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REVIEW

Mammalian Species-Specific Resistance to Mammary Cancer

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Abstract

Tumorigenesis in mammals is driven by inherited genetic variants, environmental factors and random errors during normal DNA replication that lead to cancer-causing mutations. These factors initiate uncontrolled cellular proliferation and disrupt the regulation of critical checkpoints. A few mammalian species possess unique protective mechanisms that enable them to resist widespread cancer development and achieve longevity. Tissue-specific tumor protection adds another layer of complexity to this diversity. Breast cancer is a leading cause of human mortality, particularly among females. Driven by the need for new strategies in treatment and prevention, this opinion article explores and supports the idea that herbivores are more resistant to mammary cancer than carnivores and omnivores. This diversity has occurred despite the remarkably similar basic mammary biology. Herbivores' meatless diet cannot explain the differences in cancer resistance, which have accompanied species segregation since the Jurassic era. To investigate the causes of this diversity, the characteristics of tumorigenesis in the human breast—and to a lesser extent in other carnivores—have been compared with data from retrospective analyses of bovine mammary tumor development across various locations over the past century. Well-established genomic, cellular, and systemic triggers of breast cancer exhibit different, or less pronounced tissue-specific activity in the bovine mammary gland, accompanied by novel bovine-specific protective mechanisms. Together, these factors contribute to the near absence of breast cancer in bovines and offer a basis for developing future anticancer strategies.

Keywords Breast · Mammary gland · Cancer resistance · Herbivore · Omnivore · Carnivore · Bovine

Introduction

Among the 6,495 recognized mammalian species, 290 are exclusively meat-consuming carnivores [1, 2]. This taxon exhibits limited diversity compared to the much larger group of plant-eating herbivores [3], which encompasses approximately 4,000 species playing pivotal roles in various ecosystems on Earth, with the notable exception of Antarctica [4]. A smaller group of at least 418 [5] and up to 1,172 (Animalia, the animal encyclopedia) omnivorous species, including humans, also exist, consuming both plant matter and meat. Interestingly, diet does not significantly influence species proliferation [6]. The strict dietary diversity among the three groups evolved about 145–200 million years ago during the Jurassic era. Carnivores first appeared in the early Jurassic period, followed by herbivores and omnivores which emerged during the middle and late periods, respectively [6, 7]. Despite their distinct dietary differences, carnivores, omnivores, and herbivores do not appear to differ significantly in the developmental or production characteristics of the mammary gland, a representative organ of mammals. Indeed, the postpartum mammary gland exhibits a conserved morphology consisting of a functional epithelium organized into branching ductal structures that extend from the nipple and traverse a mesenchymal stroma [8]. In all mammalian species, pregnancy is synchronized with mammary duct elongation and branching, and the formation of lobuloalveolar structures that develop into functional milk-secreting alveoli upon lactation. The synthesis and secretion of milk for the nourishment of the developing neonate involve the collaborative activity of a luminal epithelial and myoepithelial cell layers. These layers contribute to the production and release of milk, respectively, and regress upon termination of lactation to a pre-functioning state [9, 10]. The basic mechanisms regulating mammary gland development and synchronization of milk production

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with neonate development are also essentially conserved. The major systemic players are the steroid hormones estrogen and progesterone, which mediate ductal elongation and branching, respectively, during various stages of mammary development. Pituitary lactogenic hormones, primarily prolactin and to a lesser extent growth hormone, contribute to the stimulation of milk component synthesis. With some variation in the importance of its components between species [9, 11], this process involves complex intracellular mechanisms in which the functioning epithelial layers are subjected to extracellular matrix [12] and stromal [13, 14] regulation.

Importantly, detailed information on the mechanisms regulating mammary development and function has been primarily obtained from rodent-based studies, because these allow genetic manipulations of functional and regulatory genes that affect metabolic pathways, as well as epigenetic analyses supported by in-vitro assays using intact and transformed cell lines. In contrast, our understanding of mammary activity in non-rodent mammals primarily stems from statistical, retrospective, and in-vitro human studies, as well as from more production oriented analyses of farm animal mammary glands. Nevertheless, aside from certain evolutionary-dependent adaptations to specific habitats or lifestyles, there is no evidence to suggest significant differences in mammary function across the entire mammalian class. Exceptions include the lactating seal's mammary gland, which does not involute during the female's forages in the Arctic Ocean [15]; the red kangaroo (Macropus rufus), which maximizes reproductive success in variable environmental conditions by specific adaptation. Female marsupials, whose teats are located within a pouch, have each teat linked to a separate mammary gland and can simultaneously produce milk with distinct nutrient compositions to meet the nutritional needs of offspring at different developmental stages [16]. Another unique example is the platypus (Ornithorhynchus anatinus), an egg-laying monotreme that lacks nipples. Instead, it secretes milk through specialized mammary gland ducts onto the skin, where the young nurse [17]. The monotreme group is considered the most primitive branch of mammals and is thought to have evolved before the development of complex mammary structures, such as nipples, which support live-born young. Thus, the platypus exemplifies how evolution tailors adaptations to suit different physiological and ecological needs.

Amidst the overarching resemblance in mammary gland morphology and activity, a notable discrepancy in mammary predisposition to tumorigenesis emerges within various members of the mammalian class, suggesting differences in the stringency of controlling normal development and homeostasis. This discrepancy can be broadly categorized according to dietary preference: mammals belonging to the carnivore/omnivore taxa are susceptible to breast cancer, whereas herbivores are much less exposed (reviewed in [18, 19]). For example, mammary tumors are the most common neoplasm in female dogs, with up to 50% being malignant [20]. In cats, mammary tumors account for about 17% of all neoplasms, with 80–90% being malignant [21]. Wild carnivores, such as jungle cats, jaguars, leopards, lions, and tigers also develop mammary tumors, which exhibit morphological patterns similar to those in human breast cancer [19]. In contrast, mammary tumors have rarely been reported in domestic mares [22, 23], cows (Table 1), ewes [24], goats, or sows [25]. Mammary cancer is also rare in zoo and free-ranging ungulates [26–28]. These significant differences in mammary gland tumor development may have contributed to the generally lower mortality rates observed in cloven-hooved domestic or zoo mammals—compared to carnivores [29]. Pigs are cloven-hoofed animals and omnivores, capable of consuming both plant and animal matter. Notably, there are significant morphological similarities between their mammary glands and the human breast. A review of the literature by Morey-Matamalas and colleagues [30] highlights that naturally occurring mammary tumors are rare in pigs. However, porcine epithelial cells have been shown to develop neoplasia following oncogenic transformation and subsequent injection into mouse mammary glands [31]. This observation emphasizes the critical influence of the host environment on tumorigenesis and suggests that pigs may occupy an intermediate position between carnivores and herbivores in their susceptibility to mammary cancer.

