Review

DOI: 10.5582/ddt.2023.01065

Impact of anesthesia on postoperative breast cancer prognosis: A narrative review

Yi Tang[1,2], Shanshan Guo[1,2], Yao Chen[1], Li Liu[1], Minqiang Liu[1], Renliang He[1], Qiang Wu[1,*]

[1] Department of Anesthesiology, Shenzhen Third People's Hospital, Shenzhen, Guangdong, China;
[2] Medical Department of Shenzhen University, Shenzhen, Guangdong, China.

SUMMARY The incidence of breast cancer has exhibited an annually increasing trend, and the disease has become the most common malignant tumour worldwide. Currently, the primary treatment for breast cancer is surgical resection. However, metastatic recurrence is the main cause of cancer-related death in this patient population. Various factors are associated with breast cancer prognosis, and anaesthesia-induced changes in the tumour microenvironment have attracted increasing attention. To date, however, it remains unclear whether anaesthetic drugs have a positive or negative impact on cancer outcomes after surgery. The present article reviews the effects of different anaesthetics on the postoperative prognosis of breast cancer surgery to guide the choice of anaesthetic technique(s) and agents for such patients.

Keywords breast cancer, metastatic recurrence, anesthesia, techniques, agents

1. Introduction

Breast cancer is one of the primary causes of cancer-related death among females (*1*). Although surgical resection of breast cancer is the first-line treatment, other therapies, such as chemotherapy and radiation therapy, continue to play important roles (*2*). Mortality associated with breast cancer is attributable to recurrence and distant organ metastasis, with five-year survival rates ranging from 69.5% to 93.8% (*3,4*). Perioperative interventions produce substantial biological perturbations associated with the risk for recurrence after cancer surgery. Whether tumours recur or metastasise depends on the balance between immune capacity of the host and the progression of residual disease. Studies have shown that surgical stress and intraoperative anaesthesia impair host immunity (*5*). Previous studies have suggested that general anaesthetics can affect cancer progression (*6,7*). Several preclinical models have demonstrated that inhaled anaesthetics inhibit natural killer (NK) cell- and T lymphocyte-mediated immunity, resulting in increased metastasis (*8*). The present article reviews the effect of anaesthetics used during breast cancer surgery on breast cancer recurrence and survival and discusses the current status and future prospects of anaesthesia in breast cancer.

2. Inhalation anaesthesia

Inhalational anaesthetics are inhaled into the lungs through the respiratory tract to induce general anaesthesia (GA). Inhalational halogenated hydrocarbon anaesthetics, including isoflurane and sevoflurane, are known to provide a degree of cytoprotection to organs, including the heart, brain, and kidneys, and to reduce both infarct size and functional impairment in models of ischaemia-reperfusion injury (*9,10*).

However, animal and *in vitro* studies have shown that the use of volatile anaesthesia in cancer surgery may be associated with poorer cancer outcomes. In anaesthesia-induced immunosuppression, inhalation anaesthetics, such as sevoflurane, suppress cell-mediated immunity and promote tumour cell proliferation and angiogenesis. Sevoflurane induces the apoptosis of T lymphocytes and upregulates the expression of hypoxia-inducible factor-1a (HIF-1a) *in vitro*, whereas other inhalation anaesthetics, including isoflurane and desflurane, upregulate HIF-1a expression *in vitro* and *in vivo* (*11,12*) (Figure 1). In an *in-vitro* model of breast cancer cell function, sevoflurane increased proliferation, migration, and invasion in estrogen receptor (ER)-positive MCF7 cells, and increased proliferation and migration, but not invasion, in ER-negative cells (*13*). Jaura *et al.* found that serum from patients administered sevoflurane anaesthesia and opioids for primary breast cancer surgery reduced apoptosis in ER-negative breast cancer cells to a greater extent than serum from those administered propofol paravertebral anaesthesia (*14*). Similarly, clinical studies have reported that survival after cancer surgery is worse in patients who receive

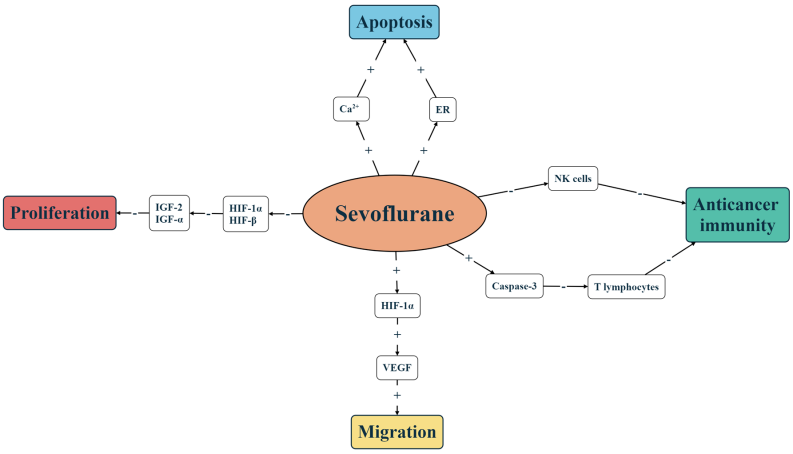

Figure 1. Mechanisms of sevoflurane on anticancer immunity, breast cancer cell proliferation, migration and apoptosis (*11-13*)**.** ER, endoplasmic reticulum; NK cells, natural killer cells; IGF, insulin-like growth factor; HIF, hypoxia inducible factor; VEGF, vascular endothelial growth factor.

