity through AhR-ERα (estrogen receptor alpha) interaction. The doses of this compound used in studies are listed Table 1. This compound also increases the expression of C-fos and C-myc proto-oncogenes[77].

GENETICALLY ENGINEERED MICE (GEM) BREAST CANCER MODEL

In 1980, the technology for the creation of "transgenic mice" was introduced to transfer cloned genes to the genome of mice, followed by focusing on cloning cellular and viral oncogenes. These genes are able to induce changes in cultured cells. It takes 6-18 months to develop tumors in this model. There are today various laboratory animals produced with various genomic alterations. The first model of transgenic mice with breast tumors was developed by Leder and Stewart (1982) at Harvard Medical School. The two researchers had previously conducted experimentations in human hybrid gene technology with lymphoma. To this end, they linked Myc proto-oncogene to regulating regions of immunoglobulin gene in Burkitt's lymphoma. This caused a shift in the expression of genes from the expression of Myc to that of B-lymphocyte gene for the development of lymphoid tumors[78].

CREATION OF GENETICALLY ENGINEERED MICE

Genetically engineered mice are divided into two groups: single-gene and multi-gene mice. Only one oncogene is carried by the driver to the tissue cells (e.g. FGF-3) in the first group, whereas more than one oncogenes are carried (e.g. FGF-2/INT-3) in the second group. Various oncogenes were introduced into the genome by different drivers. Each oncogene contributes to proliferation and tumorigenesis of target tissue cells through specific cell pathways. Breast tumor models include the application of growth factors and their receptors, nuclear oncogenes, viral oncogenes, Ras genes, INT genes, growth suppressor genes, and genes affecting the cell cycle with different drivers. Table 2 covers some of these genes and promoters shown in Table 3. Several criteria have recently been suggested for GEM models of human cancers: (1) mice must carry the same mutation that occurs in human tumors; (2) mutations should be engineered within the endogenous locus, and not expressed as a transgene; (3) mutated genes should be silent during embryogenesis and early postnatal development, except for in models of inherited pediatric tumors; (4) mutations should be within the specific target tissues in selected cell types; and (5) mutations must occur in a limited number of cells. Mouse mammary tumor virus (MMTV), which is a retrovirus transmitted through milk, and WAP (whey acid protein) are two hormone-sensitive driver genes that proliferate during pregnancy and lactation. These promoters are not mammary specific and considered to be also promoters of other tissue-specific genes. For example, MMTV is expressed in prostate, kidney, seminal vesicle, lung, and T cells. WAP is also expressed in various tissues as well as brain tissues. Thus, transgene expression may also have systemic effects. However, some transgenic mice were recently created to limit the oncogene activity according to the target tissue, which is expressed only in the mammary epithelial cells. In tumorigenic viruses, a copy of the virus's DNA may be recombined while integrating with the host cell's DNA. Accordingly, the tumorigenic gene is replicated and transferred. Nevertheless, research findings have not still demonstrated the role of hu-

TABLE 2. Models of transgenic mice that develop tumors of the breast.

Gene		*Promoter*	*Reference*
Growth factors and receptors	TGF-α	MT	87
	TGF-α	MMV-LTR	88
	Erbb2 (neu)	MMTV-LTR	87
	neu	MMTV-LTR	87
	IGF-II	MMTV-LTR	87
Nuclear oncogenes	c-myc	MMTV-LTR	87
	c-myc	WAP	87
Viral oncogenes	Polyoma middle T	MMTV-LTR	87
	SV40 large T	WAP	87
Ras genes	v-Ha-ras	MMTV-LTR	87
	Ha-ras (activated)		
	N-ras	WAP	89
Int genes	Wnt-1	MMTV-LTR	90
	Wnt-3	MMTV-LTR	91
	Wnt10-b	MMTV-LTR	92
	Int-1	MMTV-LTR	87
	Int-2	MMTV-LTR	87
	Int-6	MMTV-LTR	93
	FGF-3	MMTV-LTR	94,95
	FGF-4	MMTV-LTR	94,95
	FGF-8	MMTV-LTR	94,95
	FGF-3/Int-2	MMTV-LTR	96
	FGF-4/hst	MMTV-LTR	97
	FGF-8/AIGF	MMTV-LTR	95
	Notch-4/Int-3	MMTV-LTR	92
	Wnt-1/Int-2	MMTV-LTR	98
Growth inhibitor genes	P53	WAP	87
	TGF-β	WAP	87
	TGF-β	MMTV-LTR	87
	BRCA1/2	MMTV-LTR	99
Genes affecting the cell cycle	Cyclin-D1	MMTV-LTR	87

