

Breast Cancer and Anaesthesia

Subjects: **Oncology**

Contributor: JOSE LUIS GUERRERO ORRIACH

Breast cancer is the leading cause of mortality in women. Even when the tumor is completely resected, tumor recurrence occurs in up to one third of patients, with metastatic disease being the direct cause of death. Surgery may generate systemic inflammatory response syndrome, which causes oxidative stress, and in turn impairs the anti-tumor immunologic response. Surgical stress activates a neuroendocrine response in the hypothalamic–pituitary–adrenal axis (HPA axis) and sympathetic nervous system (SNS), which results in the suppression of cell-mediated immunity (CMI); this suppression is induced by the release of neuroendocrine mediators such as catecholamines, cortisol, and cytokines. These mediators, including vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs) and interleukin (IL) 6 and 8, are endogenous regulators that promote tumor growth and angiogenesis, thereby favoring metastasis. Recent studies reveal that the type of anaesthesia administered during cancer surgery may influence the course of the disease.

anaesthetic drugs and techniques

opioids

propofol

volatile agent

breast cancer

cancer recurrence

1. Anaesthetics and Cancer Relapse

1.1. Hypnotics

Propofol

Propofol may have beneficial effects on survival in cancer patients, including breast cancer patients. This agent inhibits tumor cell migration and proliferation, promotes tumor apoptosis and has anti-inflammatory activity [1][2][3]. This agent acts on the immune system at the level of natural killer lymphocytes (NK), which belong to innate immunity. Cho et al. [4] conducted a prospective study comparing a group of patients who received propofol-ketorolac vs. sevoflurane-fentanyl. The authors observed a reduction in NK activity in the sevoflurane group, whereas this activity was increased in the propofol group. Although evidence consistently shows that propofol has tumor-killing activity, two recent studies associate it with pro-tumor activity in breast and bladder cancer, mediated by the activation of the Nrf2 pathway and the reduction in p53 levels [5][6].

Propofol favors tumor cell apoptosis by affecting matrix metalloproteinase (MMPs) expression, which play a crucial role in extracellular protein degradation and epithelial-mesenchymal transition (EMT), activate vascular endothelial growth factor (VEGF) [7], and inhibit intrinsic apoptosis pathways [8]. Two pathways have been identified to be

involved in the inhibition of the synthesis of these proteins: the MAP-kinase pathway (ERK1/2, JNK y p38) in colon cancer [9], and NF-κB in breast cancer [10].

As for the ability to induce tumor apoptosis, several pathways have been investigated, such as the inhibition of anti-apoptosis mechanisms, including Bcl-2, Sox4, Akt/mTOR and Wnt/β-catenin, and the increase in pathways involving tumor suppressor genes such as the Bax, ING3, Fox01 and caspase pathways [11][12][13][14][15][16]. In addition, Wang et al. [17] demonstrated that propofol induces the intrinsic apoptotic signaling pathway by the release of reactive oxygen species (ROS).

Propofol may inhibit surgery-induced systemic inflammatory response syndrome throughout decreasing cell concentrations of hypoxia-inducible factor 1 (HIF1A), which is elevated in the tumor's hypoxic micro-environment and promotes cell migration and invasion [18]. Ecimovic et al. [19] demonstrated in vitro the role of NET-1 (neuroepithelial cell transforming gene-1) overexpression, a gene that is associated with tumor dissemination and which decreases with propofol exposure [20].

1.2. Halogenated

It has been suggested that inhalation agents, for the most part, have a tumorigenic effect since they both inhibit tumor cell apoptosis and stimulate tumor cell proliferation and migration. More specifically, in advanced breast cancer, elevated caveolin-1 concentrations have been associated with lower survival. This protein has been linked to higher resistance to apoptosis, migration and elevated invasivity in breast cancer cells. Ecimovic et al. [21] analyzed, in vitro, the ability of sevoflurane to stimulate tumor cell proliferation, migration and invasion in patients with positive (ER+) and negative (ER-) estrogen receptor breast cancer (with the latter not having invasive capacity).

However, Kawaraguchi et al. [22] documented that isoflurane confers a protective effect on tumor cells in colon cancer against TNF-mediated apoptosis (TRAIL or TNF-related apoptosis-inducing ligand) by interacting with caveolin-1.

Sevoflurane reduces NK activity, thereby reducing immunosurveillance and favoring progression of micrometastases. In contrast, a range of studies have been conducted to compare immunosuppression induced by halogenated anaesthetics vs. general intravenous anaesthesia, with inconsistent results [23][24][25][26][27][28]. Enlund et al. [23] found no significant differences in 1-year and 5-year survival in a sample of 1837 breast cancer patients. Kim et al. [25] compared propofol with a variety of halogenated agents (sevoflurane, desflurane, isoflurane and enflurane), without significant differences. Recent retrospective studies [26][27][28] provide cumulative evidence of the absence of significant differences between intravenous and inhalation anaesthetics in terms of recurrence or survival.

2. Analgesics

2.1. Opioids

Opioids have an immunosuppressive effect that influences cellular and humoral immunity, as they reduce NK lymphocyte activity and proliferation, cytokine production, phagocytic activity, and antibody release [29]. The type and degree of immunosuppression depends on the type, dose and time of exposure to the opioid. All synthetic opioids reduce NK activity [30][31].

Morphine inhibits T and NK lymphocyte activity, promotes lymphocyte apoptosis, reduces toll-like 4 factor in macrophages [32] and has angiogenic activity [33]. In addition, the tumorigenic activity of morphine is mediated by two independent mechanisms, namely: by direct stimulation of mu receptors in tumor cells, the overexpression of which has been associated with poor prognosis, and indirectly by promoting neo-angiogenesis through metabolic signaling pathways similar to those used by VEGF factor [34][35].

