Antiplatelet Therapy in Breast Cancer Patients Using Hormonal Therapy: Myths, Evidence and Potentialities – Systematic Review

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Abstract

Breast cancer is the most frequently diagnosed tumor in women worldwide, with a significant impact on morbidity and mortality. Chemotherapy and hormone therapy have significantly reduced mortality; however, the adverse effects are significant. Aspirin has been incorporated into clinical practice for over 100 years at a low cost, making it particularly attractive as a potential agent in breast cancer prevention and as an adjunct treatment to endocrine therapy in the prophylaxis of cardiovascular complications. The objective of this study was to evaluate the role of aspirin in reducing the incidence of breast cancer and to evaluate the impact of its use on morbidity and mortality and reduction of cardiovascular events as adjuvant therapy during breast cancer treatment with selective estrogen receptor modulators. A systematic review was performed using the PRISMA methodology and PICO criteria, based on the MEDLINE, EMBASE and LILACS databases. The original articles of clinical trials, cohort, case-control studies and meta-analyses published from January 1998 to June 2017, were considered. Most studies showed an association between the use of selective estrogen receptor modulators and the increase in thromboembolic events. The studies suggest a protective effect of aspirin for cardiovascular events during its concomitant use with selective estrogen receptor modulators and in the prevention of breast cancer. This systematic review suggests that aspirin therapy combines the benefit of protection against cardiovascular events with the potential reduction in breast cancer risk, and that the evaluation of the benefits of the interaction of endocrine therapy with aspirin should be further investigated.

Introduction

Breast cancer is the most frequently diagnosed tumor in women worldwide, with a significant impact on morbidity and mortality. According to the World Health Organization, it is estimated that more than 1.5 million new cases of breast cancer are annually diagnosed worldwide. Despite advances in treatment, breast cancer mortality is still high, with 570,000 deaths in 2015. The disease, recurrent or metastatic, remains incurable in most cases.1

Chemotherapy and hormone therapy have significantly reduced mortality, but their adverse effects are considerable. Endocrine therapy has revolutionized the treatment of breast cancer patients with positive Estrogen Receptor (ER), although there are cases that develop resistance to this therapy. An appropriate strategy would be the combination of Selective Estrogen Receptor Modulators (SERMs) or another hormonal class with other therapeutic agents, aiming at attaining a synergistic antitumor effect. The use of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, has been associated with reduced risk of breast cancer.2,3 This therapy could also antagonize thrombogenic effects in women treated with tamoxifen.

The increasing number of breast cancer survivors is confronted with the shortage of information among clinicians on the subject.

The aim of the present study is to evaluate the role of aspirin in reducing the incidence of breast cancer and to evaluate the impact of its use in reducing cardiovascular events as an adjuvant therapy during the treatment of breast cancer with SERMs.

Methods

This systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology.4 The study included original articles of clinical trials, cohort, case-control studies and meta-analyses published from January 1998 to June 2017, with full-texts in English, Spanish and Portuguese, obtained from the MEDLINE, EMBASE and LILACS databases. The research was performed using the following descriptors: (selective estrogen receptor modulators OR tamoxifen OR raloxifene hydrochloride OR toremifene) AND (platelet aggregation inhibitors OR aspirin) AND (cardiovascular disease) AND (breast CA).

This study was based on the PICO (acronym for Population, Intervention, Control and Outcome) criteria. The objective was to evaluate whether aspirin use implies in the reduction of events, especially cardiovascular events, in women with breast cancer using SERMs. The studies were selected according to the following criteria: use of SERMs in women with breast cancer; regular aspirin use; and evaluation of mortality, metastases, and adverse effects using SERMs and/or aspirin. Case reports, articles with other types of endocrine therapy, and animal experimental models were excluded.
A total of 221 abstracts met the search criteria and other 15 were manually retrieved. A total of 159 duplicated articles were eliminated and 77 abstracts were evaluated. Of these, 57 were selected for the review. We excluded 25 because they did not meet the previously established criteria, resulting in 32 full-text articles, which were evaluated in relation to their scientific quality. Five articles were excluded according to the inclusion/exclusion criteria. A total of 27 articles were analyzed, according to figure 1.

Selective estrogen receptor modulators and reduction of morbidity and mortality in breast cancer

Most breast cancers have positive ER and three main drugs are being used for their treatment and/or prevention, namely: tamoxifen, raloxifene and toremifene. All of these agents are competitive inhibitors of estrogen binding to its receptors, and have mixed agonist and antagonist activity, depending on the target tissue. Tamoxifen is the most well-studied SERM and often the drug of choice for breast cancer treatment. Its mechanism of action involves tumor cell growth inhibition through competitive ER inhibition.