man endogenous retroviruses in the development of breast cancer. On the contrary, MMTV in mice is one of the factors contributing to the development of mammary tumors, which is used as a vector for research purposes showing that when there are one hybrid gene (MMTV-LTR) and one oncogene (viral Ras gene), this gene MMTV-LTR-Ras would be controllable by steroid hormones in mammalian cultured cells. Leder and Stewart[81] developed a series of hybrid genes (MMTV-LTR) and Myc coding region to complete the Hager's work. They introduced them into the DNA of mouse embryos[79-81]. 13 strains of transgenic mice were produced thus far. In the case of the cell line MMTV-Myc, the researchers monitored the female mice until they observed tumors in the second or third pregnancy. The tumors also developed in the next-generation female mice. Researchers also produced double-transgenic mice using viral Ras oncogene (v-Ha-Ras) and Myc to examine the effects of "oncogene cooperation". They reported accelerated tumorigenesis in the target organs[81]. The process of mammary cell tumorigenesis requires different genetic modification. This technique includes examining various oncogenes. The genes expressing the target tissue (breast) markers are transferred to the cultured cells with tumorigenic potential using the above-mentioned vector. Then, these cells begin to proliferate and develop tumors in the animals under study. To do this, it is first necessary to design a plasmid vector containing the target gene. This plasmid gene contains transferred DNA (T-DNA). After designing and locating this gene in its specific promoter undergoing cell division, this gene is also divided and the target receptor or specific protein is also replicated. This leads to the identification of tumor cells[82,83]. WNT-1 is the first cloned proto-oncogene by viral activation in mouse mammary tumors. In addition, there are other proto-oncogenes, such as WNT-3 and WNT-b10. All belong to the family of fibroblastic growth factors. The overexpression of the family of WNT genes (WNT-3a, WNT-3, WNT-2, and WNT-1) and other proto-oncogenes associated with the virus facilitates the morphological transformation of mam-

TABLE 3. The promoters used in breast tumors in transgenic mice.

Promoter	*Origin*	*Reference*
MMTV-LTR	Mouse mammary tumor virus	100
WAP	Whey acidic protein	101
C3 (1)	Rat prostate steroid-binding protein	102
B-LG	Bovine β-lactoglobulin	103
MT	Metallothionein	104

mary epithelial cells. WNT-1, which is essential for continuous induced transformation of epithelial cells, is not expressed in natural cells. Some of the WNTs are expressed in the natural mammary tissue, and some are expressed in the mammary tumor tissue. WNT pathway to activate cellular proliferation was identified in some human cancers, including breast, colon, melanoma, and hepatocellular carcinoma. The most commonly used transgenic mice or GEM model is WNT-1 for breast tumor research, which is controlled by the WNT-1 promoter[84,85]. For obtaining better results, hormones like estrogen are also applied as factors with synergistic effect[86].

XENOGRAFT AND BREAST CANCER CELL LINES MODEL

In this approach, cells are usually isolated from the tumor tissue in different ways. Tumor cell lines are cultured in two-dimensional (2D) or three-dimensional (3D) culture media. These lines may be used as single-cell or co-culture of two or more cell lines in a simultaneous fashion. Moreover, these cells may be extracted from human tumors and then cultured. According to their advantages and disadvantages, each of the mentioned cell culture techniques is employed to develop breast tumors. The first human tumor cell lines were isolated from mice without thymus gland by Isaacson and Cattanach in 1962[9]. Today, these mice are also used in xenograft studies.