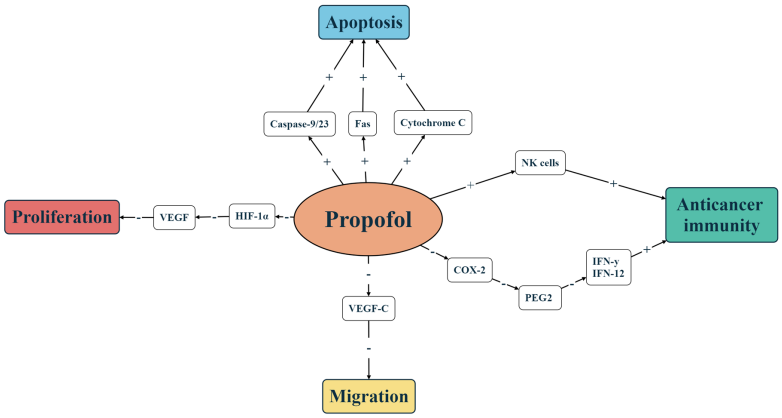

Figure 2 Mechanisms of propofol on anticancer immunity, breast cancer cell proliferation, migration and apoptosis (*23,24,26*)**.** Fas, a cell surface death receptor; NK cells, natural killer cells; VEGF, vascular endothelial growth factor; HIF, hypoxia inducible factor; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; IFN, interferon.

inhalation anaesthesia than in those who receive total intravenous anesthesia (TIVA) (*15*). Buckley also found that volatile inhalation anaesthesia and propofol had different effects on NK cell function in patients undergoing breast cancer surgery, with the former being shown to result in significant reductions (*16*). At the same time, relevant clinical studies have also confirmed that, in terms of survival rate after breast cancer surgery, the use of sevoflurane is not superior to propofol-based anaesthesia (*17,18*).

Paradoxically, inhalation anaesthesia does not always lead to worse prognosis in those with breast cancer. In a study investigating the effect of anaesthesia techniques on circulating tumour cell counts in breast cancer, the type of anaesthesia did not affect circulating tumour cell counts over time, although the administration of sevoflurane resulted in a significant increase in postoperative maximum tumour cell counts (*19*). Moreover, different inhalation anaesthetic gases are associated with varying prognoses after breast cancer surgery. Compared with sevoflurane, xenon reduces cell migration and secretion of proangiogenic factors in breast adenocarcinoma cells, thereby reducing the recurrence rate of tumour metastasis after breast cancer surgery (*20*). Relevant studies have also confirmed no significant difference in postoperative survival between different anaesthesia methods, whether inhalation or intravenous (*21,22*).

3. Intravenous anaesthesia

Anaesthetic drugs that are injected intravenously into the body and act on the central nervous system through the blood circulation to produce general anaesthetic effects are known as intravenous anaesthetics. Commonly used intravenous anaesthetics include thiopentone, ketamine, etomidate and propofol. A recent study confirmed the high priority of propofol in oncological surgery, and may also be a promising immunomodulatory drug for tumour therapy (*23*).

Studies have shown that propofol exerts antitumour effects through various mechanisms, including the inhibition of tumour viability, tumour progression, and cancer cell invasion (*24,25*) (Figure 2). For example, propofol-induced apoptosis has been observed in murine leukaemia RAW264.7 cells *in vitro* through altered levels of apoptosis-associated proteins, resulting in the induction of apoptotic gene expression and inhibition of cell growth (*26*). In *in vitro* models of breast cancer, 10% serum from patients receiving propofol anaesthesia reduced cancer cell proliferation, but not migration, compared with that from patients receiving sevoflurane anaesthesia (*27*). *In vitro* model breast cancer cells are highly aggressive and have a worse overall prognosis than ER-positive breast cancer. Therefore, the ability to attenuate proliferation or migration of this highly aggressive cell line by safely and easily altering the

manner in which anaesthesia is administered during primary cancer surgery has strong clinical implications (*27*). A retrospective analysis revealed that propofol may have a survival advantage over sevoflurane in patients with breast cancer (*28*). Propofol-based TIVA for breast cancer surgery may reduce the risk for recurrence within the first five years after modified radical mastectomy (*29*). Compared with sevoflurane inhalation anaesthesia, propofol TIVA can effectively inhibit the release of vascular endothelial growth factor-C (VEGF-C) induced by breast cancer surgery, thereby inhibiting tumour growth and metastasis (*30*).