In breast tumor cells, fentanyl exhibits an antitumoral effect by reducing levels of proteins involved in cell apoptosis and differentiation mechanisms (Bax, Bcl2, Oct4, Sox2, and Nanog) [36]. Although tramadol is a μ -receptor agonist, its analgesic effect is prevailingly mediated by the inhibition of noradrenaline and serotonin reuptake. Sacerdote et al. [37] assessed the relationship between tramadol and immune response in patients with uterine carcinoma. The authors found that tramadol not only inhibits but also stimulates NK lymphocyte activity. Thereupon, Xia et al. [38] demonstrated, *in vitro*, in breast tumor cells that tramadol reduces tumor cell proliferation, migration and invasion by up to 28 days through the inhibition of the α 2-adrenergic receptor. In a retrospective study, Kim et al. [39] observed lower rates of mortality and tumor recurrence in the group of breast cancer patients treated surgically who received tramadol. This effect is conferred by the inhibition of tumor cell proliferation, induction of apoptosis, and action on serotonergic receptors and transient receptor potential channel V1 or TRPV1.

2.2. Regional Anaesthesia and Local Anaesthetics

There is a variety of locoregional anaesthesia techniques in breast cancer surgery that have good analgesic outcomes. Paravertebral block (PVB) is the most widely used technique, although it is associated with a higher risk of severe complications. New techniques have been developed, with pectoral block type II having shown good effectiveness, and having been employed in a similar context as PVB [40]. Several studies have been published comparing general anaesthesia and combined anaesthesia: five retrospective studies, two prospective studies and a systematic review. These studies provide evidence of the beneficial effects of not using opioids and/or local anaesthetics per se [41][42][43][44][45][46][47][48].

Exadaktylos et al. [41] published the first retrospective study assessing the outcomes of 129 patients with breast cancer treated surgically, of whom 50 received combined anaesthesia (PVB+Propofol) and 79 balanced general anaesthesia. The rate of recurrence was lower in the group that received combined anaesthesia. In contrast, a recent systematic review conducted by Pérez-González et al. [48] did not show statistically significant differences between combined and general anaesthesia.

Local anaesthetics block afferent and efferent nerve response and effectively suppress sympathetic stimulation through the inhibition of hypothalamic–pituitary–adrenal (HPA) stimulation induced by surgical stress, thereby reducing HPA activity [48].

Lidocaine has been proven to exert beneficial effects in vivo and in vitro, and it is associated with a reduction in tumor cell proliferation, migration and invasion in breast, liver and lung cancer [49][50][51]. Lidocaine inhibits the proto-oncogen that releases Src, an intracellular non-tyrosine kinase protein that is involved in cell proliferation and migration processes through ICAM-1 phosphorylation, which enables neutrophils to cross the endothelium and increase immune response [51]. It has been reported to have effects on other signaling pathways such as TRPV-6 inhibition [52] or DNA demethylation in breast cancer cells [53]. Chang et al. [54] demonstrated in vitro that both lidocaine and bupivacaine induce breast cancer cell apoptosis through the activation of caspases 7, 8 and 9. In the same line, D'Agostino et al. showed that lidocaine inhibits cytoskeletal modification in breast cancer cells [55].

Evidence has been provided that lidocaine infiltration in the peritumoral region inhibits tumor growth by binding EGFR [56]. As for the immune system, lidocaine, at clinically relevant concentrations, stimulates the cytotoxic effect of NK lymphocytes [57]. A prospective, randomized trial conducted by Galoş et al. revealed that lidocaine reduced neutrophil extracellular traps, a phenomenon that has been associated with tumor recurrence [58].

2.3. NSAIDs

The enzyme cyclooxygenase (COX-2) causes an increase in prostaglandins, which are involved in immune system control and angiogenesis. Ketorolac is the most extensively studied NSAID in relation to cancer. It is a COX-1 and COX-2 inhibitor that is commonly used in the perioperative period. Evidence from retrospective studies demonstrates that perioperative administration of ketorolac reduces breast cancer recurrence by diminishing the production of prostaglandins and VEGF. Forget et al. attempted to replicate these results in patients with breast cancer at high risk of recurrence (triple negative, neutrophil/lymphocyte ratio ≥ 4) [59] in a prospective study [60] of 203 patients, without differences having been found between treatment groups.

3. Dexmedetomidine

Dexmedetomidine is a selective α_2 agonist with sympatholytic and anti-inflammatory activity that reduces IL-6, IL-8 and TNF- α concentrations and increases anti-inflammatory cytokine IL-10 levels [61].

Despite its anti-inflammatory effect, a pro-tumoral activity is attributed to dexmedetomidine. Lavan et al. [62] demonstrated in animal models that it promotes metastasis in breast, lung and colon cancer. This effect is credited to the transient immunosuppression induced by dexmedetomidine, added to the effects of surgical stress and changes in vascular patency.

In the same line, Xia et al. [63] investigated the effect of dexmedetomidine in breast cancer cells, in vitro and in vivo, in mice and concluded that dexmedetomidine promotes tumor cell proliferation, migration and invasion through the

inhibition of the α 2/ERK adrenergic receptor pathway [38].

Cata et al. [64] performed a retrospective study involving 1404 patients with non-small lung cancer (NSCLC) treated surgically to investigate a potential relationship between tumor recurrence and the use of dexmedetomidine. This relationship was not confirmed. Indeed, the results showed a significant relationship between dexmedetomidine and lower survival.

Beta-blockers and lipid lowering drugs are two of the main groups of drugs among patients undergoing a surgical procedure.

