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Review

Effects of the Hypnotic Alkylphenol Derivative Propofol on Breast Cancer Progression. A Focus on Preclinical and Clinical Studies

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Abstract. *Propofol is a hypnotic alkylphenol derivative with many biological activities. It is predominantly used in anesthesia and is the most used parenteral anesthetic agent in the United States. Accumulating preclinical studies have shown that this compound may inhibit cancer recurrence and metastasis. Nevertheless, other investigations provided evidence that this compound may promote breast cancer cell progression by modulating different molecular pathways. Clinical data on this topic are scarce and derive from retrospective analyses. For this reason, we reviewed and evaluated the available data to reveal insight into this controversial issue. More preclinical and clinical investigations are necessary to determine the potential role of propofol in the proliferation of breast cancer cells.*

Breast cancer is the most widespread malignant tumor affecting women and represents the principal cause of their death worldwide (1). It is characterized by high invasiveness, and surgical resection represents the first line of treatment (2). Unfortunately, after surgery, patients with breast cancer may develop local or distant metastases, which dramatically affects their survival rate (3).

In patients with cancer, the perioperative stress response may lead to the growth of cancer cells and to their dispersal in near or distant organs (4). In this scenario, pharmacological and non-pharmacological agents may play different roles in determining the stress response and, consequently, a potential deviation of the trajectory of the outcome. For instance, many pieces of evidence show that propofol, an alkylphenol derivative general anesthetic used for the induction and maintenance of anesthesia, may affect the long-term outcome of patients with breast cancer (5-7). Several *in vitro* studies performed on different cancer cell lines showed that due to its anti-inflammatory and anti-oxidative properties, propofol may restrain the expansion of cancer cells through the modulation of different signaling pathways (8). Conversely, because other preclinical studies showed that this compound may promote breast cancer cell progression, the matter remains not completely dissected.

This narrative review aimed to summarize these studies by discussing on the roles of propofol in breast cancer progression and recurrence.

Dissecting the Effects of Propofol on Tumor Cell Proliferation. Propofol (2, 6-diisopropylphenol) is largely used in general anesthesia, including in the setting of oncological surgery. Interestingly, recent studies featured the potential anticancer role of this compound in different types of tumors, including pancreatic, colonic, breast, hepatocellular, ovarian and prostate cancer (9-15). These investigations illustrate the molecular signaling pathways underlying the role of propofol in cancer development (16) (Table I). Specifically, as regards breast cancer, it has been

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Table I. *Molecular signaling pathways underlying the role of propofol in cancer development.*

Cancer type	Cell line	Treatment	Signaling pathways	Reference
Ovarian	ES-2	Propofol at 1, 5 and 10 μg/ml Propofol for 24 h	NFκB ↓, miR-9 ↑	19
Pancreatic	MIAPaCa-2	10-100 μM Propofol or 0.5 M Na_2CO_3 (vehicle control) for 72 h 100 μmol/l per milliliter propofol for 24, 48, 72 h; or 10, 25, 50, 100 μM gemcitabine for 72 h. For combined treatment 50 or 100 μmol/l per milliliter propofol for 24 h, then 10-100 μmol/l gemcitabine for an additional 72 h	NFκB ↓	20
Cardia	Cancer cells	Propofol at 12.5, 25 and 50 μM	MAPK/ERK ↓	21
Mouse Leydig tumor	MA 10	Propofol at 300 600 μM for 24 h	MAPK↑, AKT ↓	22
Lung adenocarcinoma	A549	Propofol at 0, 25, 50 and 100 μg/ml for 24 and 48 h	MMP2 ↓, MMP9 ↓, p38 ↓, MAPK ↓	23
Colonic	LOVO	Propofol at 2, 5 and 8 μg/ml for 24 h	ERK1/2 ↓, MMP2 ↓, MMP9 ↓	13
Pancreatic	MIAPaCa-2; Panc-1	Propofol at 25, 50, and 100 μM for 8 h	CaMK II ↓, ERK ↓, AKT ↓, ↓ HIF1α ↓, VEGF ↓, NMDA receptor	24
Pancreatic	Panc-1	Propofol at 10 μg/ml for 0-72 h	ADAM8 ↓	25
Prostate	LNCaP	Propofol at 10 and 50 μM for 8 h	HIF1α ↓, HIF1β ↓	26
Prostate	PC3, DU145, and 22RV	Docetaxel at 0, 6.25, 12.5, 25, 50 and 100 μM; Propofol at 0, 1.25, 2.5, 5, 10, 20, 40, 80, 160, and 320 μM. Docetaxel alone or with docetaxel combined with propofol	HIF1α ↓	27
Ovarian	HO-8910PM, H0-8910, SKOV-3,OVCAR-3, COC1 and ES-2	Paclitaxel at 0.01-10 μM 0.1-10 μg/ml of propofol for 72 h	SLUG ↓	29
Pancreatic	PANC-1	Propofol at 1, 5 or 10 μg/ml for 48 h, or 10 μg/ml for 12, 24 or 36 h	miR-21 ↓, SLUG ↓	30
Endometrial	Ishikawa	Propofol at 2, 4 and 6 μg/ml for 24 h	WNT/β-catenin ↓, SOX4 ↓	31
Breast	MDA-MB-468	Propofol at 6 μg/ml for 7 h	GABA-A receptor↑	32
Gallbladder	GBC-SD cells	Propofol at 0, 10, 20 and 40 μM for 72 h	NRF2 ↑	33
Breast	MDA-MB-231	Propofol at 2, 5 and 10 μg/ml for 1, 4 and 12 h	NRF2 ↑, p53 ↓	34
Breast	MDA-MB-231	Propofol at 0, 2, 5 and 10 μg/ml for 24 h	MMP2 ↓, MMP9 ↓, NFκB ↓	35