However, in some studies, there was no significant difference in prognosis after breast cancer surgery between the two drugs. In patients undergoing primary breast cancer surgery, the use of either sevoflurane or propofol without regional anaesthesia did not appear to affect the risk for recurrence after one year (*31*). In a study investigating breast cancer surgery, Huang *et al*. (*32*) reported that propofol-based TIVA did not improve postoperative survival. This may be related to the fact that anaesthetics have little effect on perioperative immune activity during cancer surgery (*33*). The same situation occurred in a study by Kim *et al.*, in which five-year overall survival after breast cancer surgery was not associated with the choice of general anaesthetic (*34*). Results comparing the effect of anaesthetics (mainly propofol versus sevoflurane) on prognosis after breast cancer surgery are summarised in Table 1. These inconsistent results may be explained by the fact that multiple factors affecting cancer surgery prognosis must be considered.

4. Opioids

Opioids are commonly used in combination with inhalation anaesthetics as analgesics and sedatives for GA. However, non-synthetic and synthetic opioids can suppress cell-mediated immunity depending on the dose and duration of use (*35*). For example, morphine stimulates the growth of tumour cells *in vitro*, and synthetic opioids, such as fentanyl and remifentanil, inhibit cell-mediated immunity. Most opioids inhibit T lymphocyte proliferation (*36*).

In particular, data from animal and *in vitro* models suggest a role for opioids in the promotion of tumour cell survival and angiogenesis. In immune cells, stimulation of m-opioid receptors reduces the release of cytokines and decreases macrophage and lymphocyte proliferation (*37*). Opioids have been shown to drive breast cancer metastasis through δ-opioid receptors and oncogenic signal transducer and activator of transcription 3 (STAT3) (*38*). At clinically relevant doses, morphine has been associated with microvascular endothelial cell proliferation, angiogenesis, and vascularisation of human breast tumour xenografts in mouse models (*39*). *In vivo* studies investigating breast cancer xenograft models

Table 1. Studies comparing effects of propofol versus sevoflurane on prognosis of breast cancer

Research Type	Country	Cancer	Anesthetic Technique	Number of patients	Evaluations	Outcomes
Retrospective clinical studies	Korea, 2016 (*29*)	Breast cancer	Propofol *vs.* sevoflurane	363 (173 *vs.* 152)	Rate of cancer recurrence; overall survival rate.	Propofol was superior to sevoflurane; no difference.
Retrospective clinical studies	Sweden, 2014 (*17*)	Breast cancer	Propofol *vs.* sevoflurane	1,837 (620 *vs.*1217)	One-year and 5-year survival rate.	One-year survival rate: propofol was superior to sevoflurane; 5-year survival rate: no difference.
Retrospective clinical studies	UK, 2016 (*18*)	Mixed cancer	Total intravenous anesthesia (TIVA) *vs.* volatile inhalational anesthesia (INHA)	7,030 (3,714 *vs.* 3,316) (2,607 in each group after PS matching)	One-year survival rate and overall mortality rate.	TIVA was superior to INHA.
Retrospective clinical studies	Korea, 2015 (*22*)	Breast cancer	Propofol *vs.* sevoflurane	325 (173 *vs.* 152)	Five year-recurrence-free survival and overall survival.	Five year-recurrence-free survival: propofol was superior to sevoflurane; 5 year-overall survival: no difference.
Retrospective clinical studies	Sweden, 2020 (*28*)	Breast cancer	Propofol *vs.* sevoflurane	6,305 (3,096 *vs.* 3,209)	Five-year survival rate.	Propofol was superior to sevoflurane.
Retrospective clinical studies	Japan, 2020 (*31*)	Breast cancer	Propofol *vs.* sevoflurane	1,034 (814 *vs.* 220)	One-year survival rate.	No difference.
Retrospective clinical studies	Taiwan China, 2019 (*32*)	Breast cancer	Propofol *vs.* desflurane	976 (344 *vs.* 632)	Mortality rate; 5-year survival rate.	No difference.
Randomized controlled trials	Switzerland, 2020 (*19*)	Breast cancer *in vitro*	Propofol *vs.* sevoflurane	210 (103 *vs.*107)	Circulating tumor cell counts at three time points postoperatively (0, 48, and 72 h)	There was no difference between these two groups with respect to circulating tumor cell counts.
Randomized controlled trials	Ireland, 2009 (*27*)	Breast cancer *in vitro*	Propofol/paravertebral *vs.* sevoflurane/opioid	22 (11 *vs.* 11)	The proliferation/migration of MDA-MB-231 cells	Propofol/paravertebral anesthesia for breast cancer surgery inhibited proliferation, but not migration.
Randomized controlled trials	Ireland, 2014 (*20*)	Breast cancer *in vitro*	Sevoflurane *vs.* xenon	/	Cell viability; migration at 24h	Xenon was superior to sevoflurane.