4. Beta-Blockers

Beta-adrenergic receptors are found both in tumor cells and the immune system [65], and seem to play a key role in carcinogenesis [66]. Beta-blockers have been proven to be involved in angiogenesis and cellular neoproliferation [67]. Exposure to beta-agonists inhibits lymphocyte NK activity [68][69] and induces an increase in T-regulator lymphocytes [70], leading to immunosuppression. Kang et al. documented that adrenergic stimulation activated the MAP-kinase cascade and, more specifically, the DUSP1 cascade, which causes resistance to chemotherapy and apoptosis [71]. Recently, Zhou et al. [72] observed that propranolol prevented T-regulator lymphocyte elevation. Another potential cellular signaling pathway is adrenergic activation of PI3K/AKT and HIF-1 α , which is also inhibited by propranolol [73].

Contradictory results were obtained in five retrospective [74][75][76][77][78] and two cohort studies [79][80] assessing recurrence in breast cancer patients after surgery due to the lack of a standard treatment administration protocol [81][82][83][84].

5. Lipid Lowering Drugs

The increased prevalence of cardiovascular disease in the recent years has resulted in an increase in the use of lipid lowering drugs, with statins being the most common pharmaceutical group. As a component of the cellular membrane, cholesterol plays an essential role in cellular division; therefore, a reduction in extracellular cholesterol should cause an inhibition of tumor cell proliferation. Cholesterol metabolites such as 27-hydroxycholesterol and 25-hydroxycholesterol may stimulate estrogen receptors (ERs) [85][86]. Alikhani et al. [87] reported an increase in breast tumor growth mediated by the PI3K/AKT pathway in hyperlipidemic mice.

Cholesterol favors a pro-inflammatory environment by the activation of macrophage toll-like receptors [88] and the inhibition of CCR7 expression in dendritic cells, which explains their antigenic effects [89]. On the other hand, cholesterol modulates lymphocyte T activity through the liver X receptor (LXR) [90].

As for the use of statins, inconsistent results were obtained in six retrospective [76][91][92][93][94][95] and five prospective studies [81][96][97][98][99] (four supporting its use and the remaining seven having not provided clinically

relevant results). In contrast, the three meta-analyses retrieved [99][100][101][102] provide consistent evidence that statins reduce breast cancer recurrence. However, these studies were conducted using non-standard methods, and prospective randomized studies are needed.

References

1. Li, R.; Liu, H.; Dilger, J.; Lin, J. Effect of Propofol on breast Cancer cell, the immune system, and patient outcome. *BMC Anesthesiol.* 2018, 18, 1–8.
2. Jiang, S.; Liu, Y.; Huang, L.; Zhang, F.; Kang, R. Effects of propofol on cancer development and chemotherapy: Potential mechanisms. *Eur. J. Pharmacol.* 2018, 831, 46–51.
3. Xu, Y.; Pan, S.; Jiang, W.; Xue, F.; Zhu, X. Effects of propofol on the development of cancer in humans. *Cell Prolif.* 2020, 53, e12867.
4. Cho, J.S.; Lee, M.H.; Kim, S.I.; Park, S.; Park, H.S.; Oh, E.; Lee, J.H.; Koo, B.-N. The effects of perioperative anesthesia and analgesia on immune function in patients undergoing breast cancer resection: A prospective randomized study. *Int. J. Med. Sci.* 2017, 14, 970–976.
5. Zhang, L.; Wang, N.; Zhou, S.; Ye, W.; Jing, G.; Zhang, M. Propofol induces proliferation and invasion of gallbladder cancer cells through activation of Nrf2. *J. Exp. Clin. Cancer Res.* 2012, 31, 66.
6. Chao, M.; Linlin, S.; Juan, W.; Li, D.; Liu, Y.; Cui, X. Propofol induces proliferation partially via downregulation of p53 protein and promotes migration via activation of the Nrf2 pathway in human breast cancer cell line MDA-MB-231. *Oncol. Rep.* 2017, 37, 841–848.
7. Gialeli, C.; Theocharis, A.D.; Karamanos, N.K. Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. *FEBS J.* 2010, 278, 16–27.
8. Mitsiades, N.; Yu, W.-H.; Poulaki, V.; Tsokos, M.; Stamenkovic, I. Matrix metalloproteinase-7-mediated cleavage of Fas ligand protects tumor cells from chemotherapeutic drug cytotoxicity. *Cancer Res.* 2001, 61, 577–581.
9. Miao, Y.; Zhang, Y.; Wan, H.; Chen, L.; Wang, F. GABA-receptor agonist, propofol inhibits invasion of colon carcinoma cells. *Biomed. Pharmacother.* 2010, 64, 583–588.
10. Li, Q.; Zhang, L.; Han, Y.; Jiang, Z.; Wang, Q. Propofol reduces MMPs expression by inhibiting NF- κ B activity in human MDA-MB-231 cells. *Biomed. Pharmacother.* 2012, 66, 52–56.
11. Zhang, Z.; Zang, M.; Wang, S.; Wang, C. Effects of propofol on human cholangiocarcinoma and the associated mechanisms. *Exp. Ther. Med.* 2018, 17, 472–478.
12. Kang, F.; Wang, S.; So, E.C.; Chang, M.; Wong, K.; Cheng, K.S.; Chen, Y.; Huang, B. Propofol may increase caspase and MAPK pathways, and suppress the Akt pathway to induce apoptosis

in MA-10 mouse Leydig tumor cells. *Oncol. Rep.* 2019, **41**, 3565–3574.

13. Chen, L.; Wan, Y.; Liu, Y.; Li, T. Propofol inhibits biological functions of leukaemia stem and differentiated cells through suppressing Wnt/β-catenin and Akt/ mTOR. *Clin. Exp. Pharmacol. Physiol.* 2020, **47**, 127–134.