CELL LINES

Approximately 100 mammary tumor cell lines have been discovered, among which only a few cases are used for research purposes. These lines are divided into Luminal A and Luminal B groups based on estrogen, progesterone, and HER2 surface markers, each group with specific tumorigenic and metastatic properties[105]. Breast tumor xenograft is usually accompanied by hormonal induction as a tumor growth promoter. This technique involves utilizing cell lines with CD^{+}_{44}/CD^{-}_{24} phenotypes as tumor-initiating cell lines. Some invasive cell lines also exhibit post-transplant metastatic power, and some have the potential for resistance against conventional antitumor drugs. The MCF7 cell line and the MCF10AT system are the most common cell lines used for cell culture and xenograft[106, 107]. The MCF10AT system is a xenograft model of transformed cells (i.e. two combined models). This system comprises T24 Ha-Ras transformed cells derived from MCF10AT natural cells to be inoculated into mammary gland fat pad after cultured in matrigel (a population of 10^5-10^7 cells)[6].

TUMOR CELL XENOGRAFT

Tumor cell xenograft is performed in three ways: (1) Subcutaneous injection (SC) of tumor cells into the mammary fat pad of animals, in which case the cells rapidly reproduce in the target region. (2) Direct injection of cells into the lymph nodes of the region (orthotopic xenograft) or even in the mammary fat pad, which is typically, accompanied by the metastasis of the tumor cells. (3) Intravenous injection (IV to caudate vein) for inducing metastasis to lung or other organs. In mammary fat pad xenograft, angiogenesis occurs more rapidly than other cases[108]. Table 4 covers some of the cell lines used for xenograft. Furthermore, the use of other cell cultures (BT-20, MDA-MB-231, SK-BR3, and SK-OV-3) was also reported by some studies[109,110]. This technique has some disadvantages such as the host's immune system response to xenografted tissue and the unpredictability of tumor growth[111]. It thus requires knowledge of intracellular relationships and mammary tumor angiogenesis[106]. The advantages include the application of various mammary cancer cell lines that could be transferred to the animal's body, the possibility of molecular studies on metastasis and tumor-adjacent cell relationships, and also the possibility of examining the treatment response of these cells[109,110].

Another technique involves isolating and culturing human tumor cells. Accordingly, tumor pieces are cultured under sterile conditions in a certain culture medium according to the origin of the tumor (Leibovitz, RPMI-1640, 12 DMEM F). The cultured pieces (a population of 10^5-10^7 cells) are then subcutaneously implanted by chest and abdomen surgery (especially the fat pad around the mammary glands). Other tumor cells are also taken from patients in the pleural fluid, and then injected into the thoracic region after washing in the culture medium solution (RPMI-1640) or even as a combination of culture medium and matrigel[147-149].

TABLE 4. Some cell lines used in tumor tissues as xenograft.