The benefits of tamoxifen have been consolidated through the US Financial Service Task Force (USPSTF) meta-analysis. In comparison with placebo, the use of tamoxifen resulted in: reduced risk of invasive breast cancer (Relative Risk – RR = 0.70; 95% Confidence Interval – 95%CI: 0.59-0.82); reduction in the incidence of non-vertebral fractures (RR = 0.66, 95%CI: 0.45-0.98); and no difference in mortality from breast cancer or from all causes. On the other hand, a pro-coagulant effect is described when tamoxifen is added to chemotherapy – especially an increase in thromboembolic events.

Raloxifene differs from tamoxifen because it does not stimulate endometrial tissue, although it exerts the same beneficial effects of tamoxifen on breast tissue. In preclinical studies, raloxifene has been shown to prevent the onset of new breast cancers, as well as prevent the growth of preexisting cancers. In the STAR (Study of Tamoxifen and Raloxifene) study, 19,747 women were randomized to receive 20 mg of tamoxifen or 60 mg/day of raloxifene for 5 years. The results showed that raloxifene had the same efficacy as tamoxifen in the prevention of breast cancer in situ, both with a 50% risk reduction (RR of 1.02, 95%CI: 0.82-1.28). However, raloxifene did not show protection against invasive types of breast cancer, whereas tamoxifen reduced its incidence by around 50%. It was observed that the group treated with raloxifene had an almost 30% reduction in thromboembolic events such as Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) (RR = 0.70, 95%CI: 0.54-0.91). Both groups had the same incidence of cerebrovascular accident, myocardial infarction and fractures.

The MORE (Multiple Outcomes of Raloxifene Evaluation) study randomized 7,705 postmenopausal patients who had osteoporosis and had no history of breast or endometrial cancer for the use of placebo or 60 mg/day or 120 mg/day of raloxifene. After 4 years of follow-up, a 72% reduction of breast cancer risk was observed. In the CORE (Continuing Outcomes relevant to Evista) study, the patients were randomized to either raloxifene 60 mg/day or placebo. A 59% reduction (RR = 0.41, 95% CI: 0.24-0.71) was observed in the incidence of breast cancer and a decrease of 66% (RR = 0.34, 95%CI: 0.18-0.66) of ER-positive invasive breast cancer, when compared with the placebo group. When analyzing both studies together, the incidence of invasive breast cancer was reduced by 66% (RR = 0.34, 95% CI: 0.22-0.50) and, for ER-positive cases, 76% (RR = 0.24, 95%CI: 0.15-0.40), relative to the placebo group. No protection was observed against non-invasive cancers.

![Figure 1 – Flowchart of the evaluated studies.](image-url)
A significant reduction in the amount of microvessels in breast cancer was observed after treatment with raloxifene 60 mg/day for 28 days in postmenopausal women without previous endocrine treatment. There is evidence that the benefits of treatment with SERMs were seen not only during the 5 years of active treatment, as well as 5 years after the end of treatment, indicating a long-term effect on the prevention of breast cancer. Adverse effects, notably the thromboembolic events and endometrial cancer, should be considered when assessing the risk-benefit ratio for each patient.

**Selective estrogen receptor modulators and thromboembolic events**

A number of studies have demonstrated that the use of tamoxifen is associated with an increased rate of venous thromboembolic events (VTE) and that there is an additional procoagulant effect when tamoxifen is added to chemotherapy. Raloxifene is also associated with a higher risk of VTE, but with a lower incidence than tamoxifen. The NSABP (National Surgical Adjuvant Breast and Bowel Project) Tamoxifen Prevention Trial allocated 13,388 women at high risk of breast cancer to receive tamoxifen or placebo. The incidence of PE and DVT increased in women who received tamoxifen, especially in patients older than 50 years (RR for PE = 3.0, 95%CI: 1.1-11.2, RR for DVT = 1.6; 95%CI: 0.9-2.9). The IBIS-1 (International Breast Cancer Intervention Study) allocated 7,154 women at risk for breast cancer to receive tamoxifen or placebo. The use of tamoxifen was associated with an increased risk of developing VTE (Odds Ratio – OR = 2.1, 95%CI: 1.1-4.1). The risk of developing PTE or PE was significantly higher during the 5 years of active treatment with tamoxifen (RR of 2.3; 95%CI 1.4-3.9) but did not persist after its cessation.