Notes: PS, propensity scores

(using human MCF-7 and MDA-MB-231 cells) revealed that prolonged application of subcutaneous morphine sulfate at therapeutic doses accelerated breast tumour growth and increased tumour growth vascularisation (*40*).

However, the association between opioids and breast cancer progression remains controversial. Preclinical studies have suggested that high-dose morphine and other opioids have antiangiogenic and proapoptotic properties (*41*). An *in vitro* study reported that papaverine radio-sensitizes lung and breast cancer cells by targeting mitochondrial complex-1 (*42*). In a cohort study from Denmark, there was no association between opioids and breast cancer recurrence, regardless of opioid type, intensity, duration of use, or cumulative dose (*43*). Studies have confirmed that intraoperative opioids have a protective effect on recurrence-free survival in triple-negative breast cancer (*44*). Another study indicated that fentanyl plays an antitumour role by inducing apoptosis and reducing the number of cancer stem cells in human breast adenocarcinoma cells (*45*). In a study by Boudreau *et al.*, involving 4,216 females with a history of breast cancer, chronic opioid consumption, defined as opioid consumption over a 150-day period, did not increase the risk for new secondary breast cancers during a median follow-up of six years (*46*). Tramadol is an atypical opioid analgesic that has demonstrated antitumour effects in breast cancer cells both *in vitro* and *in vivo* (*47,48*). A retrospective analysis revealed that tramadol use was associated with reduced breast cancer recurrence and mortality rates in patients who underwent breast cancer surgery(*47*).

Therefore, further observational studies are warranted. Currently, there is no clear evidence suggesting that opioid use should be avoided in patients with breast cancer due to concerns about the risk for breast cancer recurrence (*49*).

5. GA adjuvants

Dexmedetomidine (DEX) is a selective a_2-adrenergic receptor agonist that exerts analgesic and antiemetic effects and can be used as an anaesthetic adjuvant in cancer surgery. As an adjuvant to anaesthetics, it reduces the use of analgesics, such as tramadol, morphine, and fentanyl, prolongs the time to first analgesic request, and relieves postoperative pain (*50*). Furthermore, DEX administration has been shown to enhance host protective immunity, including increases in NK and CD4-positive(+) cells and CD4/CD8 and T-helper cell (Th)1/Th2 ratios *via* suppression of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) stimulation of the surgical stress response during cancer surgery (*51*) To a certain extent, this is beneficial in cancer surgery to prevent tumour recurrence and metastasis. However, DEX has also been reported to exert tumour-promoting effects. *In vitro* studies have shown that it promotes the proliferation, migration, and invasion of breast cancer cells by activating the A2B adrenergic receptor/ERK signalling pathway (*52*). Similar results were obtained in an *in vitro* study (*53*).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are increasingly used to treat postoperative pain and are also commonly used in female breast surgery (*54*). In patients undergoing mastectomy, postoperative analgesia using flurbiprofen axetil combined with fentanyl was associated with decreases in serum concentrations of VEGF-C, tumour necrosis factor-alpha, and interleukin-1β compared with patients receiving fentanyl only (*55*). Relevant studies have shown that flurbiprofen can reduce the serum concentrations of these factors, most likely due to its ability to reduce the use of opioids (*56*). Opioids have been shown to exert some immunosuppressive effects. Recent evidence suggests that perioperative NSAIDs (flurbiprofen axetil and ketorolac) may be associated with decreased breast cancer recurrence by inhibiting proinflammatory and protumourigenic factors in patients undergoing surgery (*57*), consistent with a previous view by Forget *et al.* (*58*).

6. Other anaesthesia techniques

Regional anaesthesia has been consistently shown to attenuate the neuroendocrine response to surgery and, therefore, perioperative immunosuppression (*59,60*). It may also reduce the amount of GA required intraoperatively, provide excellent analgesia, and reduce opioid consumption. Compared with GA, regional (spinal) anaesthesia attenuates tumour metastasis in rats inoculated with a strain of breast adenocarcinoma (*61*). In breast cancer, VEGF-C, transforming growth factor-β, placental growth factor, and fibroblast growth factor (acidic and basic) promote angiogenesis and metastases (*62*). A propofol-paravertebral anaesthetic (PPA) technique would attenuate postoperative changes in these angiogenic factors to a greater extent than balanced GA and morphine analgesia in females undergoing surgery for primary breast cancer (*63*). These findings suggest that patients who received PPA anaesthesia had higher NK cell activity than those in the GA trial arm (*16*). Serum inoculated into the endoplasmic reticulum of the ER-negative MDA-MB-231 breast cancer cell line induced less apoptosis in the GA group than in the PPA group (*63*). However, in some cases, regional anaesthesia does not always have a positive effect. Regional anaesthesia analgesia (paravertebral block and propofol) did not reduce breast cancer recurrence after potentially curative surgery compared with volatile anaesthesia (sevoflurane) and opioids (*64*).