ADAM8: A disintegrin and metalloproteinase domain-containing protein 8, AKT: protein kinase B; CaMK II: calcium ion/calmodulin-dependent protein kinase class of enzymes; ERK: extracellular signal-regulated kinases; GABA-A: γ-aminobutyric acid type A ; HIF: hypoxia-inducible faxtor; MAPK: mitogen-activated protein kinase; miR: microRNA; MMP: metalloproteinase; NF-κB: nuclear factor-κ-B; NMDA: N-methyl-D-aspartate receptor; NRF2: nuclear factor erythroid 2-related factor 2; SLUG: snail family transcriptional repressor 2 ; SOX9: SRY-Box Transcription Factor 9 ; VEGF: vascular endothelial growth factor. ↑ Up-regulated. ↓ Down-regulated.

demonstrated that propofol diminished the transient movement of MDA-MB-231 breast tumor cells by reducing the levels of matrix metalloproteinases (MMPs). This effect is mediated by the regulation of the nuclear factor κ B (NF-κB) pathway (17). A comparative role was shown in MKN45 gastric cancer cells, in which their proliferation and invasion were restrained by the up-regulation of micro-RNA-195 (*miR-195*) and the inactivation of Janus kinase/signal transducer of activation pathways (18). Propofol also reduced ES-2 ovarian cancer cell movement through the up-regulation of *miR-9* expression due to the activation of the NF-κB pathway (19). As regards pancreatic cancer, Du *et al.* found that by inactivating the NF-κB signaling pathway, propofol instigated the chemosensitization of MIAPaCa-2 pancreatic cells to gemcitabine (20). Other evidence showed that propofol suppressed the multiplication of cardia tumor cells by repressing the mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) signaling pathways (21). Furthermore, it was shown that propofol provoked death of cardia cancer cells by activating the MAPK signaling pathway and by inhibiting the protein kinase B (AKT) pathway (22). In particular, propofol suppressed the migration of A549 lung cancer cells by down-regulating the MMP2, MMP9, and p38 MAPK signaling pathways (23). Finally, propofol inhibited the invasion of LoVo human colorectal neoplastic cells through the down-regulation of MMPs, which in turn, is strictly regulated by ERK1/2 signaling (13). Moreover, it has been demonstrated that the hypoxia pathway, which plays a significant role in cancer progression and the epithelial-to-mesenchymal transition (EMT), is linked to the effects of propofol on cancer development. Specifically, experimental studies

conducted on pancreatic cancer cells (Miapaca-2 and Panc-1 cells) indicated that propofol impaired the migration of these cells by regulating the expression of the *N*-methyl-D-aspartate receptor (24). Moreover, *Gao et al*., showed that propofol, thought the involvement of the hypoxia pathway, reduced the expression of ADAM metallopeptidase domain containing metallopeptidase domain 8 in Panc-1 pancreatic cancer cells (25) and LNCaP prostate cancer cells (26). Finally, in prostate cancer cells, Quian *et al*. showed that propofol affected the EMT through the suppression of the hypoxia-inducible factor 1-alpha pathway (27).

SNAIL-related zinc-finger transcription factor SLUG (SNAIl2) signaling is another propofol-regulated pathway that may favor its anticancer role (28). Specifically, it was shown that propofol stopped the invasion of different ovarian cancer cell lines (29) and PANC-1 pancreatic cancer cells (30) by improving apoptosis through the suppression of SLUG expression.