Importantly, dietary factors have little impact on the variance in tumorigenesis among mammals, as numerous studies have shown no significant association between dietary regimens and the prevention of initial breast cancer onset, recurrence, or disease-specific mortality [32–34]. Of note, within this overarching perspective, certain foods—including plant-based ones— may marginally enhance overall health, potentially reducing the risk of breast cancer [34–36]. No conclusive evidences regarding the effect of adherence to an overall plant-based diet on breast cancer can be depict from the literature. For example, Penniecook-Sawyers [37] reports that vegetarian dietary pattern did not experience a lower risk of breast cancer as compared with non-vegetarians. Others [38] concluded that meatless diet may reduce the risk of breast cancer, especially those that are more likely to be aggressive tumors, though the association between plant-based diet quality and breast cancer remains unclear.

Conversely, a slight elevation in breast cancer risk has been linked to high consumption of processed meat, particularly observed in postmenopausal women [39].

Estrogenic pastures have been identified as endocrine disruptors in sheep, affecting reproductive properties [40].

Table 1 Retrospective studies assessing mammary tumor development in the context of widespread tumorigenesis in bovines

Country of origin/ Study duration/ Breed	Number of animals examined	Tumor count and/or tumorigenesis rate (%)	Highly affected tissues	Type of tumors in highly affected tissues	Mammary tumors (% of examined animals)	Prevalence of mammary tumorigenesis (% of all examined tumors)	References
USA/ N.I./ N.I.	13×10^6	1,300 (0.01%)	N.I.	N.I.	0	0	Feldman, 1932 [88] (reviewed in Swett et al., 1940) [89]
USA/ N.I./ N.I.	418 (313 cows,105 heifers)	N.I.	N.I.	N.I.	0	0	Swett et al., 1940 [89]
Canada/ 6 years/ N.I.	447	59 (13.2%)	Lung, Gut	Squamous cell carcinoma	0	0	Plummer, 1956 [89]
Netherlands/ 5 years/ Friesian cows	N.I.	208 tumors of adult cows, 23 tumors of calves	Hematopoietic system, Digestive system, Reproductive system	Carcinoma, Papilloma, Adenocarcinoma	1 (0.4%) (Mammary carcinoma)		Misdorp, 1967 [87]
East Africa/ 2 years/ European strain	72	10 (14%)	Vulva, Eyelid, Skin	Squamous cell carcinoma	0	0	Murray, 1968 [91]
Republic of South Africa/ 40 years/ N.I.	N.I.	606 tumors (including benign)	Skin, Lymphoid system, Eye	Squamous cell carcinoma, Papilloma, Melanoma	N.I.	0.5% (2 papillomas, 1 adenoma)	Bastianello et al., 1982 [92]
Iran/ 25 years/ Several strains	1,980 (1,335 cows, 643 calves)	140 tumors (7.07%): 138 tumors (10.3%) in adult cows, 2 tumors (0.3%) in calves	Eye, Mammary gland	Squamous cell carcinoma, Squamous cell papilloma	26 (13%)	18% (including benign tumors)	Naghshineh et al., 1991 [93]
Brazil/ 45 years/ N.I.	6,706	586 (8.73%)	Alimentary tract, Skin	Squamous cell carcinoma	1 (0.015%)	0.17%	Lucena et al., 2011 [94]
Egypt/ 2 years/ N.I.	N.I.	60 tumors	Eye	Squamous cell carcinoma, Cutaneous papilloma	0	0	Moharram et al., 2019 [95]
Italy/ 5 years/ N.I.	1,649,003	41 (0.0025%)	Alimentary system, Hematopoietic system	Hepatocellular adenoma, Carcinoma, Lymphoma	0	0	Cappelleri et al., 2022 [96]

N.I., not indicated

The presence of phytoestrogen-containing forages has been suggested to exert estrogenic effects and potentially contribute to mammary tumor development, but no conclusive evidences were provided [41]. A comprehensive survey of the literature has yielded inconclusive results also regarding the effects of phytoestrogens on breast cancer development. For example, in a review of in vivo evidence, De Lemos [42] concluded that the phytoestrogen Genistein stimulated tumor growth at low concentrations but inhibited it at high concentrations. No consistent effects of dietary phytoestrogens on indicators of cell proliferation have been observed in normal human breast tissue, although phytoestrogens may promote proliferation in existing breast cancer [43].

Thus, while broad dietary categorization is associated with susceptibility to mammary cancer, the diet type itself does not play a significant role in causing the difference among mammals. This review, along with the referenced literature, focuses on mammary carcinogenesis in two representative species with distinct dietary habits: bovines, the most extensively studied herbivore, and humans.

Breast Cancer: An Overview of Potential Predisposing Factors

Cancer stands as a prominent global cause of death, posing a significant obstacle to the enhancement of life expectancy worldwide. Within the spectrum of tumorigenesis affecting various human tissues, breast cancer holds a main position, accounting for an estimated 2.3 million new cases globally (11.7% of all cancers in 2020). Consequently, it ranks as the fourth leading cause of new death (6.9%), trailing behind lung (18%), liver (8.3%), and stomach (7.7%) cancers [44]. Despite extensive research advances leading to improved treatments, breast cancer in females continues to be the most diagnosed cancer (24.5%) and the leading cause of cancer-related deaths (15.5% of all cancers) [44]. Given these concerning statistics, exploring novel perspectives related to causes and treatment of this disease has become imperative. The intra-mammalian comparative approach aims to uncover potential cues linked to the exclusive metabolic adaptations observed in the largest mammalian population—herbivores, and especially the cow—that are associated with lower mammary cancer susceptibility. To achieve this, it is essential to delve into the fundamentals of breast cancer development with a focus on relevant factors that might be involved in the herbivores' selective adaptation to breast cancer resistance.