Cell line	Characteristics	Number of cell injection	Injection site	Animal model	Reference
MCF-7	Er and PR, no HER-2 receptor, incapable of metastasis, development of tumors of 150-200 mm^3	5×10^6 in 1 cc matrigel and culture medium	SC fat in the mammary tissue	Ovariectomized NCr (nu/nu) mice	112
MCF-7 BAG	Induction of tumor after 6 weeks	1×10^7	SC in the right flank	NCr (nu/nu) mice	113
MDA-MB-468	Development of adeno-carcinoma, no ER, PR, and HER-2 receptor, metastatic potential	1×10^7	SC into the right flank	NCr (nu/nu) mice	114
MDA-MB-453	Development of adeno-carcinoma, HER-2 receptor, no ER and PR, metastatic potential	1×10^6 and 10 µl culture medium	In the mammary fat pad	NCr (nu/nu) mice	115
MDA-MB-361	Metastatic, induced tumor after 2 weeks, development of tumors of 70 mm^3, HER-2 receptor, development of adenocarcinoma	1×10^7 and 200 µl culture medium without serum	SC in mammary tissue	NCr (nu/nu) mice	116
MDA-MB-231	Development of adeno-carcinoma, HER-2 receptor, no ER, PR, metastatic	5×10^6	Mammary fat pad or SC	SCID mice	117
UMB-1Ca	MCF-7 cell line, no estrogen receptor	2.5×10^7 in matrigel (10 mg/ml)	SC in the mammary fat pad	BALB/c athymic nude mice	118
MT-3		No ER, PR	SC in the mammary fat pad	NMRI nude mice	119
MT-1	No ER, PR		SC the mammary fat pad	NMRI nude mice	120
MCF10AT	Epithelial origin, incapable of tumorigenesis, destroyed by xenograft in immune-compromised mice, used for pre-tumor models, injection of cells (5×106) as a suspension in matrigel		SC in the mammary fat pad	CD1 nude mice	121
MC-2/5/18		1×10^6	SC in the mammary fat pad	BALB/c nude	122
SK-BR3	HER-2 receptor, no ER and PR, metastatic, development of adenocarcinoma	5×10^6 and 200 µl matrigel in the mammary tissue	SC the mammary fat pad	NOD/SCID mice	123
BT-20	No HER-2, ER and PR. metastatic	6.25×10^6	SC in the mammary fat pad	Nude mice	124
ZR-75-1	HER-2, ER, and PR, metastatic	2×10^6 and 200 µl culture medium	SC in the mammary fat pad	CD-1 (nu/nu) athymic mice	125
SUM149	No ER, metastatic, development of mammary inflammatory carcinoma		SC in the mammary fat pad	Athymic nude mice	126
SUM159	No HER-2, no ER and PR, metastatic	3×10^6	SC in the mammary fat pad in the inguinal region	NOD/SCID mice	127

Continued

TABLE 4 *CONTINUED*. Some cell lines used in tumor tissues as xenograft.

Cell line	*Characteristics*	*Number of cell injection*	*Injection site*	*Animal model*	*Reference*
159SUM	Metastatic, ER, PR, no HER-2 receptor		SC with 200 µl matrigel and culture medium in the mammary fat pad	NOD/SCID mice	128
KPL-1	Metastatic	2×10^6	SC in the mammary fat pad	Balb/c nu/nu mice	129
KPL-4	Metastatic	2×10^6	SC in the left and right mammary fat pad	Nude mice	130
HT-39	Metastatic	1×10^6	SC in the mammary fat pad	CD-I nu/nu athymic mice	131
HX99 HX104 HX106	Metastatic	1×10^6	SC in the mammary fat pad	CBA/lac mice	131
T61	Metastatic, ER		SC in the mammary fat pad	Nude mice	132
H31	Metastatic, ER		SC in mammary fat pad	Nude mice	133
Br10	Metastatic		SC in the mammary fat pad	BALB/c (nu/nu) mice	134
SE		1×10^6	SC in the mammary fat pad	BALB/c nude and SCID mice	135
WIBC-9	Development of mammary inflammatory tumor, metastatic		SC in the mammary fat pad	Athymic nude (nu/nu) mice	135 & 136
MAXF 401, 499, 583, 857 and 1162	Metastatic	Placement of 1×3×3 mm pieces of cultured tumor tissue	SC in the mammary fat pad	Athymic nude (nu/nu) mice	137
NCI/ADR	Widely considered as an ovarian tumor cell line, metastatic, used to examine multidrug resistance		IV and SC in the mammary fat pad	Athymic nude (nu/nu) mice	138
CAL51	Metastatic		SC in the mammary fat pad	Athymic nude (nu/nu) mice	139
MA-11	Metastatic, used to study the effective drugs in tumor metastases	2.5×10^6	IP	Athymic nude (nu/nu) mice	140
HBT3477	Metastatic, development of adenocarcinoma, no ER, PR and HER-2 receptor	$2.5\text{-}5\times10^6$	SC in the mammary fat pad	Athymic nude (nu/nu) mice	141
C8161	Metastatic	1×10^6 and 2×10^5	IV and SC in the mammary fat pad	Athymic nude (nu/nu) mice	142
HBT3477	Metastatic	3×10^6	SC in mammary/ abdominal region	Athymic nude (nu/nu) mice	143
GI-101	Metastatic	1×10^7	IV	Athymic nude (nu/nu) mice	144
4T1	Development of metastasis to liver, brain, lung, and bone marrow, used in immune- competent animal models to examine the effect of the immune system on mammary tumors	1×10^7	SC in the mammary fat pad	BALB/c mice	145 & 146

