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Xiaoyue Sun
Nursing School of Weifang Medical College ; Graduate Student Department , Linyi People's Hospital

Xiaoyue Sun

Fengling Wang

Aihua Wang

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SUN Xiaoyue[1, 2]，WANG Fengling[3*]，WANG Aihua[1]

1. Nursing School of Weifang Medical College，Weifang 261000，China

2. Graduate Student Department，Linyi People's Hospital，Linyi 276000，China

3. Administrative Office，Linyi People's Hospital，Linyi 276000，China

*Corresponding author：WANG Fengling，Chief superintendent nurse，Master supervisor；E-mail：ly-wfl@163.com

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Research Progress on the Pathogenesis and Preventive Treatment of Ischemic Stroke in Breast Cancer-related Ischemic Stroke

SUN Xiaoyue[1, 2], WANG Fengling[3], WANG Aihua[1]*

【**Abstract**】 Breast cancer and ischemic stroke are two important diseases that endanger human health. More and more studies have shown that the incidence of breast cancer with ischemic stroke is higher than that of the general population, however, its pathogenesis, optimal treatment, and prevention strategies are still unclear. This article summarized the evidence literature on the epidemiology, risk factors, clinical and imaging features, pathogenesis, and prevention measures of breast cancer-related ischemic stroke, aiming to sort out the research progress of breast cancer-related ischemic stroke, as well as the potential strategies to solve the above problems.

【**Key words**】 Breast neoplasms; Ischemic stroke; Blood coagulation disorders; Review

Both stroke and malignant tumors are major public health problems in the world, and suffering from both diseases at the same time will cause a serious economic burden to patients and society. Although the correlation between stroke and different tumors has been reported, the relationship between different types of malignant tumors and stroke is not consistent, which may be different because of different tumor types. Therefore, it is of great significance to select specific types of malignant tumors for the study and to guide the diagnosis and treatment of stroke-like patients. Breast cancer is the most common malignant tumor in women in China. Each year, about 270, 000 cases of breast cancer are newly diagnosed. In the next 10 to 20 years, the incidence of breast cancer will continue to rise, and the physical and mental health of sex causes serious harm[1-4]. Treatments for breast cancer include surgery, chemotherapy, and endocrine therapy, all of which can cause Coagulopathy; Hypercoagulability was found to be a major risk factor for ischemic stroke in a prospective study of cancer populations [1-2, 4]. There is a strong link between cancer and stroke. In some cases, stroke is caused by an underlying malignancy [5-6]; Studies have shown that 7.44% of cancer patients had autopsy evidence of cerebrovascular disease[7-8]; The incidence of stroke in patients with a history of breast cancer was as high as 7.0% [1]; Acute ischemic stroke was the initial clinical

manifestation in 18.30% of breast cancer patients [9]. The incidence of ischemic stroke in patients with active breast cancer is 1.5 times that of the general population [9], suggesting that breast, adenocarcinoma, may contribute to ischemic stroke in such patients, that is which is known as breast cancer-related ischemic stroke(BCRS).

Although independent risk factors, specific biomarkers, and secondary prevention of BCRS have been found in some clinical studies at home and abroad, the prevention and treatment of BCRS are still controversial because breast cancer patients are at greater risk of bleeding during this procedure [10], there is currently no uniform standard for the best drugs to prevent BCRS. Because the conclusions of different studies are not completely consistent, there is no unified conclusion on the risk, factors, potential mechanism, and control strategy of BCRS. This article reviews the published evidence on the epidemiology, risk factors, clinical manifestations, imaging features, pathogenesis, prevention, and treatment of BCRS, and explores the potential strategies to solve the above problems.