Breast cancer arises as a cellular malfunction in an exocrine tissue, attributed to individual luminal epithelial cells that have lost control over their proliferation and apoptosis. Progression toward ductal carcinoma in situ ensues, resulting in tumors with considerable heterogeneity [45]. The cellular characteristics of a specific tumor closely resemble those of intact epithelial cells at a distinct stage in their hierarchical differentiation, implying a link between the hierarchical stage of the initiating transformed cells and the resulting tumor phenotype. For example, the transcriptomes of poorly differentiated claudin-low tumor cells are similar to those of a normal breast stem cell-enriched population, whereas the more differentiated luminal A tumors show similarity to the mature luminal cells. Luminal progenitor cells seem to be the precursors for basal-like cancers [45–47].

The triggers and mechanisms governing breast tumorigenesis have been studied in the susceptible taxa, mainly humans and model animals. Most of the evidence indicates that breast cancer is triggered by genomic aberration of regulatory genes, and tumor development reflects the balance between gatekeeper and oncogene activities. About 10% of the hazardous breast cancer mutations are familial, the most lethal of these being the autosomal-dominant mutation occurring in the human *BRCA1* (17q21) and *BRCA2* (13q13) genes [48, 49]—two high-penetrance tumor-suppressor genes, whose proteins are involved in DNA repair through homologous repair of DNA. Hazardous mutations in other highly penetrant genes, including *PTEN*, *TP53*, *CDH1*, and *STK11*, were also identified. Certainly, for most other cases, deregulation of a single factor or specific mutation may not significantly impact the health or functioning of the tissue. However, the combination of several factors may lead to severe consequences, and the outcomes can vary depending on the involved genes and mammalian species [50].

Development and branching of the intact mammary ductal tree are contingent on the steroid hormones estrogen and progesterone. Notably, among the numerous factors that contribute to breast cancer, the activity of these hormones via their nuclear, and to lesser extent cytoplasmic receptors (ERα and PR, respectively) has a high and significant impact on the development of most tumors [51–53]. In fact, tumors' clinical classification and treatment are routinely determined according their expression, separately or together, with the human receptor tyrosine kinase epidermal growth factor receptor 2 (HER2). The latter is amplified in 13–15% of breast cancers and activates the Ras/mitogen-activated protein kinase (MAPK) or phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathways [45, 50, 52, 54]. The obtained expression profiles facilitate the classification of breast cancer into four primary groups: the less aggressive ER^+ PR^+ human epidermal growth factor receptor 2 $(HER2)^-$ luminal A (comprising 50–60% of cases); the more highly proliferative luminal B (constituting 10% of cases) with similar characteristics, including increased incidence of mutations in the genome guardian p53; $HER2^+$ cases that are ER^- and PR^- (representing 20% of cases with

an intermediate aggression level); and the highly aggressive basal-like triple-negative (ER^- PR^- $HER2^-$) tumors, accounting for approximately 10% of breast cancers [55]. This latter group encompasses diverse cell subtypes and exhibits relatively high expression levels of epidermal growth factor receptor (EGFR), and cytokeratins 5 and 14. Notably, this latter subgroup is prone to early recurrence and metastasis [45, 52, 56]. Many excellent reviews further characterize and subdivide these breast cancer tumors, mainly for targeting clinical treatments.

Importantly, most breast tumors, particularly ER+PR+tumors, develop well after the surge in mammary gland steroid hormone fluctuations during parity, reflecting the contribution of accumulating mutations [57]. Complementary evidence from mice reveals a detailed epigenetic mechanism underlying latent, postmenopausal mammary tumor development driven by deregulated signal transducer and activator of transcription 5 (STAT5) [58, 59]. Notably, the oncogenic effects of STAT5 on mammary tumor formation manifest long after the peaks of STAT5 expression and activity during parity, arising from stable changes in DNA methylation established during pregnancy. These epigenetic marks alter mammary gland behavior, contributing to tumorigenesis. This underscores the intricate interplay among oncogenes, tumor suppressors, and epigenetic modifications, particularly alterations in methylation activity.

A notable time point that associates breast tumorigenesis with mammalian female physiology is menopause (or estropause in mice [60], or oopause in other mammalian species [61]). Traditionally, menopause is defined as the end of menstruation in women and is an integral element in human aging that occurs at the age of 45 to 55 years. At that time, women stop releasing eggs and menstruating [62]. Menopause does not cause cancer, but premenopausal and postmenopausal periods categorize breast cancer development and types. Tumors that develop in the premenopausal period, especially at a younger age, seldom follow a more aggressive clinical course associated with a poor prognosis [45]. Many of them are unresponsive to hormones or are triple negative. Conversely, hormone-responsive tumors are more likely in postmenopausal women who have been exposed for longer periods to systemic steroids [63]. The increased risk of breast cancer associated with early menarche is also stronger in lobular tumors than in ductal tumors, but is not specific to ER^+ tumors, suggesting that breast cancer risk is not attributable only to increased time of reproductive exposure, but also to distinct mechanisms [63].

Prevention vs. Inhibition of Breast Cancer Development Can Be Exemplified by Comparing Effects of DNA-Damage Response to Anticancer Immunity

Mammalian tissues counter breast cancer development with broad prevention and/or inhibition mechanisms, many of which are not specific to the breast. Prevention mechanisms primarily involve maintaining genomic integrity and repairing DNA damage [64]. Genomic instability is a direct outcome of environmental and oncogene-induced DNA-replication stress that results in DNA damage, the most deleterious being double-strand breaks (DSB) [65]. A DNA-damage response (DDR) ensues, which involves the concerted activity of sensors (ATR, ATRIP, RADs, ATM, γH2AX, MRE11-RAD50-NBS1 complex, Ku70/Ku80, MDC1 and 53BP1), mediators (Claspin, BRCA1, P53BP, MDC1), transducers (CHK1, CHK2), and effectors (P53, CDC25) [64, 66]. Without the appropriate DDR following insults from environmental or endogenous stressors, further genomic defects may occur, leading to malignant transformation, cancer progression, and further injury to the cellular DNA-repair machinery. Cancer pathogenesis ensues through a cascade response involving activation of a series of proto-oncogenes, such as EGFR, MYC, and RAS, which are continuously triggered. In parallel, the DDR reaction is initiated via a process that includes activation of checkpoints, which arrests cell-cycle progression to allow for repair and prevention of the transmission of damaged, or generation of incompletely replicated chromosomes. It also involves anti-oncogene activity and, according to the type of damage, might result in cell senescence or apoptosis [67].