Some studies also utilized estrogen as a synergistic factor similar to the chemically induced breast cancer model. The estrogen receptors of hormone sensitive-hormone cell lines induce and enhance their growth[149]. In several studies, tumor cell cultures were applied to mice without thymus gland. The applied cell lines were The applied cell lines were $ER^-/PR^-/HER_2^-$, $Lineage^-CD^+_{24}/CD^+_{44}$, and $Lineage^-CD^-_{24}/CD^+_{44}$[147]. A disadvantage of this technique may be the lack of attention to the fact that mammary tumors comprise heterogenic cells. In techniques associated with single cell cultures, this disadvantage distinguishes the mentioned models from human tumors[6,150].

RADIATION INDUCED BREAST CANCER

Mammary tissue is one of the most sensitive tissues to ionizing radiation beams. Radiation overdose and overtime induce the development of tumors[151]. Women younger than age 20 years at exposure are at higher risk of radiation-associated breast cancer than those exposed at older ages. Women more than 50 years of age old at exposure have no measurably increased risk of breast cancer. DNA damage occurs following this radiation, which in turn may develop tumor cells[152]. Stovall et al[153] found that a radiation dose >1.0 Gy to the contralateral breast (CB) had an elevated, long-term risk of developing a second primary CB cancer. This technique usually involves the use of Balb/c mice for tumor induction. A study showed that 35 Gy/min radiotherapy could increase the probability of tumor development after 12-14 months[154]. Tumor induction in this technique depends on the weight and age of the animal under study. A study included comparing the type of animal and the type of radiation (photon, plutonium, neutron, and heavy ions) in terms of tumor development, concluding that estrogen with ionizing beams produces synergistic effect[155]. Hei et al[156] showed that a 30-cGy dose of α particles has the potential to develop tumors that could grow in mice without thymus gland. Calaf et al[157] studied cell growth, transformation, invasiveness, and tumorigenicity of the cell line MCF-10F through α particle radiation. They also evaluated the expression of the genes BRCA1, BRCA2, and RAD51 as markers of mammary tumors, using a 60-cGy dose of α particle to induce tumors in this cell line. In addition, gamma ray was applied to monitor transformation in the epithelial cell lines of mammary tumors, in which the expression of the gene P53 was also evaluated[158]. After exposure to radiation, rats were treated with tumor-promoting hormones (diethylstilbestrol or estrogen) to shorten the latency and increase the quantity of tumors available for study[152].

CONCLUSIONS

A highly effective research approach for breast cancer is to create animal models of breast cancer. Among the proposed models, the transgenic mice or GEM model is seemingly the best choice for providing specificity and possibility for development of various tumors, while the chemically induced models offer higher cost-effectiveness and greater ease of application. Nonetheless, these models are not only incapable of providing specificity, but also have the potential for developing other tumors in other tissues as well as heterogenic tumors in mammary tissues. It is thus a specifically ineffective technique for studying tumor cells. Although there are many different techniques for inducing breast cancer, what is in fact required is the quantitative and qualitative development of effective and reliable techniques.

Ethical approval

All institutional and national standards for the care and use of laboratory animals were followed. This article does not contain any studies with human participants performed by any of the authors.

Conflict of Interest:

The Authors declare that they have no conflict of interests.

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