PubMed, Medline, Web of Science and Cochrane Library were retrieved for English keywords including "Breast cancer, ischemic stroke, breast cancer-related ischemic stroke, diffusion-weighted imaging, hypercoagulability, D-dimer, Cancer pro coagulation, chemotherapeutics, radiotherapy, MP-TF, intravenous thrombolytic therapy, endovascular treatment, anticoagulant therapy ", CNKI, Wanfang Data Knowledge Service platform and VIP were retrieved for Chinese keywords including "Breast cancer, stroke, breast cancer-related ischemic stroke, diffuse-weighted imaging, hyper coagulant state, D-dimer, cancer coagulant, chemotherapy, radiation therapy, microparticle tissue factor, intravenous thrombolytic therapy, intravascular therapy, anticoagulant therapy". The retrieval time is from the establishment of the database to December 2021. Literature inclusion criteria: basic research, clinical research, and literature research related to hemorrhagic stroke in breast cancer.Literature exclusion criteria: repeated publication, unable to obtain the full text and data of literature, literature is old, literature quality is poor.

1 Epidemiological characteristic of BCRS

Ischaemic heart disease is the leading cause of death among the 20 causes of death updated by the World Health Organization in 2016, followed by cancer and stroke [11]. GLOBOCAN 2020 provides a new ranking of cancer incidence by the end of 2020, suggesting breast cancer has become the largest number of people diagnosed with cancer in the world for the first time, surpassing lung cancer in the number of new cases [12]. A Swedish study from 1970 to 2000 found that the incidence of stroke was up to 7.0% in patients with a history of breast cancer, and the comorbidities increased with the age of breast cancer patients [1]. Patients with ischemic stroke may also present with cryptogenic breast cancer at the time of diagnosis or 6 months after diagnosis [13-14]. Results of

a retrospective cohort study in Guangxi Province suggest that about 0.59% of breast cancer patients had an ischemic stroke within the first 6 months of definitive diagnosis, and 18.30% of breast cancer patients had an acute ischemic stroke as their initial clinical presentation [9]. Breast cancer patients are at increased risk of ischemic stroke [1]. The initial clinical manifestation of cryptogenic breast cancer may now be an ischemic stroke, and ischemic stroke may also be the result of long-term breast cancer treatment [15-16]. Studies have shown that patients with breast cancer have up to a threefold risk of ischemic stroke before presentation compared with cancer-free controls[17]. A retrospective study of breast cancer patients showed that 47.56% of breast cancer patients experienced an ischemic stroke within 6 months after diagnosis [9]. The incidence of ischemic stroke in patients with active breast cancer is 1.5 times that of the general population, suggesting that the occurrence of ischemic stroke in these patients may be the result of long-term breast cancer treatment [18].

2 Risk factors for BCRS

BCRS and non-cancer stroke patients share several risk factors[19], which are more common in the elderly and are associated with vascular risk factors. Foreign reports showed that hypertension, smoking, hyperlipidemia, diabetes, alcoholism, obesity, and atrial fibrillation are all risk factors[19-21]. The hypercoagulable state is common in breast cancer patients, so it is reasonable to consider the hypercoagulable state as one of the potentially important pathogenic factors of breast cancer[1, 22]. Similarly, an autopsy study found that hypercoagulability was present in about 51% of patients with ischemic stroke[8]. A retrospective study of 33 patients with cancer and ischemic stroke found that atherosclerosis of large vessels was also the most common risk factor for stroke[23]. CHENG et al. [9] showed that endocrine therapy, such as tamoxifen, increased the risk of ischemic stroke in breast cancer patients, which was consistent with the results of LIGIBEL et al. [24], LAI et al. [25] and ROSELL et al. [26]. It was speculated that the longer the tamoxifen was used or the higher daily dosage. Patients with breast cancer are at greater risk of ischemic stroke. In addition, tamoxifen reduces LDL and total cholesterol levels and increases triglyceride levels, and clinical studies have shown that tamoxifen can increase the risk of stroke[27]; Aromatase inhibitors (AIs) generally do not affect the level of low-density lipoprotein but can increase the level of high-density lipoprotein and reduce the level of triglyceride. However, compared with tamoxifen, studies on the effects of AIs on stroke are more limited[27], Therefore, more rigorous stroke assessment procedures are needed to address this issue in future trials evaluating AIs.