Among tumor-suppressor genes, mutations in breast cancer susceptibility genes *BRCA1* and *BRCA2*, which are involved in the DNA damage response (DDR), are the most prevalent, accounting for inherited breast cancer in up to 7% of unselected cases. Interacting with BACH1 and BARD1 or RAD51, respectively, distinct BRCA1–BRCA2 complexes are required for homologous recombination and DSB repair [68, 69]. Homologous recombination ensures accurate repair with sister chromatids as templates via the S/G2 cell-cycle phase, in contrast to non-homologous end joining, which directly ligates DSB ends throughout the cell cycle, but is more prone to errors [66]. During the S-phase of the cell cycle, phosphorylated BRCA1/2 translocate to the nucleus, recruit other factors, and regulate repair of DNA damage [70]. When the *BRCA1* gene is mutated or lost, the incidence of breast cancer and ovarian cancer increases significantly [48]. Indeed, the lifetime risk of breast cancer in carriers of *BRCA1* or *BRCA2* mutations is 45–80% [71, 72], while one in eight women will develop breast cancer over their lifespan in the general population. Carriers

of the *BRCA1* mutation are more likely to develop triple-negative breast cancer with basal cell characteristics [73]. This suggests a link between hormone receptor status and the BRCA1 mutation in affecting breast tumor phenotype.

A deficient DDR is often associated with activation of anticancer immunity that has an inhibitory role on tumor development. Compelling evidence has shown that DNA-damage signals and the endogenous DDR activate the innate immune response [74]. Indeed, the cellular immune system is considered a major inhibitor of a wide range of tumorigenic triggers [75, 76]. Its defensive reaction occurs in three stages: recognition, processing, and reaction. Typically, non-self-elements are recognized as foreign substances by the innate immune system which includes the natural killer (NK) cells, macrophages, dendritic cells, and neutrophils, as well the active complement system. The balance between effector and tolerogenic immune response dictates the tumor's fate (reviewed by [77]).

While the precise mechanisms by which cancer cells are identified by the immune system remain incompletely understood, it is undeniable that both innate NK cells and adaptive cytotoxic T cells play pivotal roles in immune surveillance against cancer [78]. Innate immunity recognizes changes in cells caused by transformation, such as a lack of expression of self-molecules or the induction of stress-inducible self-molecules. NK cells utilize the inhibitory receptors [79] to differentiate normal self-cells from self-cells that lack major histocompatibility complexes (MHC), and eliminate the latter transformed cells. However, in many cases, the immune system is unable to keep up with the rapid growth and spread of cancer cells. These cells create a tumor microenvironment and develop strategies to evade detection and suppress immune responses, preventing attacks from immune cells [80]. For example, two-faced macrophage activity involves a shift from an antitumor pro-inflammatory M1-like polarization state to an anti-inflammatory protumorigenic M2-like polarization state [81]. Tumor-associated macrophages also promote tumor progression by stimulating angiogenesis and lymphangiogenesis, cancer cell proliferation, and epithelial–mesenchymal transition, promoting metastasis, and inducing immunosuppression of antitumor effector immune cells [81–83]. If enough immunogenic antigens are produced during the early stages of tumor initiation, naïve T cells in the tumor microenvironment may generate a protective immune response, eliminating immunogenic cancer cells. However, the less immunogenic cancer cells may escape the immune control of T cells and survive, via a process termed cancer immunoediting [84].

Low Levels of Diagnosed Mammary Cancer Development and Mortality in Bovines

In contrast to the substantial effort dedicated to studying the mechanisms governing cancer initiation and progression, described above, significantly less emphasis has been placed on investigating and clinically applying resistance mechanisms that shield not typically investigated animals from cancer. For example, the naked mole rat, the blind rat, and the elephant do not, or only rarely develop tumors in their bodies due to distinct evolutionary resistance mechanisms: p16INK4a-dependent early contact inhibition that arrests cell growth and proliferation when cells come into contact with each other, concerted cell death, or extra copies of the TP53 gene in the genome, respectively [85]. The low tissue-specific tumorigenesis levels exhibited by the mammary glands in grass-eating herbivores, especially bovines, adds an additional layer of complexity to the broader issue of low tumorigenesis levels in these organisms.

Without tools such as ultrasound, pinpointing a growing tumor in the parenchymal and stromal fibrotic regions of a cow's mammary gland is exceedingly difficult. Unless situated in a region that directly affect lactation or behavior, these rare tumors may remain unnoticed for years, growing to substantial sizes, e.g., 45 cm x 40 cm x 25 cm [86] or 25 cm x 5 cm x 5 cm [87]. Furthermore, discerning the primary site of tumor initiation solely from dissected bovine mammary glands in retrospective studies conducted in slaughterhouses has also proven to be challenging. In addition to primary glandular, ductal, or stromal tumors, there are primary cutaneous tumors that directly invade the udder, such as melanomas or squamous cell carcinomas, as well as secondary metastatic tumors such as lymphosarcoma ([86] and references therein). Therefore, accurate and comprehensive anatomical and pathological documentation of tumor development in large bovine populations is crucial for understanding and characterizing the true nature of tumor development in the bovine mammary gland. Table 1 summarizes findings from 10 retrospective studies involving tens of thousands of cattle analyzed for tumors post-slaughter over the past century [87–96]. With the exception of one study conducted in Iran [93], all others reported the extremely rare occurrence of mammary tumors in cows. In contrast, other tumor types were observed at relatively high levels, reaching up to 14% in the analyzed cows. These included squamous cell carcinomas of the esophagus and forestomachs, squamous cell carcinoma of the vulva, carcinomas of the uterus, adrenocortical adenomas, leukemia, tumors of the urinary bladder, renal cell tumors, ophthalmic tumors, lung tumors, and skin tumors. Several case reports have also been published, some in regional journals, describing the development of rare individual mammary

tumors: carcinoma in a Holstein–Friesian dairy cow [97], and a metastatic mammary carcinoma [98] or carcinoma without metastasis [99] in mature/old cows. In the case of the exceptional study [93], the vast majority of the developing tumors were identified as squamous cell papilloma, i.e., a benign epithelial tumor. These tumors are frequently caused by bovine papillomavirus (BPV) [100]. Infection of cattle with BPV-1 can cause papillomatosis of the teats, udder, and penis; BPV-1 and BPV-2 can both cause cutaneous papillomas. BPV is transmitted by direct contact, fomites, and possibly insects. Calves are easily infected by the papillomavirus penetrating through cut or abraded skin. Thus, the reported tumors might have resulted from local treatment or an infectious environment. Regardless, most of these retrospective studies reported that while mammary tumors are indeed rare in cattle, other organs, and especially the eye, intestinal tract, and reproductive system, are highly subject to tumorigenesis.