14. Yang, C.; Gao, J.; Yan, N.; Wu, B.; Ren, Y.; Li, H.; Liang, J. Propofol inhibits the growth and survival of gastric cancer cells in vitro through the upregulation of ING3. *Oncol. Rep.* 2017, **37**, 587–593.

15. Gao, C.; Ren, C.; Liu, Z.; Zhang, L.; Tang, R.; Li, X. GAS5, a FoxO1-activated long noncoding RNA, promotes propofol-induced oral squamous cell carcinoma apoptosis by regulating the miR-1297-GSK3β axis. *Artif. Cells Nanomed. Biotechnol.* 2019, **47**, 3985–3993.

16. Du, Q.; Liu, J.; Zhang, X.; Zhang, X.; Zhu, H.; Wei, M.; Wang, S. Propofol inhibits proliferation, migration, and invasion but promotes apoptosis by regulation of Sox4 in endometrial cancer cells. *Braz. J. Med. Biol. Res.* 2018, **51**.

17. Wang, H.; Zhao, L.; Wu, J.; Hong, J.; Wang, S. Propofol induces ROS-mediated intrinsic apoptosis and migration in triple-negative breast cancer cells. *Oncol. Lett.* 2020, **20**, 810–816.

18. Tanaka, T.; Takabuchi, S.; Nishi, K.; Oda, S.; Wakamatsu, T.; Daijo, H.; Fukuda, K.; Hirota, K. The intravenous anesthetic propofol inhibits lipopolysaccharide-induced hypoxia-inducible factor 1 activation and suppresses the glucose metabolism in macrophages. *J. Anesth.* 2009, **24**, 54–60.

19. Ecimovic, P.; Murray, D.; Doran, P.; McDonald, J.; Lambert, D.; Buggy, D.J. Direct effect of morphine on breast cancer cell function in vitro: Role of the NET1 gene. *Br. J. Anaesth.* 2011, **107**, 916–923.

20. Ecimovic, P.; Murray, D.; Doran, P.; Buggy, D.J. Propofol and bupivacaine in breast cancer cell function in vitro—Role of the NET1 gene. *Anticancer. Res.* 2014, **34**, 1321–1331.

21. Ecimovic, P.; McHugh, B.; Murray, D.; Doran, P.; Buggy, D. Direct effect of sevoflurane on breast cancer cell function in vitro: BAPCPC1–1. *Eur. J. Anaesthesiol.* 2010, **27**, 1.

22. Kawaraguchi, Y.; Horikawa, Y.T.; Murphy, A.N.; Murray, F.; Miyanohara, A.; Ali, S.S.; Head, B.P.; Patel, P.M.; Roth, D.M. Patel, H.H. Volatile anesthetics protect cancer cells against tumor necrosis factor-related apoptosis- inducing ligand-induced apoptosis via caveolins. *Anesthesiology* 2011, **115**, 499–508.

23. Enlund, M.; Berglund, A.; Andreasson, K.; Cicek, C.; Enlund, A.; Bergkvist, L. The choice of anaesthetic—Sevoflurane or propofol—and outcome from cancer surgery: A retrospective analysis. *Upsala J. Med Sci.* 2014, **119**, 251–261.

24. Lee, J.H.; Kang, S.H.; Kim, Y.; Kim, H.-A.; Kim, B.S. Effects of propofol-based total intravenous anesthesia on recurrence and overall survival in patients after modified radical mastectomy: A

retrospective study. *Korean J. Anesthesiol.* 2016, **69**, 126–132.

25. Kim, M.; Kim, D.W.; Kim, J.H.; Lee, K.-Y.; Park, S.; Yoo, Y.C. Does the type of anesthesia really affect the recurrence-free survival after breast cancer surgery? *Oncotarget* 2017, **8**, 90477–90487.

26. Yoo, S.; Lee, H.-B.; Han, W.; Noh, D.-Y.; Park, S.-K.; Kim, W.H.; Kim, J.-T. Total intravenous anesthesia versus inhalation anesthesia for breast cancer surgery: A retrospective cohort study. *Anesthesiology* 2019, **130**, 31–40.

27. Huang, Y.-H.; Lee, M.-S.; Lou, Y.-S.; Lai, H.-C.; Yu, J.-C.; Lu, C.-H.; Wong, C.-S.; Wu, Z.-F. Propofol-based total intravenous anesthesia did not improve survival compared to desflurane anesthesia in breast cancer surgery. *PLoS ONE* 2019, **14**, e0224728.

28. Shiono, S.; Shibata, S.C.; Kabata, D.; Shintani, A.; Ikeda, T.; Fujino, Y. Comparison of 1-year recurrence-free survival between sevoflurane and propofol use for general anesthesia management in primary breast cancer surgery. *J. Anesth.* 2020, **34**, 694–701.

29. Snyder, G.L.; Greenberg, S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. *Br. J. Anaesth.* 2010, **105**, 106–115.

30. Gong, L.; Qin, Q.; Zhou, L.; Ouyang, W.; Li, Y.; Wu, Y.; Li, Y. Effects of fentanyl anesthesia and sufentanil anesthesia on regulatory T cells frequencies. *Int. J. Clin. Exp. Pathol.* 2014, **7**, 7708–7716.

31. Sacerdote, P.; Gaspani, L.; Rossoni, G.; Panerai, A.; Bianchi, M. Effect of the opioid remifentanil on cellular immune response in the rat. *Int. Immunopharmacol.* 2001, **1**, 713–719.

32. Franchi, S.; Moretti, S.; Castelli, M.; Lattuada, D.; Scavullo, C.; Panerai, A.E.; Sacerdote, P. Mu opioid receptor activation modulates Toll like receptor 4 in murine macrophages. *Brain Behav. Immun.* 2012, **26**, 480–488.