To some extent, local anaesthesia also controls breast cancer metastasis through the principle of local anaesthetics, such as lidocaine, which blocks voltage-gated sodium channels (*65-67*). This was also confirmed by *in vitro* experiments (*68*), which demonstrated the benefits of local anaesthesia in breast cancer surgery.

7. Conclusion

Current randomised controlled studies do not provide sufficient evidence to suggest that anaesthesia techniques are associated with recurrence rates or long-term outcomes in patients undergoing breast cancer surgery. Both preclinical and clinical studies have provided conflicting data regarding the effects of inhalation anaesthetics, propofol, and opioids on immune response and breast cancer growth. There is a strong correlation between patient underlying condition (*69,70*), cancer grade, risk for cancer recurrence, and postoperative death (*4*). Interestingly, in the clinical studies reviewed here, it was found that the same anaesthetic drug exhibited inconsistent associated prognosis in different types of cancer surgery. A simple comparison of sevoflurane and propofol in breast cancer surgery does not clearly indicate which of the two is superior. Furthermore, other GA adjuvant drugs also demonstrate bilateral effects, and only local anaesthesia can more clearly indicate its ability to improve prognosis in breast cancer surgery. However, due to the lack of multicentre or multi-country large clinical trials, it is not possible to draw definitive conclusions regarding which anaesthetic is more favourable for the long-term effect of breast cancer recurrence and metastasis. The above comparison results present certain challenges for anaesthesiologists in selecting appropriate anaesthetic drugs for breast cancer surgery. It is worth exploring whether the different effects of drugs on breast tumour subtypes should be considered while assessing the basic situation of patients and whether there are inconsistent signalling pathway mechanisms. As such, it cannot be ruled out that all perioperative factors comprehensively affect prognosis after breast cancer surgery.

Acknowledgements

We thank Shenzhen Science and Technology Innovation Commission for its support.

Funding: This work was supported by a grant from Shenzhen Science and Technology Innovation Commission, Basic Research (General Project), JCYJ20210324131410029.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023; 73:17-48.
2. Gralow JR, Burstein HJ, Wood W, Hortobagyi GN, Gianni L, von Minckwitz G, Buzdar AU, Smith IE, Symmans WF, Singh B, Winer EP. Preoperative therapy in invasive breast cancer: Pathologic assessment and systemic therapy issues in operable disease. J Clin Oncol. 2008; 26:814-819.
3. Chen CS, Liu TC, Lin HC, Lien YC. Does high surgeon and hospital surgical volume raise the five-year survival rate for breast cancer? A population-based study. Breast Cancer Res Treat. 2008; 110:349-356.
4. Yoo S, Lee HB, Han W, Noh DY, Park SK, Kim WH, Kim JT. Total intravenous anesthesia versus inhalation anesthesia for breast cancer surgery: A retrospective cohort study. Anesthesiology. 2019; 130:31-40.
5. Kim R. Anesthetic technique and cancer recurrence in oncologic surgery: Unraveling the puzzle. Cancer Metastasis Rev. 2017; 36:159-177.
6. Yuki K, Eckenhoff RG. Mechanisms of the immunological effects of volatile anesthetics: A review. Anesth Analg. 2016; 123:326-335.
7. Buggy DJ. Anesthesia, analgesia, and perioperative intervention in cancer surgery: The potential to influence outcome. Int Anesthesiol Clin. 2016; 54:1-3.
8. Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: Mediating mechanisms and prophylactic measures. Anesth Analg. 2003; 97:1331-1339.
9. Wu L, Zhao H, Wang T, Pac-Soo C, Ma D. Cellular signaling pathways and molecular mechanisms involving inhalational anesthetics-induced organoprotection. J Anesth. 2014; 28:740-758.
10. Pagel PS, Crystal GJ. The discovery of myocardial preconditioning using volatile anesthetics: A history and contemporary clinical perspective. J Cardiothorac Vasc Anesth. 2018; 32:1112-1134.
11. Tavare AN, Perry NJS, Benzonana LL, Takata M, Ma D. Cancer recurrence after surgery: Direct and indirect effects of anesthetic agents. Int J Cancer. 2012; 130:1237-1250.
12. Loop T, Dovi-Akue D, Frick M, Roesslein M, Egger L, Humar M, Hoetzel A, Schmidt R, Borner C, Pahl HL, Geiger KK, Pannen BHJ. Volatile anesthetics induce caspase-dependent, mitochondria-mediated apoptosis in human T lymphocytes *in vitro*. Anesthesiology. 2005; 102:1147-1157.
13. Ecimovic P, McHugh B, Murray D, Doran P, Buggy DJ. Effects of sevoflurane on breast cancer cell function *in vitro*. Anticancer Res. 2013; 33:4255-4260.
14. Jaura AI, Flood G, Gallagher HC, Buggy DJ. Differential effects of serum from patients administered distinct anaesthetic techniques on apoptosis in breast cancer cells *in vitro*: A pilot study. Br J Anaesth. 2014; 113 Suppl 1:i63-67.
15. Lee JH, Kang SH, Kim Y, Kim HA, Kim BS. 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.
16. Buckley A, McQuaid S, Johnson P, Buggy DJ. Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: A pilot study. Br J Anaesth. 2014; 113 Suppl 1:i56-62.
17. 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. Ups J Med Sci. 2014; 119:251-261.
18. Wigmore TJ, Mohammed K, Jhanji S. Long-term survival for patients undergoing volatile versus IV anesthesia for