Perhaps the most comprehensive report on tumorigenesis in cattle involved the examination of 586 tumors in Brazilian cattle that were analyzed after necroscopy of 6,706 cows over a period of 45 years [94]. Tumors were pathologically characterized and catalogued according to target organs and latency period—up to about 16 years. The highest susceptibility to the neoplastic disease was identified in the alimentary tract (24% of the tumors). This was followed, in decreasing order of frequency, by tumors of the skin and subcutis (22%), hematopoietic tissue (17%), the eye and periorbital tissues (15%), the urinary tract (7.5%), the female reproductive system (3.6%), the endocrine system (2.7%), the liver and pancreas (2%), and the nervous system and respiratory system (1% each). Importantly, only a single tumor, representing 0.17% of the total number of tumors, was detected in the mammary gland. In that study, bracken fern toxicity was hypothesized to be involved in inducing digestive tract tumorigenesis due to its immunosuppressive effect [94]. Importantly, the mammary gland—a highly cancer prone tissue in humans and carnivores—was almost completely resistant to this inducer of tumor development. Indeed, it has been established that the signaling output of an oncogenic driver can vary significantly among tissues, and that specific somatic internal and environmental factors shape the tissue's susceptibility to carcinogenesis [101]. For example, oncogenic KRAS triggers the tumor-suppressive p19ARF pathway extensively in mesenchymal tissues, such as the musculature, but not in epithelial cells of the lung [102].

Taken together, these studies highlight the tissue-specific resistance of the bovine mammary gland to tumorigenesis, raising an inevitable question: What mechanisms safeguard the mammary gland in herbivores, particularly cows, against mammary tumorigenesis?

Once the credibility of the findings supporting this resistance—compared to the human breast and carnivore mammary glands—has been established, the next highly challenging step is to identify the biological basis of this phenomenon, which may involve multiple levels.

Diverse Roles of BRCA1/2 in Humans and Bovines

DNA damage and DDR have received comparatively little attention in bovines compared to humans or laboratory animals. The few systems that have been examined to a limited extent in bovines, perhaps for commercial reasons involving embryonic development, are sperm integrity [103–105] and the cumulus–oocyte complex [106, 107]. Upon DNA damage, reduced fertility potential was observed. Hatching rates, which mark fertilization potential, were also highly affected by irradiation, with values almost halved at the lowest irradiation dose examined (0.6 Gy) [108]. Key players in the DDR and DSB-repair mechanisms were partially elucidated in bovine cumulus cells cultured under bovine serum albumin-induced DSB conditions and the engagement of a conserved DDR pathway, which entailed the activation of BRCA1, BRCA2, and Tp53, was confirmed [107]. Taken together, these findings refute the notion that bovine tissues might have a higher resistance to DNA damage or a more effective DDR.

Compared to the *p53* gene which has been found mutated in most cancer types, *BRCA1* is an example of a specific breast cancer gene. Mutations in this important DDR-encoding gene increase the risk of breast and ovarian cancers by up to 80%, but to a much lower level for other cancer types [109]. The mammary gland's specific reliance on intact *BRCA1* and *BRCA2* genes for cancer prevention renders them prime candidates for elucidating the basis of the bovine mammary gland's unique resistance to tumorigenesis. This inevitably raises an important question: why do uncorrected DSB in these genes fail to result in bovine mammary tumorigenesis, whereas such mutations initiate carcinogenesis in humans [71, 72], dogs [110], and cats [111]? In mice, a null mutation in *BRCA1*, with [112] or without *p53* [113], resulted in embryonic lethality at E6–13 that was associated with growth retardation, increased apoptosis, aneuploidy, and chromosome damage.

It has been suggested that the human *BRCA1* gene diverged from its domestic farm animal counterparts approximately 88 million years ago [114], resulting in some degree of discrepancy [115]. Nonetheless, Krum et al. [116] hypothesized that crucial structural and functional components were conserved, given that human *BRCA1* sequences can genetically complement loss-of-function alleles in

mice, where BRCA1 shares less than 60% amino acid identity [117, 118]. The human and bovine genes are situated on chromosome 19, and chromosome 17, respectively [116]. This chromosomal location lies within a conserved genomic region, also observed in mice on chromosome 11 [119]. The predicted bovine protein product shares 72.5% sequence identity with the human protein, exhibiting conservation of amino acids crucial for BRCA1 structure and function [116]. Notably, a potential area of significance is the C-terminal domain of the gene, which differs by lacking 7 amino acids in the bovine genome compared to the human counterpart [116]. Despite this disparity, the bovine protein retains its ability for nuclear localization, but its C-terminal domain shows significantly reduced activation of a luciferase reporter plasmid compared to the one in humans [116], probably due to lack or reduced interaction with additional proteins need for BRCA1 activity [120]. Indeed, The C-terminal domain of BRCA1contains two BRCT motifs in tandem that are present in other proteins known to have a function in DNA repair and DDR. The BRCT domains of BRCA1 specifically mediate the interaction of BRCA1with signaling kinases and other proteins involved in cell cycle checkpoints [121].

Over 100 BRCA1 mutations have been identified worldwide in the human population, but the most studied ones, in terms of distribution and lethality, occur in defined ethnic groups [122]. Focusing on 9 mutations observed in Ashkenazi Jewish, Swedish, and Canadian populations, with frequencies ranging from 0.1 to 1.36% in the Jewish population [122–125], a comparison revealed homology between humans and bovines in regions corresponding to mutation hotspots: 185delAG, the most frequent mutation among Ashkenazi Jews, as well as 1128insA, 1293del40, and 4184del4. A single-base mismatch was observed in the region of 5382insC. This observation suggests a comparable likelihood for the occurrence of these mutations in the bovine genome which, apparently, does not manifest in notable tumorigenic consequences. Of note, a unique observation in bovines identified polymorphisms in the *BRCA1* gene which was associated with susceptibility to mammary mastitis [119], though no connection to mammary cancer has been established.