A meta-analysis of seven trials and 30,023 patients, which compared outcomes in women with breast cancer assigned to treatment with tamoxifen or an aromatase inhibitor, found a higher rate of VTE in those receiving tamoxifen (2.8% vs. 1.6%). An analysis of 13 trials of the NSABP, which evaluated the risk of contralateral breast cancer in 20,878 women who received tamoxifen after primary treatment for this disease, found an increased risk of VTE with tamoxifen. The risks of PE, DVT and superficial phlebitis increased two to three-fold in patients treated with tamoxifen, and 11 to 15-fold in patients treated with tamoxifen plus chemotherapy. The STAR (Study of Tamoxifen and Raloxifene) study suggested a lower incidence of DVT and PE in women treated with raloxifene vs. those treated with tamoxifen. This study randomized 19,747 women at risk for breast cancer to raloxifene and tamoxifen use for 5 years.

**Selective estrogen receptor modulators and cerebrovascular accident**

In the EBCTCG (Early Breast Cancer Trialists' Collaborative Group) meta-analysis, which compared 21,457 women to receive tamoxifen or placebo, there was an increase in cerebrovascular accident (CVA) rates, but without statistical significance. In a case-control study of 11,045 women with breast cancer, the risk of CVA was not increased by the use of tamoxifen. In a meta-analysis that evaluated the use of tamoxifen in primary or secondary prevention in 39,601 breast cancer patients, the frequency of ischemic CVA was higher in those who received tamoxifen than in the controls. Tamoxifen was associated with an increased risk of CVA, but with a low absolute risk.

In the RUTH (Raloxifene Use for The Heart) study, raloxifene was associated with an increased risk of fatal CVA when compared with placebo. The IBIS-1 study did not show statistical significance between the treatment groups (tamoxifen vs. placebo) regarding cerebrovascular or cardiovascular events. A sub-analysis of the MORE study suggested that in women at high risk for arterial events, raloxifene reduced the incidence of coronary events and CVA. However, after 8 years of treatment, the incidence of cardiovascular, coronary, or cerebrovascular events did not significantly differ between the raloxifene and placebo groups. In the STAR study, the risk of CVA was similar in the raloxifene and tamoxifen groups.

**Selective estrogen receptor modulators and lipid profile**

There is evidence of changes in the lipid profile with the use of SERMs. The reduction of serum total cholesterol and low-density lipoprotein cholesterol (LDL-c) levels is a consensus. However, an increase in serum triglyceride levels has also been reported. Sawada and Sato reported that tamoxifen reduced total and LDL cholesterol levels, as well as significantly increased triglycerides. Atalay et al. did not find a significant effect of tamoxifen on total cholesterol or high-density lipoprotein-cholesterol (HDL-c) but reported a borderline increase in triglycerides. Taken together, these studies suggest that although tamoxifen consistently lowers LDL-c levels, the effects on HDL-c are mild, and tamoxifen use increases serum triglyceride levels. Changes in the lipid profile associated with the use of tamoxifen are summarized in Table 1.

**Selective estrogen receptor modulators and coronary artery disease**

Even after consolidation of the clinical use of tamoxifen, there is no definitive evidence of its effect on coronary artery disease. However, a meta-analysis of seven trials and 30,023 patients, which compared outcomes in women with breast cancer assigned to treatment with tamoxifen or an aromatase inhibitor, found a higher rate of VTE in those receiving tamoxifen (2.8% vs. 1.6%).

| Changes | Total cholesterol | LDL-c | HDL-c | Triglycerides |
|---------|------------------|-------|-------|--------------|
| Tamoxifen | Reduction | Reduction | Mild alteration | Increase |

LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol.
artery disease (CAD). Evidence suggests a modest protective effect of tamoxifen against death from CAD. There is a controversy over the effects of SERMs on atherosclerosis and its complications (Table 2). The publication of the RUTH (Raloxifene Use for The Heart) study\textsuperscript{21} confirmed a neutral effect of raloxifene. Evidence available in the world literature suggests neutral effects or discrete benefits of SERM use in overall cardiovascular risk.\textsuperscript{25}

In the NSABP study,\textsuperscript{26} 13,388 women at increased risk of breast cancer were assigned to receive tamoxifen 20 mg/day or placebo. Cardiovascular follow-up was available for 13,194 women, of which 1,048 had clinically manifest CAD. The rates of cardiovascular events were not significantly different between women receiving tamoxifen and those receiving placebo, regardless of the preexisting disease. A case-control study of women diagnosed with breast cancer found that the use of tamoxifen was not associated with a reduced risk of myocardial infarction for the observed 137 cases of myocardial infarction.\textsuperscript{17} Another case-control study demonstrated that women with breast cancer who received tamoxifen had a reduced risk of angina pectoris or myocardial infarction (OR = 0.4, 95%CI: 0.2-0.7) compared to patients who did not receive it.\textsuperscript{28}

Nordenskjold et al.\textsuperscript{29} reported a significant reduction in mortality due to CAD in women who received 5 years vs. 2 years of tamoxifen, with a higher dose of 40 mg/day. The study carried out by the Early Breast Cancer Trialists' Collaborative Group\textsuperscript{30} reported a reduction in mortality from CAD in more than 15,000 women randomized to receive approximately 5 years of tamoxifen vs. placebo, although there was no statistical significance (120 vs. 132 deaths, p = 0.06).