33. Cheng, S.; Guo, M.; Liu, Z.; Fu, Y.; Wu, H.; Wang, C.; Cao, M. Morphine Promotes the Angiogenesis of Postoperative Recurrent Tumors and Metastasis of Dormant Breast Cancer Cells. *Pharmacol.* 2019, **104**, 276–286.

34. Heaney, Á.; Buggy, D.J. Can anaesthetic and analgesic techniques affect cancer recurrence or metastasis? *Br. J. Anaesth.* 2012, **109**, i17–i28.

35. Gupta, K.; Kshirsagar, S.; Chang, L.; Schwartz, R.; Law, P.-Y.; Yee, D.; Hebbel, R.P. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. *Cancer Res.* 2002, **62**, 4491–4498.

36. Kocak, N.; Ozen, F.; Yildirim, I.H.; Duran, Y. Fentanyl Inhibits Tumorigenesis from Human Breast Stem Cells by Inducing Apoptosis. *Asian Pac. J. Cancer Prev.* 2017, **18**, 735–739.

37. Sacerdote, P.; Bianchi, M.; Gaspani, L.; Manfredi, B.; Maucione, A.; Terno, G.; Ammatuna, M.; Panerai, A.E. The Effects of Tramadol and Morphine on Immune Responses and Pain After Surgery in Cancer Patients. *Anesth. Analg.* 2000, 90, 1411–1414.

38. Xia, M.; Tong, J.H.; Zhou, Z.Q.; Duan, M.L.; Xu, J.G.; Zeng, H.J.; Wang, S.H. Tramadol inhibits proliferation, migration and invasion via α 2-adrenoceptor signaling in breast cancer cells. *Eur. Rev. Med. Pharmacol. Sci.* 2016, 20, 157–165.

39. Kim, M.H.; Oh, J.E.; Park, S.; Kim, J.H.; Lee, K.-Y.; Bai, S.J.; Song, H.; Hwang, H.J.; Kim, D.W.; Yoo, Y.C. Tramadol use is associated with enhanced postoperative outcomes in breast cancer patients: A retrospective clinical study with in vitro confirmation. *Br. J. Anaesth.* 2019, 123, 865–876.

40. Versyck, B.; van Geffen, G.-J.; Chin, K.-J. Analgesic efficacy of the Pecs II block: A systematic review and meta-analysis. *Anaesthesia* 2019, 74, 663–673.

41. Exadaktylos, A.K.; Buggy, D.J.; Moriarty, D.C.; Mascha, E.; Sessler, D.I. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology* 2006, 105, 660–664.

42. Starnes-Ott, K.; Goravanchi, F.; Meininger, J.C. Anesthetic Choices and Breast Cancer Recurrence: A Retrospective Pilot Study of Patient, Disease, and Treatment Factors. *Crit. Care Nurs. Q.* 2015, 38, 200–210.

43. Kairaluoma, P.; Mattson, J.; Heikkilä, P.; Pere, P.; Leidenius, M. Perioperative Paravertebral Regional Anaesthesia and Breast Cancer Recurrence. *Anticancer Res.* 2016, 36, 415–418.

44. Tsigonis, A.M.; Al-Hamadani, M.; Linebarger, J.H.; Vang, C.A.; Krause, F.J.; Johnson, J.M.; Marchese, E.; Marcou, K.A.; Hudak, J.M.; Landercasper, J. Are cure rates for breast cancer improved by local and regional anesthesia? *Reg. Anesth. Pain Med.* 2016, 41, 339–347.

45. Cata, J.P.; Mac Gregor, M.C.; Valero, V.; Black, W.; Black, D.M.; Goravanchi, F.; Ifeanyi, I.C.; Hernandez, M.; Rodriguez-Restrepo, A.; Gottumukkala, V. The Impact of Paravertebral Block Analgesia on Breast Cancer Survival After Surgery. *Reg. Anesth. Pain Med.* 2016, 41, 696–703.

46. Finn, D.M.; Ilfeld, B.M.; Unkart, J.; Madison, S.J.; Suresh, P.J.; Sandhu, N.P.S.; Kormylo, N.J.; Malhotra, N.; Loland, V.J.; Wallace, M.S.; et al. Post-mastectomy cancer recurrence with and without a continuous paravertebral block in the immediate postoperative period: A prospective multi-year follow-up pilot study of a randomized, triple-masked, placebo-controlled investigation. *J. Anesth.* 2017, 31, 374–379.

47. Sessler, D.; Pei, L.; Huang, Y.; Fleischmann, E.; Marhofer, P.; Kurz, A.; Mayers, D.B.; A Meyer-Treschan, T.; Grady, M.; Tan, E.Y.; et al. Recurrence of breast cancer after regional or general anaesthesia: A randomised controlled trial. *Lancet* 2019, 394, 1807–1815.

48. Pérez-González, O.; Cuéllar-Guzmán, L.F.; Soliz, J.; Cata, J.P. Impact of Regional Anesthesia on Recurrence, Metastasis, and Immune Response in Breast Cancer Surgery: A Systematic Review of the Literature. *Reg. Anesth. Pain Med.* 2017, 42, 751–756.

49. Kim, R. Anesthetic technique and cancer recurrence in oncologic surgery: Unraveling the puzzle. *Cancer Metastasis Rev.* 2017, 36, 159–177.

50. Freeman, J.; Crowley, P.D.; Foley, A.G.; Gallagher, H.C.; Iwasaki, M.; Ma, D.; Buggy, D.J. Effect of Perioperative Lidocaine, Propofol and Steroids on Pulmonary Metastasis in a Murine Model of Breast Cancer Surgery. *Cancers* 2019, 11, 613.