Overall, these findings indicate that propofol may suppress the development of different cancer cells by influencing diverse signaling pathways (31-34). Despite what might be expected, it was additionally indicated that propofol may promote the proliferation of diverse cancer cells, particularly breast cancer cells, primarily through the modulation of the NF-E2-related factor 2 (NRF2) pathway (17). These discrepancies may be associated with the experimental conditions such as i) different concentrations of propofol adopted; ii) different types of cancer cells; ii) different schedules of treatment.

The dual role of propofol on breast cancer development: a controversial issue. Distinctive pre-clinical studies have suggested that propofol has opposing effects on breast cancer development by involving diverse genetic signaling pathways (Table I). Discrepancies among studies are not only due to different experimental conditions but also to the heterogeneity of breast cancer itself (35, 36). It is important to underline that although breast cancer is normally identified as a single disease, it includes up to 21 diverse histological subtypes which respond distinctly to treatments and lead to multiple and diverse outcomes. This issue needs to be considered in terms of data interpretation.

Tumor growth-inhibitory effects. Several preclinical studies highlighted that propofol suppressed the proliferation and migration of breast cancer cells (Table II). Specifically, it was demonstrated that propofol repressed the migratory activity of breast cancer cells by down-regulating MMP2 and MMP9 expression, through the alteration of the NF-kB signaling pathway (17). Subsequently, a study conducted on MDA-MB-231 cells treated with two engineered conjugates of propofol, namely propofol-eicosapentaenoic and propofol-docosahexaenoic, highlighted for the first time the features of propofol-induced anticancer activity (37). Similarly to the previous report, it was later demonstrated that propofol attenuated the migration of MDA-MB-231 and MCF-7 cells, by managing the neuroepithelial-transforming 1 gene-expression profile (10). Similarly, a group of researchers provided evidence that by regulating the expression of H19, propofol diminished the proliferation of MDA-MB-231cells (38). Yu *et al*. subsequently showed that propofol increased the apoptosis of MDA-MB-435 cells by acting directly on *miR-24*/p27 molecular signaling (39). Du *et al*. discovered a regulatory association between propofol and EMT of MCF-7 cells through the deregulation of *miR-21* which can interact with the phosphoinositide 3-kinase (PI3K)/AKT and WNT/β-catenin pathways (40). Moreover, Li *et al*. conducted an *in vivo* study in two mouse models of breast cancer and demonstrated that mice receiving sevoflurane during surgical excision of primary tumor develop more lung metastases than those receiving propofol (41). Interestingly, different studies were conducted using MDA-MB-231 cells treated with serum from surgical breast cancer patients receiving different propofol/paravertebral block anesthesia or sevoflurane/opioid general anesthesia to elucidate the roles of propofol on breast cancer development (42-44). The data showed that the combination of regional anesthesia with propofol was more effective in the attenuation of breast cancer cell proliferation than the use of a volatile-opioid anesthetic regimen, thus reducing the risk of metastasis formation. Unfortunately, the underlying signaling pathway has not been completely elucidated, thus suggesting the need for additional studies.

Tumor growth-promoting effects. In two different studies, Garib *et al*. demonstrated that propofol enhanced the migration of MDA-MB-468 cells by regulating the activation of γ-aminobutyric acid type A (32, 45). Another study reported that propofol also increased the proliferation of MDA-MB-231 cells by reducing the expression of p53 through the regulation of the NRF2 signaling pathway (36).

Clinical research on the role of propofol in the outcome of patients with breast cancer. Uniquely in contrast to preclinical examinations, few clinical studies have been conducted on propofol breast development according to Li *et al*. (46). Moreover, these data come mainly from retrospective analyses. For instance, Enlud *et al*. carried out a retrospective study on the survival rate of patients subjected to mastectomy for breast cancer who were administered propofol *versus* those who underwent volatile anesthesia. In this setting, propofol enhanced survival rates or reduced cancer recurrence. Nevertheless, after correcting for confounders, these differences were not statistically significant (6). Moreover, *Kim et al*. showed that the effects of total intravenous anesthesia (TIVA) were comparable with