Selective estrogen receptor modulators and aspirin

Cancer can lead to a state of hypercoagulability, platelet abnormalities and thromboembolic events. Platelets can contribute to the metastasis process by promoting angiogenesis and by releasing the Vascular Endothelial Growth Factor (VEGF).\textsuperscript{31,32} the platelets and coagulation cascade components involve tumor cells, which prevents lysis by natural killer cells, allowing the spread of metastases.

Tamoxifen rapidly increases free calcium in human platelets.\textsuperscript{33,34} Johnson et al.\textsuperscript{35} demonstrated that tamoxifen and its metabolite 4-hydroxytamoxifen altered the platelet function, with a reduction in the angiogenic and metastatic potential. Angiogenic proteins are released during the platelet activation process, and platelet deposition is observed at the tumor site.\textsuperscript{36} The alpha and beta forms of ER were found in the platelet membrane.\textsuperscript{37,38} Some studies have suggested that estradiol, as well as the tamoxifen metabolites, can increase platelet aggregation, suggesting that ER function may influence the release of intraplatelet proteins, such as VEGF and endostatin, when platelets are stimulated in the tumor environment.\textsuperscript{39}

Holmes et al.\textsuperscript{40} carried out a study that evaluated the concentrations of VEGF and endostatin before and after tamoxifen or aromatase inhibitors in 30 women with breast cancer. Tamoxifen therapy resulted in increased VEGF concentrations in platelets, but no change in plasma VEGF levels. The use of aspirin attenuated the increase in the VEGF levels associated with tamoxifen and reduced serum levels of VEGF. The data from this study suggest that antiplatelet therapy may interfere with angiogenic protein levels in women treated with endocrine therapy.

Women with breast cancer who used tamoxifen and 45 days of aspirin had reduced intraplatelet VEGF levels, as well as increased serum and intraplatelet levels of the antiangiogenic factor thrombospondin-1.\textsuperscript{41} These changes were reversed with the aspirin discontinuation. In this study, a dose of 325 mg/day was used. Aspirin decreased the pro-angiogenic effects of tamoxifen, suggesting that antiplatelet therapy may improve tamoxifen efficacy.

**Table 2 – Events associated with the use of selective estrogen receptor modulators (SERMs)**

| Study, year | Type of study | Patients (n) | Assessed/ compared SERMs | Breast cancer | VTE | CVA | CAD |
|-------------|---------------|-------------|--------------------------|--------------|-----|-----|-----|
| STAR, Vogel et al.\textsuperscript{9} 2006 | Clinical trial | 19,747 postmenopausal women | Tamoxifen and raloxifene | Risk reduction of 50% (in situ - tamoxifen and raloxifene and invasive - tamoxifen) | Increase, raloxifene < tamoxifen of 30% | Reduction (tamoxifen and raloxifene) | Increase (tamoxifen and raloxifene) |
| MORE, Cauley et al.\textsuperscript{9} 2001 | Clinical trial | 7,705 postmenopausal women | Raloxifene and placebo | Risk reduction of 72% after 4 years | Increase | Neutral | Neutral |
| CORE / Martino et al.\textsuperscript{4} / 2004 | Clinical trial | 5,213 postmenopausal women | Raloxifene and placebo | Risk reduction of 59% | Increase | | |
| NSABP / Fisher et al.\textsuperscript{1} / 1998 | Clinical trial | 13,388 at risk for breast cancer | Tamoxifen and placebo | Risk reduction of 49% | Increase | Increase | Neutral |
| IBIS-1 / Cuzick et al.\textsuperscript{5} / 2002 | Clinical trial | 7,152 at risk of breast cancer | Tamoxifen and placebo | Risk reduction of 32% | Increase | Neutral | Neutral |
| RUTH / Barret-Connor et al.\textsuperscript{21} / 2006 | Clinical trial | 10,101 postmenopausal women | Raloxifene and placebo | Invasive cancer risk reduction of 55% | Increase of 44% | Increase of 49% | Neutral |

VTE: venous thromboembolism; CAD: coronary artery disease.
Cheng et al.\textsuperscript{42} carried out a study that showed that aspirin not only inhibits the growth of the MCF-7 RE-positive breast cancer cell line, but also has a potential function to overcome resistance to tamoxifen in MCF-7/TAM cell lines. The concomitant action of aspirin makes cells more sensitive to tamoxifen, indicating that aspirin can regulate proteins to overcome tamoxifen resistance.