51. Wall, T.P.; Crowley, P.D.; Sherwin, A.; Foley, A.G.; Buggy, D.J. Effects of Lidocaine and Src Inhibition on Metastasis in a Murine Model of Breast Cancer Surgery. *Cancers* 2019, 11, 1414.

52. Jiang, Y.; Gou, H.; Zhu, J.; Tian, S.; Yu, L. Lidocaine inhibits the invasion and migration of TRPV6-expressing cancer cells by TRPV6 downregulation. *Oncol. Lett.* 2016, 12, 1164–1170.

53. Li, K.; Yang, J.; Han, X. Lidocaine Sensitizes the Cytotoxicity of Cisplatin in Breast Cancer Cells via Up-Regulation of RAR β 2 and RASSF1A Demethylation. *Int. J. Mol. Sci.* 2014, 15, 3519.

54. Chang, Y.-C.; Liu, C.-L.; Chen, M.-J.; Hsu, Y.-W.; Chen, S.-N.; Lin, C.-H.; Chen, C.-M.; Yang, F.-M.; Hu, M.-C. Local Anesthetics Induce Apoptosis in Human Breast Tumor Cells. *Anesth. Analg.* 2014, 118, 116–124.

55. D'Agostino, G.; Saporito, A.; Cecchinato, V.; Silvestri, Y.; Borgeat, A.; Anselmi, L.; Uguzzioni, M. Lidocaine inhibits cytoskeletal remodelling and human breast cancer cell migration. *Br. J. Anaesth.* 2018, 121, 962–968.

56. Mammoto, T.; Higashiyama, S.; Mukai, M.; Mammoto, A.; Ayaki, M.; Mashimo, T.; Hayashi, Y.; Kishi, Y.; Nakamura, H.; Akedo, H. Infiltration anesthetic lidocaine inhibits cancer cell invasion by modulating ectodomain shedding of heparin-binding epidermal growth factor-like growth factor (HB-EGF). *J. Cell. Physiol.* 2002, 192, 351–358.

57. Ramirez, M.F.; Tran, P.; Cata, J.P. The Effect of Clinically Therapeutic Plasma Concentrations of Lidocaine on Natural Killer Cell Cytotoxicity. *Reg. Anesth. Pain Med.* 2015, 40, 43–48.

58. Galoş, E.V.; Tat, T.-F.F.; Popa, R.; Efrimescu, C.-I.I.; Finnerty, D.; Buggy, D.J.; Ionescu, D.C.; Mihu, C.M. Neutrophil extracellular trapping and angiogenesis biomarkers after intravenous or inhalation anaesthesia with or without intravenous lidocaine for breast cancer surgery: A prospective, randomised trial. *Br. J. Anaesth.* 2020, 125, 712–721.

59. Forget, P.; Machiels, J.-P.; Coulie, P.G.; Berlière, M.; Poncelet, A.J.; Tombal, B.; Stainier, A.; Legrand, C.; Canon, J.-L.; Kremer, Y.; et al. Neutrophil:Lymphocyte Ratio and Intraoperative Use of Ketorolac or Diclofenac are Prognostic Factors in Different Cohorts of Patients Undergoing Breast, Lung, and Kidney Cancer Surgery. *Ann. Surg. Oncol.* 2013, 20, 650–660.

60. Forget, P.; Bouche, G.; Duhoux, F.P.; Coulie, P.G.; Decloedt, J.; Dekleermaker, A.; Guillaume, J.-E.; Ledent, M.; Machiels, J.-P.; Mustin, V.; et al. Intraoperative ketorolac in high-risk breast cancer patients. A prospective, randomized, placebo-controlled clinical trial. *PLoS ONE* 2019, **14**, e0225748.

61. Li, B.; Li, Y.; Tian, S.; Wang, H.; Wu, H.; Zhang, A.; Gao, C. Anti-inflammatory Effects of Perioperative Dexmedetomidine Administered as an Adjunct to General Anesthesia: A Meta-analysis. *Sci. Rep.* 2015, **5**, 12342.

62. Lavon, H.; Matzner, P.; Benbenishty, A.; Sorski, L.; Rossene, E.; Haldar, R.; Elbaz, E.; Cata, J.; Gottumukkala, V.; Ben-Eliyahu, S. Dexmedetomidine promotes metastasis in rodent models of breast, lung, and colon cancers. *Br. J. Anaesth.* 2018, **120**, 188–196.

63. Xia, M.; Ji, N.-N.; Duan, M.-L.; Tong, J.-H.; Xu, J.-G.; Zhang, Y.-M.; Wang, S.-H. Dexmedetomidine regulate the malignancy of breast cancer cells by activating α 2-adrenoceptor/ERK signaling pathway. *Eur. Rev. Med. Pharmacol. Sci.* 2016, **20**, 3500–3506.

64. Cata, J.P.; Singh, V.; Lee, B.M.; Villarreal, J.; Mehran, J.R.; Yu, J.; Gottumukkala, V.; Lavon, H.; Ben-Eliyahu, S. Intraoperative use of dexmedetomidine is associated with decreased overall survival after lung cancer surgery. *J. Anaesthesiol. Clin. Pharmacol.* 2017, **33**, 317–323.

65. Cole, S.W.; Sood, A.K. Molecular Pathways: Beta-Adrenergic Signaling in Cancer. *Clin. Cancer Res.* 2012, **18**, 1201–1206.

66. Phadke, S.; Clamon, G. Beta blockade as adjunctive breast cancer therapy: A review. *Crit. Rev. Oncol.* 2019, **138**, 173–177.