cancer surgery: A retrospective analysis. Anesthesiology. 2016; 124:69-79.
19. Hovaguimian F, Braun J, Z'graggen BR, Schläpfer M, Dumrese C, Ewald C, Dedes KJ, Fink D, Rölli U, Seeberger M, Tausch C, Papassotiropoulos B, Puhan MA, Beck-Schimmer B. Anesthesia and circulating tumor cells in primary breast cancer patients: A randomized controlled trial. Anesthesiology. 2020; 133:548-558.
20. Ash SA, Valchev GI, Looney M, Ni Mhathuna A, Crowley PD, Gallagher HC, Buggy DJ. Xenon decreases cell migration and secretion of a pro-angiogenesis factor in breast adenocarcinoma cells: Comparison with sevoflurane. Br J Anaesth. 2014; 113 Suppl 1:i14-21.
21. Kim MH, Kim DW, Kim JH, Lee KY, Park S, Yoo YC. Does the type of anesthesia really affect the recurrence-free survival after breast cancer surgery? Oncotarget. 2017; 8:90477-90487.
22. Hong B, Lee S, Kim Y, Lee M, Youn AM, Rhim H, Hong SH, Kim YH, Yoon SH, Lim C. Anesthetics and long-term survival after cancer surgery-total intravenous versus volatile anesthesia: A retrospective study. BMC Anesthesiol. 2019; 19:233.
23. Gu L, Pan X, Wang C, Wang L. The benefits of propofol on cancer treatment: Decipher its modulation code to immunocytes. Front Pharmacol. 2022; 13:919636.
24. Kim R. Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. J Transl Med. 2018; 16:8.
25. Crone V, Hasselager RP, Fransgaard T, Gögenur I. Anaesthetic technique and outcomes after colorectal cancer surgery. Dan Med J. 2020; 67:A04190255.
26. Wu RSC, Liu KC, Tang NY, Chung HK, Ip SW, Yang JS, Chung JG. cDNA microarray analysis of the gene expression of murine leukemia RAW 264.7 cells after exposure to propofol. Environ Toxicol. 2013; 28:471-478.
27. Deegan CA, Murray D, Doran P, Ecimovic P, Moriarty DC, Buggy DJ. Effect of anaesthetic technique on oestrogen receptor-negative breast cancer cell function *in vitro*. Br J Anaesth. 2009; 103:685-690.
28. Enlund M, Berglund A, Ahlstrand R, Walldén J, Lundberg J, Wärnberg F, Ekman A, Sjöblom Widfeldt N, Enlund A, Bergkvist L. Survival after primary breast cancer surgery following propofol or sevoflurane general anesthesia-A retrospective, multicenter, database analysis of 6305 Swedish patients. Acta Anaesthesiol Scand. 2020; 64:1048-1054.
29. Lee JH, Kang SH, Kim Y, Kim HA, Kim BS. 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.
30. Yan T, Zhang GH, Wang BN, Sun L, Zheng H. Effects of propofol/remifentanil-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF-β and prognosis after breast cancer surgery: A prospective, randomized and controlled study. BMC Anesthesiol. 2018; 18:131.
31. Shiono S, Shibata SC, 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.
32. Huang YH, Lee MS, Lou YS, Lai HC, Yu JC, Lu CH, Wong CS, Wu ZF. Propofol-based total intravenous anesthesia did not improve survival compared to desflurane anesthesia in breast cancer surgery. PloS One. 2019; 14:e0224728.
33. Oh CS, Lee J, Yoon TG, Seo EH, Park HJ, Piao L, Lee SH, Kim SH. Effect of equipotent doses of propofol versus sevoflurane anesthesia on regulatory T cells after breast cancer surgery. Anesthesiology. 2018; 129:921-931.
34. Kim R, Kawai A, Wakisaka M, Kin T. Current status and prospects of anesthesia and breast cancer: Does anesthetic technique affect recurrence and survival rates in breast cancer surgery? Front Oncol. 2022; 12:795864.
35. Yardeni IZ, Beilin B, Mayburd E, Alcalay Y, Bessler H. Relationship between fentanyl dosage and immune function in the postoperative period. J Opioid Manag. 2008; 4:27-33.
36. Sacerdote P, Bianchi M, Gaspani L, Manfredi B, Maucione A, Terno G, Ammatuna M, Panerai AE. The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. Anesth Analg. 2000; 90:1411-1414.