3 Clinical manifestations and imaging features of BCRS

Most of the clinical manifestations of BCRS patients are mainly focused on neurological symptoms, such as hemiplegia, dizziness, mental hypothermia or delirium, dyslexia, ataxia, etc., [28], and there is no significant difference in

neurological symptoms compared with those of patients without cancer stroke on admission[29-30]. However, the disease of BCRS patients progresses faster and is easily life-threatening according to the comparison. Diffusion-weighted imaging (DWI) images of BCRS are characterized by multiple infarcts [31], which involve multiple vascular areas in the lesion mode and present clinical symptoms such as diffuse encephalopathy or multifocal cerebral infarction. Even with the application of MRI technology, it is difficult to make a clear diagnosis, and can only be found at autopsy [32].

4 Pathogenesis

4.1 Hypercoagulable state of the blood The coagulation mechanism related to breast cancer is very complex and not very clear before the project. There may be the interaction of many factors, such as blood hypercoagulable state, toxic side effects of radiotherapy and chemotherapy, and direct effects of cancer. Blood hypercoagulability is an important mechanism for the occurrence of BCRS[33]. Both hematological tumors and breast cancer have abnormal coagulation and fibrinolysis mechanisms in their pathogenesis. There is evidence supporting that breast cancer patients have micro inflammatory states, and excessive release of inflammatory transmitters may be associated with indirect activation of the coagulation system, which leads to accelerated release of inflammatory factors by neutrophils and mononuclear cells, forming a clot-activated cycle [34-35]. Studies have shown that the level of plasma D-dimer of BCRS is significantly increased, and plasma D-dimer is related to the formation of hypercoagulable substances such as microthrombi in blood. It is speculated that plasma D-dimer may be a biomarker of breast cancer-induced hypercoagulable state[36-37]. Mucins secreted by carcinoma cells bind to P-lectin and L-lectin to induce thrombus formation[38]. Some studies showed that cysteine protease was a cancer pro-coagulation agent (CP) which can activate factor X in vitro in a unique way[39]. However, KAZMIERCZAK et al.[40], MIELICKI et al.[41] found that Cysteine protease is not associated with the coagulation system, so the mechanism of cysteine protease's coagulation-promoting properties in thrombus formation remains unclear.

4.2 Anti-tumor therapy Cancer drugs can increase the risk of blood clots. Studies have shown that certain breast cancer chemotherapy drugs, such as platinum compounds, methotrexate (M), and L-asparaginase (L-ASP), can significantly increase the risk of ischemic death and thrombosis [42]. Chemotherapeutic agents cause coagulation activation, induce the release of microparticles (MP), improve the assembly speed of the coagulation complex, and combine with the main initiating tissue factor (TF) of coagulation in vivo to form microparticle tissue factor (MP-TF)[43]. TF is highly expressed in cancer cells of breast cancer patients during chemotherapy, which may lead to the formation of the MP-TF mechanism [44-45]. The study showed that in patients

with distant metastatic breast cancer (IV Stage), MP-TF level increased significantly; MP-TF level in stage I to III breast cancer patients were similar to those in a healthy control group, and MP-TF level was not affected by chemotherapy[46]. Whether this chemotherapy can affect MP-TF levels in breast cancer patients is still controversial. In addition, vascular endothelial cells play a role in inhibiting blood clotting under normal conditions, and exposure of endothelial cells to chemotherapy drugs may also lead to the loss of their function[47].

Cerebrovascular events are the main cause of high non-tumor mortality in breast cancer patients caused by radiotherapy[48]. The target areas of radiotherapy for breast cancer mainly include the upper and lower clavicle, armpit, chest wall, and inner breast lymph node area. Studies by ADDISON et al.[49] showed that the risk of stroke was significantly increased for cancer patients who received radiotherapy in the neck area. However, due to minimal exposure to the neck during radiotherapy for breast cancer patients, the research results showed that the risk of stroke was not increased.WOODWARD et al.[50] also analyzed older breast cancer patients and similarly found no association between the use of supraclavicular radiotherapy for breast cancer and the increased incidence of hospitalization after stroke. At present, there is no consensus on whether radiotherapy can cause stroke or non-tumor death in breast cancer patients.

