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REVIEW ARTICLE

Surgery for triple-negative breast cancer: does the type of anaesthesia have an influence on oxidative stress, inflammation, molecular regulators, and outcomes of disease?

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Summary

Breast cancer is the most frequently diagnosed cancer in females. Triple negative breast cancer (TNBC) is a molecular subtype of breast cancer which has a high mortality rate because of aggressive proliferation, quick occurrence of metastasis, and lack of effective treatment. New data show evidence that the type of anaesthesia can affect breast cancer recurrence and long-term outcome. Because TNBC lacks targets for modern specific therapy, a perioperative period could be the field of investigations for the long-term outcomes in TNBC influence.

We reviewed the literature on research focusing on the influence of anaesthetics to oxidative stress, inflammation, molecular regulators, and TNBC oncological outcomes.

Key words: *inflammation, oxidative stress, propofol, sevoflurane, triple negative breast cancer*

Introduction

Breast cancer is the most frequently diagnosed cancer in females, accounting for 12% of the total new cancer cases and 25% of all cancers in women in 2012 [1]. TNBC and basal-like tumours account for approximately 15% of all invasive breast cancers [2,3]. In general, breast cancer incidence rates are high in developed countries (Western and Northern Europe, North America, Australia and New Zealand) and lower in less developed countries. These variations in incidence could be explained largely by differences in reproductive and hormonal factors and the availability of early detection services [4,5].

TNBC occurs more often in young, premenopausal women. Women with TNBC are more likely to be diagnosed with advanced disease stage, including visceral and nodal metastases. More than 50% of TNBCs do not respond to chemotherapy, and patients who do not obtain a complete pathologic response have a higher likelihood of disease relapse, frequent distant recurrences, and a poorer prognosis than patients with non-TNBC subtypes. Because TNBC lacks targets for modern specific therapy and has a poor prognosis (5-year survival 74.5%) among all breast cancer patients (5-year survival greater than 95%), surgery and periop-

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erative factors, such as anaesthesia, may be very important [6]. In recent years, new evidence has emerged showing that anaesthesia may affect the long-term outcome after cancer surgery. Some general anaesthetics (ketamine, thiopental and halothane) suppress the natural killer (NK) cells and increase metastases. Inhaled anaesthetics upregulate the hypoxia-inducible factor (HIF), which can facilitate the spread of cancer and contribute to cancer recurrence. Propofol is better than inhaled anaesthesia in terms of immunity; it also induces apoptosis of breast cancer cells [7]. General anaesthesia combined with regional anaesthesia/analgesia improves the immune outcome and reduces the metastatic burden in animals, risk of metastases in breast cancer, vascular endothelial growth factor (VEGF), and the transforming growth factor (TGF)-β expression [7].

The goal of this review was to present data showing how the type of anaesthesia acts as a master switch in establishing an intricate link between oxidative stress, inflammation, molecular regulators, and cancer, and how the type of anaesthesia impacts long-term outcomes after surgery for TNBC.

Oxidative stress, inflammation and molecular regulators

Several important factors influence the development, growth and metastatic spread of malignant tumours. Oxidative stress and inflammation are among the most important factors.

Carcinoma cell oxidative stress can be induced by overproduction of reactive oxygen species (ROS) because of downregulation of NADPH-oxidase [8]. It also can be induced by overexpression of thymidine phosphorylase that is seen in the majority of breast carcinomas [9]. A breast tumour rapidly outgrows its blood supply, leading to glucose deprivation and hypoxia. Glucose deprivation rapidly induces cellular oxidative stress within the MCF-7 breast carcinoma cell line, although it does not cause oxidative stress in non-transformed cell lines [10,11]. This may be because glucose deprivation depletes intracellular pyruvate within the breast carcinoma cell, preventing the decomposition of endogenous oxygen radicals [10]. Because oxygen radicals are powerful DNA damaging agents, they may cause strand breaks, alterations in guanine thymine bases, and sister chromatide exchange [12]. Genetic instability due to persistent carcinoma cell oxidative stress therefore increases the malignant potential of the tumour [13]. Oxidative stress can activate a number of transcription factors including NK-B, AP-1, p53 and HIF-1α. There is significant evidence implicating the involvement of p53 mutations as a genetic driver in tumorigenesis and tumour progression of TNBC [14].