The RUTH\textsuperscript{31} study evaluated the effects of antiplatelet therapy concomitant with the use of raloxifene regarding the risk of VTE. The increased risk of VTE with raloxifene when compared to placebo was not different between the women who used antiplatelet agents and those who did not use it.\textsuperscript{43} The key findings of the abovementioned studies are summarized in Table 3.

**Aspirin and Cancer Prevention**

A prospective observational study of 4,164 women with breast cancer showed that, among women who were alive at least 1 year after the breast cancer diagnosis, the use of aspirin was associated with a reduction in the risk of recurrence and death from breast cancer.\textsuperscript{44} Contrarily, another study with 27,426 women with breast cancer showed that there was no association between aspirin use and death from breast cancer.\textsuperscript{45}

A retrospective cohort study was carried out in Taiwan with 148,739 diabetic women, of which 27,378 used aspirin at a dose ranging from 75 mg to 165 mg/day, which were compared to women who did not use aspirin. Overall, aspirin use reduced the risk of breast cancer by 18% (Hazard Ratio – HR = 0.82, 95%CI: 0.71-0.94). Specifically, a cumulative dose of aspirin > 88,900mg was observed to reduce the risk of breast cancer by 47%.\textsuperscript{46} A cohort in Scotland identified 4,627 women with breast cancer throughout 11 years. The use of aspirin after the diagnosis was identified in 1,035 women (22.4%). Most of them used a 75 mg dose/day. It was concluded that low-dose aspirin was associated with reduced risk of death from all causes and breast cancer.\textsuperscript{47} Another cohort, with 27,616 postmenopausal women, identified 938 cases of breast cancer in 6 years of follow-up, meaning a RR of 0.71 (95% CI: 0.58-0.87) for those who took aspirin at least six times a week, when compared with those who did not use the medication.\textsuperscript{48} Evidence from case-control and cohort studies suggest an approximately 10% reduction in the risk of breast cancer for aspirin use.\textsuperscript{49,50}

Similar results were found with other NSAIDs and Cyclooxygenase-2 inhibitors (COX-2).\textsuperscript{51}

Rothwell et al.\textsuperscript{52} analyzed seven randomized trials for the regular use of aspirin with a minimum duration of 4 years to determine the effect of aspirin on the risk of death from cancer. Daily aspirin reduced death rates from several types of cancer during and after the studies. The benefit increased with treatment duration and was consistent in all the different studied populations.

Harris et al.\textsuperscript{53} found 393 cases of breast cancer in 32,505 patients after 5 years of follow-up. This study reported a 50% reduction in the incidence of breast cancer using ibuprofen (p < 0.01) and 40% with regular aspirin use (p < 0.05), suggesting that other NSAIDs may also be effective in breast cancer prophylaxis.

Aspirin emerged as the most likely NSAID for use in chemoprevention due to its benefits also in preventing cardiovascular events. Other NSAIDs have also been studied as adjuvants in the chemoprevention of several types of cancer, especially colorectal, breast and stomach neoplasms, although these drugs do not offer cardioprotection.\textsuperscript{54} Mortality reduction is more evident in colon cancer, probably in prostate and possibly also in breast neoplasms.\textsuperscript{55,56}

**Discussion**

The clinical trials mentioned in this review report an increase in VTE with the use of SERMs and, regarding cerebrovascular and coronary events, the results were discordant. The currently used treatment, consisting of chemotherapy and hormone therapy, has reduced breast cancer mortality, but morbidity