67. Coelho, M.; Soares-Silva, C.; Brandão, D.; Marino, F.; Cosentino, M.; Ribeiro, L. β -Adrenergic modulation of cancer cell proliferation: Available evidence and clinical perspectives. *J. Cancer Res. Clin. Oncol.* 2017, **143**, 275–291.

68. Shakhar, G.; Ben-Eliyahu, S. In vivo beta-adrenergic stimulation suppresses natural killer activity and compromises resistance to tumor metastasis in rats. *J. Immunol.* 1998, **160**, 3251–3258.

69. Chung, J.F.; Lee, S.J.; Sood, A.K. Immunological and pleiotropic effects of individual β - blockers and their relevance in cancer therapies. *Expert Opin. Investig. Drugs* 2016, **25**, 501–505.

70. Kohm, A.P.; Sanders, V.M. Norepinephrine and β 2-adrenergic receptor stimulation regulate CD4+ T and B lymphocyte function in vitro and in vivo. *Pharmacol. Rev.* 2001, **53**, 487–525.

71. Kang, Y.; Nagaraja, A.; Armaiz-Pena, G.N.; Dorniak, P.L.; Hu, W.; Rupaimoole, R.; Liu, T.; Gharpure, K.; Previs, R.A.; Hansen, J.M.; et al. Adrenergic Stimulation of DUSP1 Impairs Chemotherapy Response in Ovarian Cancer. *Clin. Cancer Res.* 2016, **22**, 1713–1724.

72. Zhou, L.; Li, Y.; Li, X.; Chen, G.; Liang, H.; Wu, Y.; Tong, J.; Ouyang, W. Propranolol attenuates surgical stress-induced elevation of the regulatory T cell response in patients undergoing radical

mastectomy. *J. Immunol.* 2016, **196**, 3460–3469.

73. Lin, Z.; Wang, L.; Huang, G.; Wang, W.; Lin, H. Propranolol inhibits the activity of PI3K, AKT, and HIF-1 α in infantile hemangiomas. *Pediatr. Surg. Int.* 2018, **34**, 1233–1238.

74. Ganz, P.A.; Habel, L.A.; Weltzien, E.K.; Caan, B.; Cole, S.W. Examining the influence of beta blockers and ACE inhibitors on the risk for breast cancer recurrence: Results from the LACE cohort. *Breast Cancer Res. Treat.* 2011, **129**, 549–556.

75. Melhem-Bertrandt, A.; Chavez-MacGregor, M.; Lei, X.; Brown, E.N.; Lee, R.T.; Meric-Bernstam, F.; Sood, A.K.; Conzen, S.D.; Hortobagyi, G.N.; Gonzalez-Angulo, A.-M. Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. *J. Clin. Oncol.* 2011, **29**, 2645–2652.

76. Botteri, E.; Munzone, E.; Rotmensz, N.; Cipolla, C.; De Giorgi, V.; Santillo, B.; Zanelotti, A.; Adamoli, L.; Colleoni, M.; Viale, G.; et al. Therapeutic effect of β -blockers in triple-negative breast cancer postmenopausal women. *Breast Cancer Res. Treat.* 2013, **140**, 567–575.

77. Sakellakis, M.; Kostaki, A.; Starakis, I.; Koutras, A. β -Blocker Use and Risk of Recurrence in Patients with Early Breast Cancer. *Chemotherapy* 2015, **60**, 288–289.

78. Chen, L.; Chubak, J.; Boudreau, D.M.; Barlow, W.E.; Weiss, N.S.; Li, C.I. Use of Antihypertensive Medications and Risk of Adverse Breast Cancer Outcomes in a SEER–Medicare Population. *Cancer Epidemiol. Biomark. Prev.* 2017, **26**, 1603–1610.

79. Powe, D.G.; Voss, M.J.; Zänker, K.S.; Habashy, H.O.; Green, A.R.; Ellis, I.; Entschladen, F. Beta-Blocker Drug Therapy Reduces Secondary Cancer Formation in Breast Cancer and Improves Cancer Specific Survival. *Oncotarget* 2010, **1**, 628–638.

80. Sørensen, G.V.; Ganz, P.A.; Cole, S.W.; Pedersen, L.A.; Sørensen, H.T.; Cronin-Fenton, D.P.; Garne, J.P.; Christiansen, P.M.; Lash, T.L.; Ahern, T. Use of β -Blockers, Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers, and Risk of Breast Cancer Recurrence: A Danish Nationwide Prospective Cohort Study. *J. Clin. Oncol.* 2013, **31**, 2265–2272.

81. Boudreau, D.M.; Yu, O.; Chubak, J.; Wirtz, H.S.; Bowles, E.J.A.; Fujii, M.; Buist, D.S.M. Comparative safety of cardiovascular medication use and breast cancer outcomes among women with early stage breast cancer. *Breast Cancer Res. Treat.* 2014, **144**, 405–416.

82. Li, C.; Li, T.; Tang, R.; Yuan, S.; Zhang, W. β -Blocker use is not associated with improved clinical outcomes in women with breast cancer: A meta-analysis. *Biosci. Rep.* 2020, **40**.

83. Childers, W.K.; Hollenbeak, C.S.; Cheriyath, P. β -blockers reduce breast cancer recurrence and breast cancer death: A meta-analysis. *Clin. Breast Cancer* 2015, **15**, 426–431.

84. Kim, H.Y.; Jung, Y.J.; Lee, S.H.; Jung, H.J. Pak, K. Is Beta-Blocker Use Beneficial in Breast Cancer? A Meta-Analysis. *Oncology* 2017, **92**, 264–268.

85. Baek, A.E.; Nelson, E.R. The Contribution of Cholesterol and Its Metabolites to the Pathophysiology of Breast Cancer. *Horm. Cancer* 2016, 7, 219–228.