37. Wang J, Barke RA, Ma J, Charboneau R, Roy S. Opiate abuse, innate immunity, and bacterial infectious diseases. Arch Immunol Ther Exp (Warsz). 2008; 56:299-309.
38. Tripolt S, Neubauer HA, Knab VM, Elmer DP, Aberger F, Moriggl R, Fux DA. Opioids drive breast cancer metastasis through the δ-opioid receptor and oncogenic STAT3. Neoplasia. 2021; 23:270-279.
39. Gupta K, Kshirsagar S, Chang L, Schwartz R, Law PY, Yee D, Hebbel RP. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. Cancer Res. 2002; 62:4491-4498.
40. Bimonte S, Barbieri A, Rea D, Palma G, Luciano A, Cuomo A, Arra C, Izzo F. Morphine promotes tumor angiogenesis and increases breast cancer progression. Biomed Res Int. 2015; 2015:161508.
41. Weingaertner IR, Koutnik S, Ammer H. Chronic morphine treatment attenuates cell growth of human BT474 breast cancer cells by rearrangement of the ErbB signalling network. PloS One. 2013; 8:e53510.
42. Benej M, Hong X, Vibhute S, Scott S, Wu J, Graves E, Le QT, Koong AC, Giaccia AJ, Yu B, Chen CS, Papandreou I, Denko NC. Papaverine and its derivatives radiosensitize solid tumors by inhibiting mitochondrial metabolism. Proc Natl Acad Sci U S A. 2018; 115:10756-10761.
43. Cronin-Fenton DP, Heide-Jørgensen U, Ahern TP, Lash TL, Christiansen PM, Ejlertsen B, Sjøgren P, Kehlet H, Sørensen HT. Opioids and breast cancer recurrence: A Danish population-based cohort study. Cancer. 2015; 121:3507-3514.
44. Montagna G, Gupta HV, Hannum M, Tan KS, Lee J, Scarpa JR, Plitas G, Irie T, McCormick PJ, Fischer GW, Morrow M, Mincer JS. Intraoperative opioids are associated with improved recurrence-free survival in triple-negative breast cancer. Br J Anaesth. 2021; 126:367-376.
45. Kocak N, Ozen F, Yildirim IH, Duran Y. Fentanyl inhibits tumorigenesis from human breast stem cells by inducing apoptosis. Asian Pac J Cancer Prev. 2017; 18:735-739.
46. Boudreau DM, Chen L, Yu O, Bowles EJA, Chubak J. Risk of second breast cancer events with chronic opioid use in breast cancer survivors. Pharmacoepidemiol Drug Saf. 2019; 28:740-753.
47. Kim MH, Oh JE, Park S, Kim JH, Lee KY, Bai SJ, Song H, Hwang HJ, Kim DW, Yoo YC. 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.
48. Kim MH, Lee JR, Kim KJ, Jun JH, Hwang HJ, Lee W, Nam SH, Oh JE, Yoo YC. Identification for antitumor effects of tramadol in a xenograft mouse model using orthotopic breast cancer cells. Sci Rep. 2021; 11:22113.
49. Cronin-Fenton D. Opioids and breast cancer recurrence. Curr Opin Support Palliat Care. 2019; 13:88-93.
50. Liu C, Wang W, Shan Z, Zhang H, Yan Q. Dexmedetomidine as an adjuvant for patients undergoing breast cancer surgery: A meta-analysis. Medicine. 2020; 99:e23667.
51. Wang K, Wu M, Xu J, Wu C, Zhang B, Wang G, Ma D. Effects of dexmedetomidine on perioperative stress, inflammation, and immune function: systematic review and meta-analysis. Br J Anaesth. 2019; 123:777-794.
52. Xia M, Ji NN, Duan ML, Tong JH, Xu JG, Zhang YM, Wang SH. Dexmedetomidine regulate the malignancy of breast cancer cells by activating α2-adrenoceptor/ERK signaling pathway. Eur Rev Med Pharmacol Sci. 2016; 20:3500-3506.
53. Lavon H, Matzner P, Benbenishty A, Sorski L, Rossene E, Haldar R, Elbaz E, Cata JP, Gottumukkala V, Ben-Eliyahu S. Dexmedetomidine promotes metastasis in rodent models of breast, lung, and colon cancers. Br J Anaesth. 2018; 120:188-196.
54. Klifto KM, Elhelali A, Payne RM, Cooney CM, Manahan MA, Rosson GD. Perioperative systemic nonsteroidal anti-inflammatory drugs (NSAIDs) in women undergoing breast surgery. Cochrane Database Syst Rev. 2021; 11:CD013290.
55. Wen Y, Wang M, Yang J, Wang Y, Sun H, Zhao J, Liu W, Zhou Z, Deng H, Castillo-Pedraza C, Zhang Y, Candiotti KA. A comparison of fentanyl and flurbiprofen axetil on serum VEGF-C, TNF-α, and IL-1ß concentrations in women undergoing surgery for breast cancer. Pain Pract. 2015; 15:530-537.