| Author, year | Type of study | Patients (n) | SERMs and/or aspirin | Main Conclusions |
|-------------|--------------|--------------|---------------------|-----------------|
| Holmes et al.,\textsuperscript{43} 2006 | Clinical trial | 30 | Tamoxifen or aromatase inhibitor + ASA | ASA attenuated the increase in VEGF associated with tamoxifen |
| Holmes et al.,\textsuperscript{44} 2010 | Prospective Cohort | 4,164 | ASA | Reduction in the recurrence and death from breast cancer |
| Holmes et al.,\textsuperscript{41} 2013 | Clinical trial | 12 | Tamoxifen + ASA | Reduction in VEGF and increase in TSP-1 |
| Holmes et al.,\textsuperscript{45} 2014 | Case-control | 27,426 | ASA | There is no benefit during end-stage illness |
| Yang et al.,\textsuperscript{46} 2017 | Retrospective Cohort | 148,739 | ASA | Reduction in breast cancer risk in diabetes |
| Fraser et al.,\textsuperscript{47} 2014 | Cohort | 4,627 | ASA | Reduction in death risk from all causes |
| Jhonson et al.,\textsuperscript{48} 2002 | Prospective Cohort | 27,616 | ASA | Reduction in breast cancer risk |
| Harris et al.,\textsuperscript{49} 1999 | Prospective Cohort | 32,505 | ASA/ibuprofen | Reduction in breast cancer risk |
| Duvernay et al.,\textsuperscript{50} 2010 (RUTH Trial) | Clinical trial | 10,101 | Raloxifene + ASA | Did not change the risk of VTE |

ASA: acetylsalicylic acid; VEGF: vascular endothelial growth factor; TSP-1: thrombospondin 1; VTE: venous thromboembolism.
and mortality are still high, with considerable side effects and high financial costs. There are great expectations regarding new treatments, with low toxicity and cost reduction.

Aspirin has been incorporated into clinical practice for over 100 years at a low cost, making it attractive as a potential adjunct treatment. The observational studies included in this review suggest a reduction in the risk of breast cancer in patients regularly taking aspirin. Randomized clinical trials are required to assess the impact of aspirin use on breast cancer prevention, whether associated with endocrine therapy or disease-free survival in breast cancer patients.

Aspirin use is a consensus for the secondary prevention of myocardial infarction and ischemic CVA in patients with pre-existing cardiovascular disease and for primary prevention in high-risk groups. Current indications for the prophylactic use of aspirin are based on cardiovascular risk, considering the side effects, especially gastrointestinal bleeding, of which incidence increases with age. Other potential benefits of using aspirin need to be proven in the context of cancer.

### Conclusion

Breast cancer is the most frequently diagnosed tumor in women worldwide, with a significant impact on morbidity and mortality. Although there are controversies in the analyzed studies, considering the possible benefits regarding breast cancer prevention and reduction in cardiovascular events, this systematic review suggests that therapy with selective estrogen receptor modulators and aspirin should be better investigated, and emphasizes the need for randomized trials. Future studies should address issues such as dose, age at the start, duration, efficacy, and safety of a clearly defined treatment regimen.

### Author contributions

Conception and design of the research and Acquisition of data: Leite AM, Martins WA; Analysis and interpretation of the data: Leite AM, Macedo AVS, Jorge AJL, Martins WA; Writing of the manuscript: Leite AM; Critical revision of the manuscript for intellectual content: Macedo AVS, Jorge AJL, Martins WA.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

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### Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

### References

1. Ch Yiannakopoulou E. Interaction of salicylates and the other nonsteroidal anti-inflammatory agents with breast cancer endocrine treatment: systematic review. Am J Clin Oncol. 2015;38(6):641-4.
2. Harris RE, Chlebowski RT, Jackson RD, Frid DJ, Ascenso JL, Anderson G, et al; Women's Health Initiative. Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women’s Health Initiative. Cancer Res. 2003;63(18):6096-101.
3. Takkouche B, Regueira-Mendez C, Emfian M. Breast cancer and use of nonsteroidal anti-inflammatory drugs: a meta-analysis. J Natl Cancer Inst. 2008;100(20):1439-47.
4. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9.
5. Cosman F, Lindsay R. Selective estrogen receptor modulators: clinical spectrum. Endocr Rev. 1999;20(3):418-34.
6. Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, et al; Early Breast Cancer Trialists Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomized trials. Lancet. 2011;378(9793):771-84.
7. Nelson HD, Smith ME, Griffin JC, Fu R. Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013;158(8):604-14.
8. Cuzick J, Forbes J, Edwards R, Edwards R, Baum M, Cawthorn S, et al; IBIS investigators. First results from the International Breast Cancer Intervention Study (IBIS-II): a randomized prevention trial. Lancet. 2002;360(9366):817-24.
9. Fisher B, Costantino JP, Wickerham LD, Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 1998;90(18):1371-88.
10. Jordan VC, Morrow M. Tamoxifen, raloxifene, and the prevention of breast cancer. Endocr Rev. 1999;20(3):253-78.
11. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al; National Surgical Adjuvant Breast and Bowel Project (NSABP). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006;295(23):2727-41.
12. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women. Results from the MORE randomized trial. JAMA. 1999;282(23):2189-97.
13. Cauley JA, Norton L, Lippman ME, Eckert S, Krueger KA, Purdie DW, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. Breast Cancer Res Treat. 2001;65(2):125-34. Erratum in: Breast Cancer Res Treat 2001;67(2):191.
14. Martino S, Cauley JA, Barrett-Connor E, Powles TJ, Menschon J, Disch D, et al.; CORE Investigators. Continuing outcomes relevant to Exista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst. 2004;96(23):1751-61.