A number of biologically active molecules upregulate or downregulate these processes. One of the important cytokines, interleukin-10 (IL-10), is a pleiotropic anti-inflammatory cytokine that can exert a dual proliferative and inhibitory effect on breast cancer [15]. IL-10 inhibits interferon gamma (IFN-γ) and tumour necrosis factor alpha (TNF-α) production by NK cells *in vitro* [16] and promotes NK cell cytotoxicity in preclinical models [17].

VEGF, one of the main angiogenesis regulation factors, is necessary for tumour growth and metastasis [18]. In patients with breast cancer, VEGF has been reported to be associated with poor prognosis in primary breast cancer [19]. VEGF serum and plasma levels have been found to be elevated in patients with larger tumours and with metastatic disease [20,21]. TNBCs are considered highly proliferative tumours and have high levels of micro vessel density and VEGF [22].

Oxidative stress and inflammation are interrelated processes. Oxidative stress and inflammation and/or their molecular regulators may influence both immediate and distant outcomes of breast surgery including tumour relapse and metastases. Surgical trauma can generate a ROS rich tumour microenvironment which leads cellular processes to tumour growth and metastasis. Oxidative stress activates inflammatory pathways leading to transformation of a normal cell to a tumour cell, and its survival, proliferation, chemoresistance, radioresistance, invasion, angiogenesis and stem cell survival [23]. It appears that the perioperative window is an under-utilised time interval in the treatment strategy of TNBC.

Possible influences of surgery and type of anaesthesia on long-term outcomes

A few treatment options are available for breast cancer, including surgical resection, chemotherapy, radiation, immunotherapy, and various pharmacotherapies. Because TNBC lacks targets for modern specific therapy and has a poor prognosis compared to other breast cancer patients, surgery remains the main treatment for these patients. Current diagnostic and therapeutic advances now allow us to surgically resect many cancers at earlier stages compared with years past when the same tumours would not have been identified until after they had further grown and spread [24]. However, both surgery itself and anaesthesia may have an impact on tumour recurrence and metastases, and it is generally recognized that anaesthetic

Table 1. Different factors' effect and action mechanism on cancer recurrence and metastasis

Perioperative factors	*Mechanism of action*
Surgery	Immune suppression, enables tumour cell adhesion, increases the release of metalloproteinases and vascular endothelial growth factor (VEGF), release of malignant cells into circulation
Volatile anesthesia	Suppression of immune response - including suppression of natural killer cells, inhibition in various lymphocyte functions such as proliferation and cytokine production may induce apoptosis in lymphocytes in vitro
Propofol	Inhibition of cyclooxygenase, thus restricting angiogenesis, inhibits cellular adhesion and migration and induces apoptosis in breast cancer cells, reduces the concentration of cytokines (IL-1, TNF-α, and IL-6) and stimulates neutrophils to increase nitric oxide synthesis, decreases the invasion ability of human cancer cells (HeLa, HT1080, HOS and RPMI-7951). Inhibition of pulmonary metastasis of murine osteosarcoma (LM 8) cells in mice model
Hypoxia	Tumour angiogenesis augmentation

techniques and other perioperative factors may affect long-term outcomes after cancer surgery (Table 1) [7]. Surgery produces immune suppression, enables tumour cell adhesion, and increases the release of metalloproteinases and VEGF. All these factors promote cancer progression, metastases, increase motility and invasiveness of cancer cells, and increase neovascularization. Surgery for cancer can release malignant cells into circulation, some of which may develop into metastases. The major first-line defence against development of primary tumours and metastases is NK cells [25]. However, general anaesthesia may suppress the immune response [26], and therefore the possible association between anaesthesia and subsequent tumour proliferation and recurrence of cancer have been studied intensively [27].