56. Doleman B, Leonardi-Bee J, Heinink TP, Boyd-Carson H, Carrick L, Mandalia R, Lund JN, Williams JP. Pre-emptive and preventive NSAIDs for postoperative pain in adults undergoing all types of surgery. Cochrane Database Syst Rev. 2021; 6:CD012978.
57. Desmedt C, Demicheli R, Fornili M, Bachir I, Duca M, Viglietti G, Berlière M, Piccart M, Sotiriou C, Sosnowski M, Forget P, Biganzoli E. Potential benefit of intra-operative administration of ketorolac on breast cancer recurrence according to the patient's body mass index. J Natl Cancer Inst. 2018; 110:1115-1122.
58. Forget P, Bentin C, Machiels JP, Berliere M, Coulie PG, De Kock M. Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery. Br J Anaesth. 2014; 113 Suppl 1:i82-87.
59. Buggy DJ, Smith G. Epidural anaesthesia and analgesia: Better outcome after major surgery?. Growing evidence suggests so. BMJ. 1999; 319:530-531.
60. Tsuchiya Y, Sawada S, Yoshioka I, Ohashi Y, Matsuo M, Harimaya Y, Tsukada K, Saiki I. Increased surgical stress promotes tumor metastasis. Surgery. 2003; 133:547-555.
61. Bar-Yosef S, Melamed R, Page GG, Shakhar G, Shakhar K, Ben-Eliyahu S. Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. Anesthesiology. 2001; 94:1066-1073.
62. Gisterek I, Matkowski R, Lacko A, Sedlaczek P, Szewczyk K, Biecek P, Halon A, Staszek U, Szelachowska J, Pudelko M, Bebenek M, Harlozinska-Szmyrka A, Kornafel J. Serum vascular endothelial growth factors a, C and d in human breast tumors. Pathol Oncol Res. 2010; 16:337-344.
63. Looney M, Doran P, Buggy DJ. Effect of anesthetic technique on serum vascular endothelial growth factor C and transforming growth factor β in women undergoing anesthesia and surgery for breast cancer. Anesthesiology. 2010; 113:1118-1125.
64. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, Mayers DB, Meyer-Treschan TA, Grady M, Tan EY, Ayad S, Mascha EJ, Buggy DJ, Collaboration BCR. Recurrence of breast cancer after regional or general anaesthesia: A randomised controlled trial. Lancet. 2019; 394:1807-1815.
65. Baptista-Hon DT, Robertson FM, Robertson GB, Owen SJ, Rogers GW, Lydon EL, Lee NH, Hales TG. Potent inhibition by ropivacaine of metastatic colon cancer SW620 cell invasion and NaV1.5 channel function. Br J Anaesth. 2014; 113 Suppl 1:i39-i48.
66. Fraser SP, Diss JKJ, Chioni A-M, *et al.* Voltage-gated sodium channel expression and potentiation of human breast cancer metastasis. Clin Cancer Res. 2005; 11:5381-5389.
67. Lucchinetti E, Awad AE, Rahman M, Feng J, Lou PH, Zhang L, Ionescu L, Lemieux H, Thébaud B, Zaugg M. Antiproliferative effects of local anesthetics on mesenchymal stem cells: potential implications for tumor spreading and wound healing. Anesthesiology. 2012; 116:841-856.
68. Chang YC, Liu CL, Chen MJ, Hsu YW, Chen SN, Lin CH, Chen CM, Yang FM, Hu MC. Local anesthetics induce apoptosis in human breast tumor cells. Anesth Analg. 2014; 118:116-124.
69. Arendt LM, McCready J, Keller PJ, Baker DD, Naber SP, Seewaldt V, Kuperwasser C. Obesity promotes breast cancer by CCL2-mediated macrophage recruitment and angiogenesis. Cancer Res. 2013; 73:6080-6093.
70. Kolb R, Phan L, Borcherding N, *et al.* Obesity-associated NLRC4 inflammasome activation drives breast cancer progression. Nat Commun. 2016; 7:13007.

Received August 22, 2023; Revised October 20, 2023; Accepted October 21, 2023.

*Address correspondence to:
Qiang Wu, Department of Anesthesiology, Shenzhen Third People's Hospital, No. 29 Bujibulan Road, Longgang District, Shenzhen 518112, China.
E-mail: wuqiang@mail.sustech.edu.cn

Released online in J-STAGE as advance publication October 31, 2023.