Table II. *The effects of propofol on breast cancer progression.*

Breast cancer cell line	Cell line	Effect on breast cancer development, signaling pathways	Reference
MDA-MB-231	Propofol at 0, 2, 5 and 10 μg/ml for 24 h	Impairment of migration and invasiveness MMP2 ↓, MMP9 ↓, NF-κB ↓	17
MDA-MB-231	Propofol at 3 to 8 μg/ml 20 to 50 μM for 24 h Propofol-DHA or propofol-EPA at 25 μM for 24 h	Inhibition of cell migration and adhesion, and enhancement of apoptosis	37
MDA-MB-231, MCF-7	Propofol at 1-10 μg/ml; Bupivacaine at 0.5-100 μg/ml for 6-24 h.	Inhibition of migration NET1 ↓	10
MDA-MB-231	Propofol at 25, 50, and 100 μM for 24 h	Inhibition of migration and the invasion of breast cancer cell H19 ↓	38
MDA-MB-435	Propofol at 10 μM for 6 h	Enhancement of the apoptosis of breast cancer cells. Cleaved caspase-3 ↑, p27 ↑ , miR-24 ↓	39
MCF-7	Propofol at 0-10 μg/ml for 48 h	Inhibition of the proliferation, EMT and enhancement of apoptosis of breast cancer cells. miR-21 ↑, p53 ↑, WNT/β-catenin ↓, PI3K/AKT ↓	40
MDA-MB-468	Propofol at 3, 6, 9 mg/l, etomidate at 2, 3, 4 μg/ml, and lidocaine at 1.25, 2.5, 5 μg/ml up to 10 h	Enhancement of migratory activity of tumor cells	41
MDA-MB-468	Propofol at 6 μg/ml for 3 h	Enhancement of migration of tumor cells. Activation of GABA-A receptor. Reorganization of the actin cytoskeleton. $[Ca^{2+}]$ ↑	32
MDA-MB-231	Propofol at 2, 5 and 10 μg/ml for 1, 4 and 12 h	Increased proliferation, which was at least partially associated with inhibition of expression of p53. Induced cell migration, which was involved in activation of the NRF2 pathway	34

DHA: Docosahexaenoic acid; EMT: epithelial–mesenchymal transition; EPA: eicosapentaenoic acid; GABA-A: γ-aminobutyric acid type A; H19: imprinted maternally expressed transcript; miR: microRNA; MMP: metalloproteinase; NET1: neuroepithelial cell-transforming 1; NF-κB: nuclear factor kappa B; NRF2: nuclear factor erythroid 2-related factor 2; PI3K/AKT: phosphoinositide 3-kinase/protein kinase B. ↑ Up-regulated. ↓ Down-regulated.

those of volatile anesthesia in terms of cancer recurrence and overall survival (47). On the other hand, in another retrospective analysis, *Lee et al.* found that propofol-based TIVA reduced the risk of breast cancer recurrence 5 years after surgery (7). Wingmore *et al.* also found significantly better long-term survival rates for patients receiving propofol [3, 714 patients, 504 deaths (13.5%)] compared to patients receiving volatile anesthetics [3, 316 patients, 796 deaths (24%)] following cancer surgery (48). Recently, different results were obtained in a retrospective study in which propofol TIVA was compared with volatile anesthetics in patients subjected to breast cancer surgery. The authors showed that neither propofol nor desflurane affected patient prognosis and survival (49). Similar negative findings were described by *Sessler et al.* in a recent randomized controlled clinical trial. They demonstrated that regional anesthesia-analgesia (paravertebral block and propofol) did not lower breast cancer recurrence after surgery compared with opioids and volatile anesthesia (sevoflurane) (50).

Altogether, these contrasting results suggest a need for prospective studies to elucidate this controversial issue. The principal aim of such clinical studies is to find a convincing relationship between propofol and breast cancer outcomes. To date, four prospective studies which compared propofol with sevoflurane in patients with breast cancer are available (51-54). Altogether, these studies highlighted the effects of propofol on outcomes of patients subjected to breast cancer surgery. Importantly propofol has also been shown to reduce the development and severity of acute and chronic pain following surgery (55).

Using systems biology, the mechanism of propofol-induced effects on breast cancer cells should be explored through various 'omics' technologies, as reported by Wang *et al.* (56) On the other hand, cancer cell lines can only reflect part of the overall impact of propofol on cancer, as propofol may affect the progression of cancer in many other aspects.

Conclusion

In this narrative review, we dissected the effects of propofol on the development of breast tumors. Propofol may exert its pro- or antitumor activity on breast cancer by regulating different molecular mechanisms that have not been fully elucidated. Moreover, the high heterogeneity of breast cancer may obscure a consistent mechanism of action for propofol. Unexpectedly, in clinical settings, a few reports demonstrated that propofol may advance breast cancer development. Because available clinical data are scarce, these findings

require further confirmation. Thus, more pre-clinical and clinical investigations are necessary to translate the pre-clinical studies into clinical practice, potentially in order to develop new propofol-based therapies that will improve the outcomes of a patient subjected to breast oncological surgery.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

The present article was mainly written by SB, AC and MC. All Authors contributed toward data analysis, drafting and critically revised the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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