15. Cuzick J, Sestak I, Bonanni B, Costantino, JP, Cummings S, DeCensi A, et al.; SERM Chemoprevention of Breast Cancer Overview Group. Selective estrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet. 2013;381(9880):1827-34.

16. Amir E, Seruga B, Niraula S, Carlsson L, Ocaña A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. J Natl Cancer Inst. 2011;103(17):1299-309.

17. McCaskill-Stevens W, Wilson J, Bryant J, Mamounas E, Carvey L, James J, et al. Contralateral breast cancer and thrombembolic events in African American women treated with tamoxifen. J Natl Cancer Inst. 2004;96(23):1762-9. Erratum in: J Natl Cancer Inst. 2005;97(1):71.

18. Onitilo AA, McCarty CA, Wilke RA, Glurich I, Engel JM, Flockhart NO, et al. Coronary heart disease mortality after 5 years of adjuvant chemotherapy and hormonal therapy for early breast cancer on recurrence and non-relapse mortality: an overview of the randomized trials. Lancet. 2005;365(9472):1687-717.

19. Geiger AM, Fischberg GM, Chen W, Bernstein L. Stroke risk and tamoxifen therapy: results from a randomized trial. J Natl Cancer Inst. 2004;96(20):1528-36.

20. Bushnell CD, Goldstein LB. Risk of ischemic stroke with tamoxifen treatment for breast cancer: a meta-analysis. Neurology. 2004;63(20):1230-3.

21. Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, et al. Raloxifene Use for the Heart (RUTH) Trial Investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med. 2006;355(2):125-37.

22. Cuzick J, Forbes JF, Sestak I, Cawtohorn S, Hamed H, Holli K, et al. International Breast Cancer Intervention Study I Investigators. Long-term results of tamoxifen prophylaxis for breast cancer - 96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst. 2007;99(4):272-82.

23. Sawada S, Sato K. Effect of anastrozole and tamoxifen on serum lipid levels in Japanese postmenopausal women with early breast cancer. [abstract]; Breast Cancer Res Treat. 2003;82(Suppl 1):531-532.

24. Atalay G, Dirix L, Biganzoli L, Beex L, Nooij M, Cameron D, et al. The effect of exemestane on serum lipid profile in postmenopausal women with metastatic breast cancer: a companion study to EORTC Trial 10951. "Randomised phase II study in first line hormonal treatment for metastatic breast cancer with exemestane or tamoxifen in postmenopausal patients". Ann Oncol. 2004;15(2):211-7.

25. Cuzick J, Forbes JF, Sestak I, Cawtohorn S, Hamed H, Holli K, et al. International Breast Cancer Intervention Study I Investigators. Long-term results of tamoxifen prophylaxis for breast cancer - 96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst. 2007;99(4):272-82.

26. Reis SE, Costantino JP, Wickerham DL, Tan-Chiu E, Wang J, Kavanah M. Cardiovascular effects of tamoxifen in women with and without breast disease: breast cancer prevention trial. J Natl Cancer Inst. 2001;93(16):16-21.

27. Geiger AM, Chen W, Bernstein L. Myocardial infarction risk and tamoxifen therapy for breast cancer. Br J Cancer. 2005;92(9):1614-20.

28. Bradbury BD, Lash T, Kaye JA, Jick SS. Tamoxifen-treated breast carcinoma patients and the risk of acute myocardial infarction and newly-diagnosed angina. Cancer. 2005;103(6):1114-21.

29. Nordenskjold B, Rosell J, Rutqvist LE, Malmström PO, Bergh J, Bengtsson NO, et al. Coronary heart disease mortality after 5 years of adjuvant tamoxifen therapy; results from a randomized trial. J Natl Cancer Inst. 2005;97(21):1609-10.

30. Early Breast Cancer Trialists’ Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet. 2005;365(9472):1687-717.

31. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer. 2011;11(2):123-34.

32. Smyth SS, McEver RP, Weyrich AS, Morrell CN, Hoffman MR, Aregalli GM, et al; 2009 Platelet Colloquium Participants. Platelet functions beyond hemostasis. J Thromb Haemost. 2009;7(11):1759-66.