Two main anaesthesia methods are mostly used in breast cancer surgery: general anaesthesia using volatile anaesthetics and total intravenous anaesthesia (TIVA). Some research has shown that general anaesthesia may suppress the immune response [28] including suppression of NK cells, and therefore the risk of recurrence may increase in patients undergoing breast cancer surgery under general anaesthesia. In mice models, isoflurane and halotane inhibited interferon-induced NK cell production [29]. On the other hand, propofol, which is the most popular hypnotic used in TIVA, may attenuate an adverse immune response to surgery and also has anti-tumour activity, possibly related to inhibition of cyclooxygenase, thus restricting angiogenesis, a key factor in the growth and dissemination of cancers [30]. These observations have created considerable interest in the possible association between the type of anaesthesia and (long-term) outcomes of breast cancer surgery. Studies show dose-dependent and time-dependent suppressive effects of volatile anaesthetics on immune cells, including NK cells and T lymphocytes [31-33]. Volatile anaesthetics also inhibit various lymphocyte functions such as proliferation and cytokine production [26].

HIF expression in tumour cells promotes tumour cell proliferation and induces the secretion of angiogenic factors including VEGF and angiopoietin 2, which augment tumour angiogenesis. Therefore, hypoxia is strongly associated with tumour progression and metastasis [34]. In a comprehensive review, Tavare et al. described the direct effect of anaesthetics on HIF-1 which is up-regulated by inhaled anaesthetics and inhibited by propofol [35]. This phenomenon is thought to occur via receptor-mediated signals modifying HIF gene expression. It has been hypothesized that an up-regulation of HIFs may contribute to cancer recurrence [7].

Particularly in cancer patients, immunosuppression attributable to anaesthetics, such as the dysfunction of NK cells and lymphocytes, may accelerate the growth and metastases of residual malignant cells, thereby worsening prognoses [37].

Propofol seems to exhibit a different profile, as it exerts protective effects through various mechanisms, including an anti-inflammatory effect, inhibition of COX-2 and reduction of PGE-2, weak β-adrenoreceptor binding, enhancement of anti-tumor immunity, and NK cells function preservation [30,36,37]. Clinical data suggest that select β2-receptor antagonist intake by patients for cardiac indications was associated with higher recurrence-free and overall survival in the TNBC subgroup. Patients receiving perioperative β-blockers have a lower rate of postoperative cancer recurrence and

metastases [14]. Propofol conjugates (propofol-docosahexaenoate and propofol-eicosapentaenoate) have been shown to inhibit cellular adhesion and migration and to induce apoptosis in breast cancer cells [38]. The studies conducted by González-Correa et al. [39] showed that propofol reduces the concentration of cytokines (IL-1, TNF-α, and IL-6) and stimulates neutrophils to increase nitric oxide synthesis [7]. It was found that clinically relevant concentrations of propofol (1–5 mg/ml) decreased the invasion ability of human cancer cells (HeLa, HT1080, HOS and RPMI-7951). In the HeLa cells treated with propofol, formation of actin stress fibres as well as focal adhesion were inhibited, and propofol had little effect on the invasion ability of the HeLa cells with active Rho A (Val14-Rho A). In addition, continuous infusion of propofol inhibited pulmonary metastasis of murine osteosarcoma (LM 8) cells in mice. These results suggest that propofol inhibits the invasion ability of cancer cells by modulating Rho A, and that this agent might be an ideal anaesthetic for cancer surgery [40].

It is known that activation of specific genes during the perioperative period can influence cancer recurrence and metastasis. *In vitro* studies on both oestrogen receptor positive and negative breast cancer cells found that propofol reduced expression of the Neuroepithelial Cell Transforming Gene 1 (NET1) which in turn reduced the migration of these breast cancer cells [41]. The NET1 gene expression is involved in the promotion of cancer cells migration.