Taken together with the difference in the C-terminal activity, these data indicate a redundancy in bovine mammary BRCA1/2 DDR activity compared to its essential role in humans. If BRCA1/2 genes indeed play a less significant role in maintaining genomic integrity in the bovine mammary gland compared to their critical function in the human breast, alternative mechanisms or genes could compensate for this activity. One plausible alternative is the involvement of other DDR and repair pathways, such as those mediated by ATM, ATR, or other non-homologous end-joining and homologous recombination proteins, like RAD51, XRCC4, or MRE11/RAD50/NBS1 complex. Additionally, species-specific adaptations, including differences in cellular replication stress response or unique epigenetic regulation, may contribute to genomic stability in the bovine mammary gland. Further research into these mechanisms, including transcriptomic and proteomic analyses, could help identify alternative pathways or genes compensating for reduced BRCA1/2 activity in bovines. This line of investigation might also reveal broader evolutionary differences in mammary gland biology between species.

Mastitis and its Role in Tumorigenesis: a Human and Bovine Perspective

Mastitis is inflammation of the mammary gland which is usually caused by bacterial infection. It is most common when a woman is breastfeeding [126], but it can happen at other times as well. In humans, mastitis has been associated with increased risk of breast cancer [127–131]. In cows, especially in dairy cattle, mastitis is the most common disease. It occurs mostly during lactation, and somatic cell count in the milk serves as a good indicator of the situation [132]. Numerous high-quality studies have been conducted to characterize this disease ([133–135] and references therein).

Cows differ from humans in their longer lactation periods, which are associated with higher incidences and longer durations of mastitis. This difference may reflect less hygienic conditions and anatomically different teat structures: cows have a single large lactiferous duct draining a cistern, which may allow for higher bacterial penetration and habitation compared to the 15 to 20 ducts, each 0.4–0.7 mm in diameter, that drain each lobe of the human breast [136]. Contrary to clinical mastitis, subclinical mastitis shows no visible abnormality in the udder and is detected by an increase in somatic cell count [137]. In contrast to its effect on promoting breast cancer in humans, chronic sub-clinical mastitis which persists in the bovine heard [135] may alert the innate immune system to better fight cancer in the bovine mammary gland, especially in older bovines which are more susceptible to inflammation due to wider or permanently partially-open teat canal [135]. With the infiltration of leukocytes and subsequent inflammation, the impact of continuous or repeated inflammatory mediators can eliminate tumor cells and prevent tumor development [138] due to the expression of tumor-specific antigens (neoantigens) and tumor-associated antigens [139]. These antigens activate antitumor immunity and, under certain conditions, may also induce rejection of early neoplasms, a concept known as immunosurveillance [139, 140].

Indeed, it has already been shown that inducing inflammation locally in the bladder with a vaccine containing an attenuated Mycobacterium bovis strain successfully treats squamous bladder cancer [141]. At the molecular level, the expression of transforming growth factor (TGF)-β1 and fibroblast growth factor 2 (FGF2) is induced by Staphylococcus aureus, a gram-positive bacterium that causes mastitis in bovine mammary gland by activating the transcription factors activation protein 1 (AP1) and nuclear factor-kappa B (NF-κB) [142]. Notably, breast cancer patients with low levels of FGF2 had a significantly shorter disease-free survival compared to those with elevated FGF2 [143]. TGFβ1 is a secreted tumor suppressor that inhibits epithelial cell proliferation due to cell-cycle arrest in the G1 phase [144]. Taken together, while mastitis is a breast cancer risk factor in humans, its chronic occurrence in bovines may activate antitumor immunity and induce gatekeeper genes, potentially reducing susceptibility to mammary cancer.

Reproductive Cycles, Steroid Hormones and Physiological Factors: a Comparative Analysis of Their Roles in the Different Susceptibility of Human and Bovine to Mammary Cancer

The major systemic hormonal effectors that control mammary epithelial cell proliferation and mediate latent hormone responsive tumor initiation and progression are estrogen and progesterone, acting via their cognate receptors: ERα, ERβ and PR, respectively. In both humans and bovines, these hormones regulate mammary epithelial cell proliferation and differentiation during two reproduction-associated cycles: the shorter menstrual/estrous cycles [145] and the longer parity cycles which include pregnancy lactation and involution [9]. The effect of these hormones, especially estrogen, on resulting breast tumorigenesis has been associated with two main stages: (i) surges of cell proliferation during the actual cycles, which may lead to mutations [146, 147] and (ii) latent epigenetic effects [148, 149].

The menstrual/ estrous cycle is a recurring process characterized by changes in ovary-secreted hormones under the control of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH stimulates the growth and development of ovarian follicles, and LH is necessary to maintain luteal function. Human females experience menstrual cycles averaging 28 days, while bovine females experience estrous cycles averaging 21 days. Higher numbers of cumulative menstrual cycles have been associated with increased breast cancer risk [150, 151]. This probably reflects the induced cell proliferation in the breast during phase I of the menstral cycle [145]. Importantly such induction in cell proliferation was not observed in the bovine gland [152], or is limited to a few cycles [153]. Estrogen levels, a main inducer of latent tumor development, rise twice during the human menstrual cycle: in the late follicular phase and during the luteal phase [154]. In contrast, only a single surge of estrogen, produced by the dominant follicle, characterizes the bovine estrous cycle [155]. These differences suggest that steroid hormones mediate a higher proliferation-induced mutagenic effect in the human breast during the menstrual cycle compared to their role in the bovine mammary gland during estrus.

Evidences from transplantation assays suggest that bovine mammary stem cells are less responsive to estrogen and progesterone effects compared to their higher reactivity in the mouse mammary gland. In these assays, combined estrogen and progesterone treatment very rarely induces elongation and branching of the mammary ductal network from capsule-like structures developed from transplanted stem cells [143]. Nevertheless, data are still not sufficient to empirically associate these findings with the lower rate of tumorigenesis in the bovine gland compared to the human breast. Finally, estrogen activity in the bovine gland might involve different pathways compared to humans due to differences in responsive target genes [142].

Pregnancy and lactation, a critical stages of the parity cycle should be also considered for their distinct effect on mammary tumorigenesis in humans and bovines. Indeed, human breast epithelial cells maintain a degree of proliferation during nursing [138], whereas 99.7% of the epithelial cells in the non-pregnant lactating bovine mammary gland are essentially differentiated cells [139] that are less prone to transformation. In this respect, bovines, particularly domestic ones, are often pregnant while lactating. Similarly, free-ranging ungulates in nature can remain pregnant while continuing to lactate. The hypothesis that lactation reduces breast cancer risk has been examined in many case–control studies and a few large cohort investigations in humans, but the results are not conclusive. Several studies have statistically linked a higher number of parity cycles to a lower risk of luminal breast cancer. This association is attributed to the induced differentiation of mammary epithelial cells during lactation [140, 141]. However, other epidemiological evidence suggests that lactation-related protection in the general human population is minimal and primarily limited to long lifetime durations of breastfeeding ([156] and references therein).