33. Dobryndyva Y, Weatherman RV, Teebly JP, Morrell AN, Fitzgerald MC, Fichandler CE, et al. Tamoxifen stimulates calcium entry into human platelets. J Cardiovasc Pharmacol. 2007;50(4):380-90.

34. Shah VP, Chegini HA, Vishneski SR, Weatherman RV, Blackmore PF, Dobryndyva Y. Tamoxifen promotes superoxide production in platelets by activation of PI3 kinase and NADPH oxidase pathways. Thromb Res. 2012;129(1):36-42.

35. Johnson KE, Forward JA, Tippdy MD, Ceglowski JR, El-Husayni S, Kulenthirarajan R, et al. Tamoxifen Directly Inhibits Platelet Angiogenic Potential and Platelet-Mediated Metastasis. Arterioscler Thromb Vasc Biol. 2017;37(4):664-74.

36. Boudreau N, Myers C. Breast cancer-induced angiogenesis: multiple mechanisms and the role of the microenvironment. Breast Cancer Res. 2003;5(3):140-6.

37. Jayachandran M, Miller VM. Human platelets contain estrogen receptor α, cavelin-1 and estrogen receptor associated proteins. Platelets. 2003;14(2):75-81.

38. Khetawat G, Faraday N, Nelem ML, Vijayan KV, Bolton E, Nogo SJ, et al. Human megakaryocytes and platelets contain the estrogen receptor β and antiestrogen receptor AR antagonist regulates AR expression. Blood. 2000;95(7):2289-96.

39. Moro L, Reineri S, Pirandata D, Pietrapierna D, Lova P, Bertoni A, et al. Nongenomic effects of 17β-estradiol in human platelets: potentiation of thrombin-induced aggregation through estrogen receptor β and Src kinase. Blood. 2005;105(1):115-21.

40. Holmes CE, Huang JC, Pace TR, Howard AB, Muss HB. Tamoxifen and aromatase inhibitors differentially affect vascular endothelial growth factor and endostatin levels in women with breast cancer. Clin Cancer Res. 2008;14(10):3070-6.

41. Holmes CE, Jasielec J, Levis JE, Skelly J, Muss HB. Initiation of aspirin therapy modifies angiogenic protein levels in women with breast cancer receiving tamoxifen therapy. Clin Transl Sci. 2011;4(5):386-90.

42. Cheng R, Liu YJ, Cui JW, Yang M, Liu XL, Li P, et al. Aspirin regulation of c-myc and cyclinD1 proteins to overcome tamoxifen resistance in estrogen receptor-positive breast cancer cells. Oncotarget. 2017;8(18):30252-64.

43. Duveymos CV, Yeo AA, Wong M, Cox DA, Kim HM. Antplatelet therapy use and the risk of venous thromboembolic events in the Raloxifene Use for the Heart (RUTH) trial. J Womens Health (Larchmt). 2010;19(8):1459-65.

44. Holmes MD, Chen WY, Li L, Fichandler CE, Spiegelman D, Haffner S, et al. Aspirin intake and breast cancer survival - a nation-wide study using prospectively recorded data in Sweden. BMC Cancer. 2014 Jun 2;14:202.

45. Muir H, Brandt S, Koster MP, Atkinson C, Newby D, Riddel B. Aspirin use and survival after breast cancer. J Clin Oncol. 2017;35(9):1008-10.
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49. Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol. 2012;23(6):1403-15.

50. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol. 2012;13(5):518-27.

51. Li Y, Brasky TM, Nie J, Ambrosone CB, McCann SE, Shields PG, et al. Use of nonsteroidal anti-inflammatory drugs and survival following breast cancer diagnosis. Cancer Epidemiol Biomarkers Prev. 2012;21(1):239-42.

52. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomized trials. Lancet. 2011;377(9759):31-41.

53. Harris RE, Kasbari S, Farrar WB. Prospective study of nonsteroidal anti-inflammatory drugs and breast cancer. Oncol Rep. 1999;6:71-3.

54. Cuzick J, Otto F, Baron JA, Brown PH, Burn J, Greenwald P, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol. 2009;10(5):501-7.

55. Elwood PC, Morgan G, Pickering JE, Galante J, Weightman AL, et al. Aspirin in the treatment of cancer: reductions in metastatic spread and in mortality: a systematic review and meta-analyses of published studies. PLoS One. 2016;11(4):e0152402.

56. Chen WY, Holmes MD. Role of aspirin in breast cancer survival. Curr Oncol Rep. 2017;19(7):48.