4.3 Direct tumor effect Although the incidence of venous thromboembolism in breast cancer patients is the lowest among cancer patients[51-52], and artery embolism directly caused by breast cancer is also rare in 10 cases, such as a tumor or pia invasion into the arteriovenous sinus, tumor embolism, tumor compression, etc.[8], breast cancer does cause stroke[53], which was reported by UNER et al.[54].

5 BCRS prevention and control measures

5.1 BCRS revascularization The effective treatment of BCRS at home and abroad still remains unclear, only intravenous thrombolysis and intravascular therapy are currently available. The 2019 update of the American Stroke Association (ASA) Guidelines for Health Care Professionals suggests that alteplase thrombolytic therapy is an option for patients with ischemic stroke and systemic cancer with an estimated survival of >6 months [55]. BCRS is not a special contraindication for thrombolytic therapy. For BCRS patients with normal thrombocyte count, no cocoagulant dysfunction, or no recent surgery history, ASA evaluation can be followed, and stroke thrombolytic therapy guidelines should be considered as the reference for treatment [56]. MASRUR et al. [57] believed that the incidence of cerebral hemorrhage caused by thrombolytic therapy in BCRS patients was not significantly different from that in non-cancer patients. Studies have shown that intravenous thrombolytic therapy for BCRS is safe and effective [58]. However, endovascular therapy may be a good alternative therapy for BCRS patients with abnormal coagulation or older age [59]. BHATIA et al. [60] reported the clinical data of a patient with BCRS, enboluses were

removed from the cerebrovascular by a mechanical thrombus removal device after the onset of BCRS, and the postoperative prognosis of the patient's neurological function was good.

In conclusion, intravenous thrombolysis or endovascular therapy can be a reasonable vascular recanalization strategy for breast cancer-related complications without thrombolytic contraindications and BCRS patients with systemic conditions, but further confirmation is needed in large-sample, multi-center randomized clinical trials.

5.2 BCRS prevention The clinical treatment of BCRS is difficult and seriously affects the quality of life of patients [61]. Therefore, the prevention of BCRS is increasingly valued by clinicians. At present, there is no unified conclusion on the vascular risk factors in patients with BCRS, but some risk factors (such as hypertension, smoking, hyperlipidemia, diabetes, alcoholism, obesity, etc.) are still important links in the primary prevention of BCRS. Studies have shown that the above risk factors will eventually affect the coagulation system of the body, resulting in an imbalance of the coagulation and anticoagulation system [62]. Therefore, regular detection of thromboplastin graphs combined with four indexes of routine coagulation for breast cancer patients has a high clinical diagnostic value for thrombosis [63]. Studies have shown that ischemic stroke is a serious complication of breast cancer patients, and preventive application of anticoagulant therapy or antiplatelet therapy can reduce the occurrence of thrombotic events [64]. However, secondary prevention of ischemic stroke in this group is different from that in the general population, and the bleeding risk caused by preventive therapy should be taken into account. More than 30% of stroke patients may have micro bleeding in brain tissue without clinical manifestations [65]. Studies have shown that micro bleeding in brain tissue is a risk factor for cerebral hemorrhage after anticoagulant therapy [66], and magnetic resonance imaging (MRI) examination is sensitive to micro bleeding in brain tissue, so preventive MRI examination is necessary. In addition, high-sensitive troponin and brain natriuretic peptide precursors can also be used as biomarkers to predict bleeding [67-68]. Research evidence on the application of different prevention strategies for BCRS is very limited. large sample, multi-center and prospective randomized controlled clinical trials are expected to evaluate the risk of thrombosis, anticoagulation, and bleeding to determine the best preventive measures for BCRS.

In conclusion, with the continuous extension of the survival of breast cancer patients, the harm of BCRS is increasingly apparent. Attention to BCRS patients should be paid to clarify the risk factors, clinical and imaging characteristics, and pathogenesis of BCRS, to provide new ideas for the treatment and prevention of BCRS, and explore new directions for the cross-disciplinary development of malignant tumors and the brain.

Author contributions: Sun Xiaoyue proposed research ideas, collated literature, and wrote papers; Wang

Aihua is responsible for literature collection and paper revision; Wang Fengling is responsible for the quality control and proofreading of the article，as well as the overall supervision and management of the article.

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