The interval between the age at menarche and the age at first birth is another factor associated with the risk of hormonally sensitive types of breast cancer among White women [157]. In comparison, this interval is much shorter in bovines, which begin cycling at approximately 12–13 months of age and are typically pregnant by 15 months (https://www.msdvetmanual.com/multimedia/table/features-o

f-the-reproductive-cycle source). While this longer interval may contribute to the observed resistance to mammary cancer in bovines, its validity as a protective factor is uncertain, as this effect has not been observed among Black women.

Age is another consideration, as humans typically live longer than bovines, and breast cancer—particularly hormone-sensitive types—often develops later in life [158]. While age cannot be entirely dismissed as a factor, evidence suggests it may not be the primary reason for humans' higher susceptibility to breast cancer. For one, a significant proportion of tumors, especially triple-negative types, occur in women at relatively young ages [159]. Additionally, carnivorous pets with lifespans comparable to bovines exhibit relatively high cancer incidence rates throughout their lives. In terms of the specific post-reproductive period, cows in zoo conditions and humans spend a similar proportion of their lives (55–60%) in oopause or menopause, respectively [161], thus negating the putative effect of this period on the differences in susceptibility to mammary tumorigenesis. Finally, bovines rarely develop cancer, even at advanced ages. Swett and colleagues [89] conducted a thorough examination of the udders of 313 lactating cows and 105 heifers and freemartins. Among the lactating cows, 31% were eight years or older—an age considered beyond the typical "cancer age" for bovines [86]—yet no neoplastic changes were observed in any of the cases. Indeed, the cancer-dependent mutation theory fails to explain several phenomena, including the disproportionate relationship between cancer frequency and animal body size (discussed below) as well as the scaling of cancer incidence with animal lifespan. It has been suggested that specific evolutionary forces contribute, for example, to species-specific differences in the number of mutational "hits" required for malignant transformation and signaling pathways crucial for tumor initiation and maintenance are different for cells of different species [57, 85, 160]. Nevertheless, detailed and distinct protective mechanisms have been presented only for few individual species [85].

Differences Between Humans and Bovines in the Prolactin–STAT5 Tumorigenic Axis

Another example of the differences in hormonal regulation between bovine and human mammary activity, which potentially contribute to the lower susceptibility of the bovine mammary gland to cell transformation, involves the STAT5 latent tumorigenic effect. STAT5 funnels extracellular signals from cytokines, hormones, and growth factors into transcriptional activity in the mammary gland [161, 162]. In mice, STAT5 is mandatory for mammary gland development and differentiation [125, 163] and, independently, provides the intracellular machinery for prolactin-induced milk-protein production [164]. STAT5 enhances the progression of WAP–TGFα-induced mammary tumors [165] and its overexpression and forced activation were sufficient to cause parity-dependent postestropausal mammary carcinogenesis [58]. Prolactin treatment in MCF-12 A human mammary epithelial cell cultures increased the levels of STAT5 phosphorylation and β-casein expression [166]. STAT5 is also expressed in a high proportion of human breast cancers and statistically associated with higher levels of differentiation and a better prognosis and response to endocrine therapy when co-expressed with ERα (Reviewed in [167, 168]). In contrast to its activity in the mouse mammary gland and the breast, STAT5 is not activated during lactation in the bovine mammary gland, where the stimulation of high-level expression of milk-protein genes is probably not through activation of the prolactin receptor–JAK2–STAT5 pathway [169]. This information suggests that STAT5's oncogenic potential might at least be lower in the bovine mammary gland compared to the human breast.

Tissue-Specific Suppression of Bovine Mammary Tumorigenesis

A mammary-specific herbivore barrier to bovine mammary carcinogenesis was proposed by Ledet et al. [170]. In conditioned medium of mammary-derived mammospheres, they identified bovine and equine sphingomyelins as bioreactive inducers of triple-negative breast cancer cells' death in vitro, acting as a tumor suppressor of these cells in a xenograft mouse model in vivo. In contrast, conditioned medium from canine mammary mammospheres did not exert this inhibitory effect. Although complete elimination of cancer cells by the sphingomyelins was not demonstrated, and the study did not include the secretome of other relevant tissues to confirm a mammary-specific effect, this information significantly contributes to the expanding list of herbivore defenses against tumorigenesis. It also aligns with other findings in the field, such as the production of large quantities of high-molecular-mass hyaluronan in naked mole rats [171], which prevent whole-body tumorigenesis. Notably, the sphingomyelins' effect appears to be suppressive rather than preventative of tumorigenesis and was insufficient to block hormone-responsive tumor development, which might involve additional proliferation stimuli.

Anticancer activity can be also deduced from the characteristics of a recently identified bovine mammary stroma layer. This layer is adjacent to the parenchyma and has no reported match in the human breast or mouse mammary gland. It hosted significantly better bovine mammary epithelial stem cell development and activity