Differences between mechanisms of action of volatile anaesthesia and propofol-based TIVA in cancer surgery inspired multiple studies comparing cancer surgery outcomes using these two types of anaesthesia. However, the majority of these studies were retrospective analyses [42-44]. Wigmore et al. [42] retrospectively analysed long-term survival for patients undergoing volatile versus IV anaesthesia for cancer surgery. They analysed more than 5200 patients who underwent surgery either under volatile inhalational anaesthesia or TIVA and found that volatile inhalational anaesthesia was associated with a hazard ratio of 1.59 (1.30 to 1.95) for death on univariate analysis and 1.46 (1.29 to 1.66) after multivariate analysis of known confounders in the matched group. So they concluded that this retrospective analysis demonstrates an association between the type of anaesthetic delivered and survival. Enlund et al. [43] examined the possible association between patient survival after radical cancer surgery and the use of sevoflurane or propofol anaesthesia. A total of 2838 patients registered for surgery for breast, colon, or rectal cancers were included in a database. This was record-linked to regional clinical quality registers. Cumulative 1- and 5-year overall survival rates were assessed using the Kaplan–Meier method, and estimates were compared between patients given propofol (n = 903) or sevoflurane (n = 1,935). In a second step, Cox proportional hazard models were calculated to assess the risk of death adjusted for potential effect modifiers and confounders. Differences in overall 1- and 5-year survival rates for all three sites combined were 4.7% ($p = 0.004$) and 5.6% ($p < 0.001$), respectively, in favour of the propofol group. The 1-year survival for patients operated for colon cancer was almost 10% higher after propofol anaesthesia. Propofol anaesthesia had been an advantage for the 1-year survival of patients diagnosed with colon and breast cancer but not for patients with rectal cancer. After 5 years, however, there was no difference in survival for patients suffering from breast cancer. However, following adjustment for confounders, the observed differences in overall survival were eliminated for all cancer sites. The authors concluded that propofol anaesthesia might be better in surgery for some cancer types, but the retrospective design of this study, with uneven distributions of several confounders, distorted the picture. These uncertainties emphasize the need for a randomized controlled trial. In another study, Lee et al. [44] compared the use of sevoflurane-based anaesthesia and propofol-based TIVA in 363 breast cancer patients who underwent modified radical mastectomy. It was observed that propofol-based total intravenous anaesthesia substantially reduced tumour recurrence after breast cancer surgery. Regarding overall survival, there was no difference between the two groups. The propofol group showed a significantly lower rate of cancer recurrence ($p=0.037$), with an estimated hazard ratio of 0.550 (95% CI 0.311–0.973). This retrospective study provides the possibility that propofol-based TIVA for breast cancer surgery can reduce the risk of recurrence during the initial 5 years after modified radical mastectomy.

Few studies showed that regional anaesthesia is a beneficial technique in breast cancer patients [6,45,46]. Basic science studies indicate an encouraging role of local anaesthetics in attenuating tumour recurrence [47]. Starnes-Ott et al. investigated differences in patient, disease, and treatment factors between women who received outpatient surgical treatment of breast cancer with paravertebral and general anaesthesia, compared with women who received general anaesthesia alone. The data from 358 remaining patients were analysed. The patients were grouped according to

anaesthesia type, which included paravertebral with general anaesthesia (n=193) and general anaesthesia alone (n=165). Breast cancer recurrence was detected in 1.7% of the study population (paravertebral regional block with general anaesthesia: n=4; and general anaesthesia alone: n=2). Overall, no association between anaesthesia type and recurrence was detected (p=0.53), with an unadjusted estimated hazard ratio of 1.84 (95% confidence interval, 0.34-10.08) [45]. Accumulated basic and clinical data suggest that total intravenous anaesthesia with propofol, cyclooxygenase antagonists and regional anaesthesia can decrease negative consequences associated with perioperative immunosuppression. Volatile anaesthesia, systemic morphine administration, unnecessary blood transfusions, intraoperative hypoxia, hypotension, hypothermia, and hyperglycaemia should be avoided [6]. In a retrospective study, 129 patients received general anaesthesia for surgery for breast cancer [50]. Patients who received paravertebral block for analgesia had nearly 4 times greater recurrence-free survival (RFS) compared to those who received intravenous patient controlled analgesia (PCA) (6 vs 24%, p=0.013).

Conclusions

TNBC shows a high recurrence rate and poor prognosis. New data show an increasing evidence of the advantage of TIVA compared with volatile anaesthesia in breast cancer surgery. Nevertheless, data is still lacking in the case of TNBC. To confirm the validity of these findings in TNBC patients, new multicentre, randomized, prospective studies are necessary. The effects of TIVA and volatile anaesthesia on TNBC need to be defined. The results of these studies may provide an answer if the data in animal models and *in vitro* studies can be applied in clinical practice.

Conflict of interests

The authors declare no conflict of interests.

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