86. DuSell, C.D.; Umetani, M.; Shaul, P.W.; Mangelsdorf, D.J.; McDonnell, D.P. 27-Hydroxycholesterol is an endogenous selective estrogen receptor modulator. *Mol. Endocrinol.* 2008, 22, 65–77.

87. Alikhani, N.; Ferguson, R.D.; Novosyadlyy, R.; Gallagher, E.J.; Scheinman, E.J.; Yakar, S.; LeRoith, D. Mammary tumor growth and pulmonary metastasis are enhanced in a hyperlipidemic mouse model. *Oncogene* 2012, 32, 961–967.

88. Strachan, D.C.; Ruffell, B.; Oei, Y.; Bissell, M.J.; Coussens, L.M.; Pryer, N.; Daniel, D. CSF1R inhibition delays cervical and mammary tumor growth in murine models by attenuating the turnover of tumor-associated macrophages and enhancing infiltration by CD8+T cells. *OncolImmunology* 2013, 2, e26968.

89. Villablanca, E.J.; Raccosta, L.; Zhou, D.; Fontana, R.; Maggioni, D.; Negro, A.; Sanvito, F.; Ponzoni, M.; Valentinis, B.; Bregn, M.; et al. Tumor- mediated liver X receptor- α activation inhibits CC chemokine receptor-7 expression on dendritic cells and dampens antitumor responses. *Nat. Med.* 2010, 16, 98–105.

90. Bensinger, S.J.; Bradley, M.N.; Joseph, S.B.; Zelcer, N.; Janssen, E.M.; Hausner, M.A.; Shih, R.; Parks, J.S.; Edwards, P.A.; Jamieson, B.D.; et al. LXR Signaling Couples Sterol Metabolism to Proliferation in the Acquired Immune Response. *Cell* 2008, 134, 97–111.

91. Brewer, T.M.; Masuda, H.; Liu, D.D.; Shen, Y.; Liu, P.; Iwamoto, T.; Kai, K.; Barnett, C.M.; Woodward, W.A.; Reuben, J.M.; et al. Statin use in primary inflammatory breast cancer: A cohort study. *Br. J. Cancer* 2013, 109, 318–324.

92. Chae, Y.K.; Valsecchi, M.E.; Kim, J.; Bianchi, A.L.; Khemasuwan, D.; Desai, A.; Tester, W. Reduced risk of breast cancer recurrence in patients using ACE inhibitors, ARBs, and/or statins. *Cancer Invest.* 2011, 29, 585–593.

93. Li, Y.R.; Ro, V.; Steel, L.; Carrigan, E.; Nguyen, J.; Williams, A.; So, A.; Tchou, J. Impact of long-term lipid-lowering therapy on clinical outcomes in breast cancer. *Breast Cancer Res. Treat.* 2019, 176, 669–677.

94. Sakellakis, M.; Akinosoglou, K.; Kostaki, A.; Spyropoulou, D.; Koutras, A. Statins and risk of breast cancer recurrence. *Breast Cancer Targets Ther.* 2016, 8, 199–205.

95. Shaitelman, S.F.; Stauder, M.C.; Allen, P.; Reddy, S.; Lakoski, S.; Atkinson, B.; Reddy, J.; Amaya, D.; Guerra, W.; Ueno, N.; et al. Impact of statin use on outcomes in triple negative breast cancer. *J. Cancer* 2017, 8, 2026–2032.

96. Ahern, T.P.; Pedersen, L.; Tarp, M.; Cronin-Fenton, D.P.; Garne, J.P.; Silliman, R.A.; Sørensen, H.T.; Lash, T.L. Statin prescriptions and breast cancer recurrence risk: A Danish nationwide

prospective cohort study. *JNCI J. Natl. Cancer Inst.* 2011, 103, 1461–1468.

97. Harborg, S.; Heide-Jørgensen, U.; Ahern, T.P.; Ewertz, M.; Cronin-Fenton, D.; Borgquist, S. Statin use and breast cancer recurrence in postmenopausal women treated with adjuvant aromatase inhibitors: A Danish population-based cohort study. *Breast Cancer Res. Treat.* 2020, 183, 153–160.

98. Kwan, M.L.; Habel, L.A.; Flick, E.D.; Quesenberry, C.P.; Caan, B. Post-diagnosis statin use and breast cancer recurrence in a prospective cohort study of early stage breast cancer survivors. *Breast Cancer Res. Treat.* 2007, 109, 573–579.

99. Tryggvadottir, H.; Huzell, L.; Gustbée, E.; Simonsson, M.; Markkula, A.; Jirström, K.; Rose, C.; Ingvar, C.; Borgquist, S.; Jernström, H. Interactions Between ABCB1 Genotype and Preoperative Statin Use Impact Clinical Outcomes Among Breast Cancer Patients. *Front. Oncol.* 2018, 8, 428.

100. Lv, H.; Shi, D.; Fei, M.; Chen, Y.; Xie, F.; Wang, Z.; Wang, Y.; Hu, P. Association Between Statin Use and Prognosis of Breast Cancer: A Meta-Analysis of Cohort Studies. *Front. Oncology* 2020, 10, 1461–1468.

101. Manthrvadi, S.; Shrestha, A.; Madhusudhana, S. Impact of statin use on cancer recurrence and mortality in breast cancer: A systematic review and meta-analysis [Internet]. *Int. J. Cancer* 2016, 139, 1281–1288.

102. Mansourian, M.; Haghjoo-Javanmard, S.; Eshraghi, A.; Vaseghi, G.; Hayatshahi, A.; Thomas, J. Statins use and risk of breast cancer recurrence and death: A systematic review and meta-analysis of observational studies. *J. Pharm. Pharm. Sci.* 2016, 19, 72–81.

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