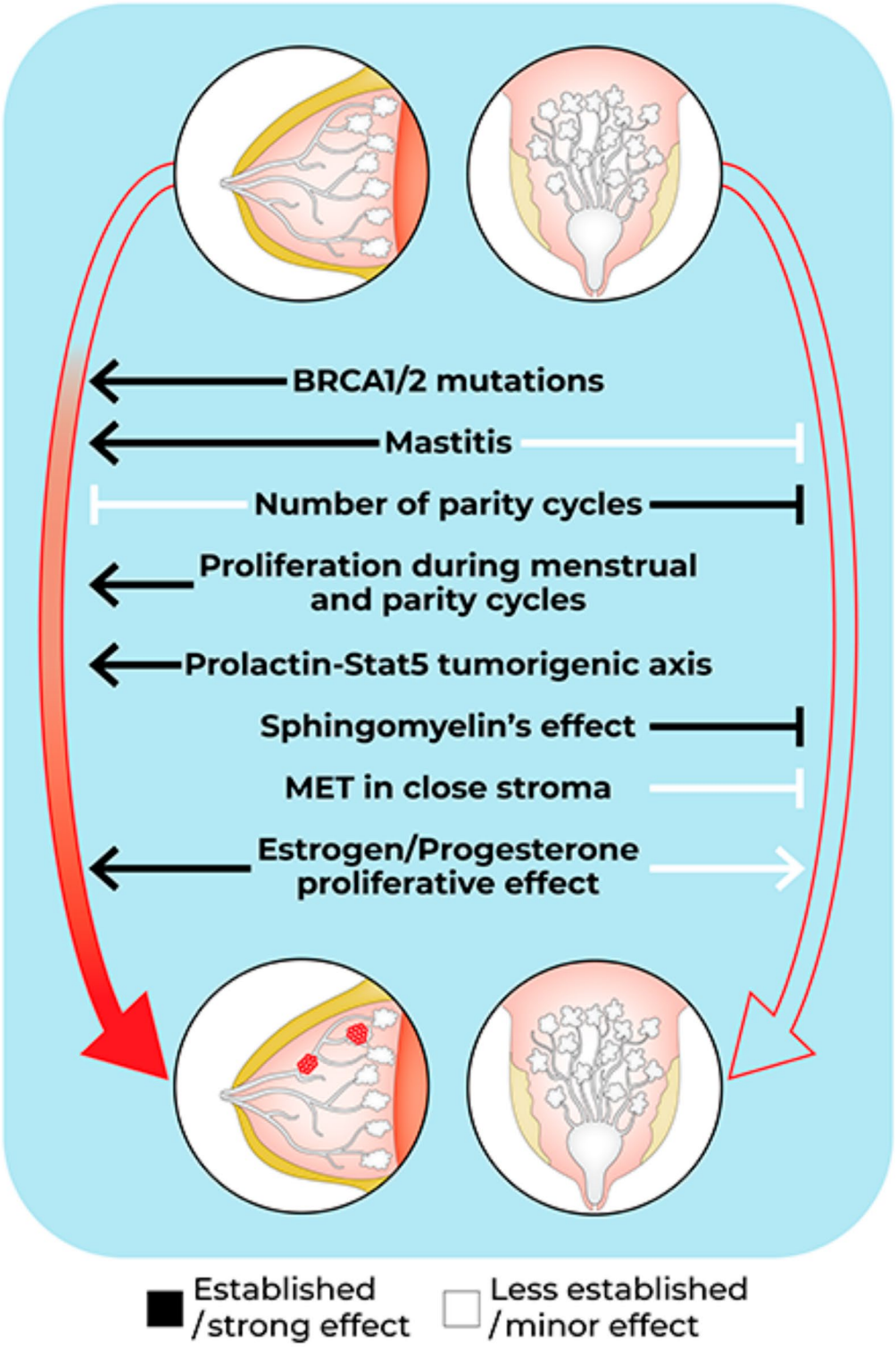

Fig. 1 Comparative analysis of factors contributing to tumor resistance in the bovine mammary gland. This illustration contrasts key elements that either promote or inhibit tumor development in the human breast (left panel) and the bovine mammary gland (right panel). Side red arrows illustrate the development of ductal and alveolar tumors in the human breast, which are absent in the bovine mammary gland, highlighting its resistance to tumor formation. Horizontal arrows represent factors that promote tumorigenesis, while blunt-ended lines indicate inhibitory factors. MET refers to mesenchymal-to-epithelial transition

compared to the distant stroma in transplanted NOD-SCID immunocompromised mice [172]. Interestingly, this "close

stroma" region maintains epithelial-like characteristics and activity, and mesenchymal-to-epithelial transition. While the opposite process, epithelial-to-mesenchymal transition, has been established as a biological process in metastatic cancer [173], anticancer activities have been recently associated with the mesenchymal-to-epithelial transition in vitro and in vivo; e.g., it was found to occur during the generation of induced pluripotent stem cells from sarcoma cells that were de-differentiated to a pre-mesenchymal stem cell state through reprogramming [174]. Thus, through the mesenchymal-to-epithelial transition, the bovine mammary close stroma may add an anticancer shield for developing mammary cells.

Conclusions

The data presented in this opinion article suggest that the lower susceptibility of herbivores to mammary carcinogenesis, compared to omnivores and carnivores, is not due to their meatless diet. Instead, it appears to result from a series of morphological and metabolic adaptations that have evolved since the Jurassic era, contributing to the phylogenetic divergence of these species. The increased resistance of herbivores, particularly bovines, to mammary cancer cannot be attributed to a single factor. Rather, it is likely the result of a combination of various adaptations (Fig. 1). According to Peto's Paradox, large-bodied animals have evolved additional tumor-suppressor mechanisms to counterbalance the increased number of cells in their bodies [175, 176]. Likewise, it seems that herbivores have developed an extra layer of protection contributing to their specific resistance to mammary tumors. However, there is no evidence to suggest that the inhibition of mammary tumor development was the primary target of natural selection. Given that the signaling pathways of oncogenic drivers vary significantly not only between tissue types [101], but also within the same tissue in different mammalian species, further research is needed. In this research, bovine mammary cells should be exposed, both in vivo and in vitro, to a broad range of environmental, genetic, and cellular oncogenic insults. This may offer new strategies for developing mammary-specific anticancer therapies and prevention methods. To align with the mechanisms illustrated in Fig. 1, these studies may utilize both existing [177, 178] and newly developed bovine mammary epithelial cell lines with targeted mutations in genomic regions affecting BRCA1/2 activity. This approach could help identify compensatory genes involved in the putative redundant role of BRCA1/2 in the bovine mammary DDR. Discovering such genes, along with their inducers and regulators, may provide novel therapeutic targets. Similarly, exposing human mammary epithelial cells—or transformed bovine mammary epithelial cells at various stages of transformation—to the secretome of mastitis-causing bacteria could uncover factors that suppress tumorigenesis.

The PRL-STAT5 axis appears to play a more prominent role in humans and mice than in bovines. Monitoring activated STAT5 levels during pregnancy, particularly in high-risk cases, might help mitigate its potential latent tumorigenic effects. Additionally, differences in estrogen surge patterns during reproductive cycles between bovines and humans underscore the importance of developing strategies to counteract estrogen-induced tumorigenesis. Raising awareness of environmental estrogenic compounds is equally important.

Finally, the species-specific effects of sphingomyelin, secreted by bovine and equine mammary cells, in inducing triple-negative breast cancer cell death, highlight the need to identify biologically active agents across mammalian species. Such discoveries could lead to innovative treatments for breast cancer.

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Declarations

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