Comparison of Changes in Lipid Profiles of Eastern Chinese Premenopausal Women with Early-Stage Breast Cancer Treated with Different Endocrine Therapy: A Retrospective Study

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Research Article

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Comparison of Changes in Lipid Profiles of Eastern Chinese Premenopausal Women with Early-Stage Breast Cancer Treated with Different Endocrine Therapy: A Retrospective Study

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Abstract

Background: Adjuvant endocrine therapy improves the prognosis of early breast cancer with hormone receptor positivity. However, there is no systematic report on the effect of endocrine therapy (especially ovarian function suppression, OFS) on serum lipids in premenopausal women. This retrospective cohort study aimed to determine whether various endocrine treatments had different effects on blood lipids in young premenopausal breast cancer patients.

Methods: This study enrolled 160 premenopausal patients with stage I-III breast cancer in eastern China. The initial diagnostic information was retrieved from patient's medical records, including age at the time of diagnosis, tumor characteristics, anticancer treatment, weight and

height, and past medical history. They have no history of cardiovascular disease. The changes of blood lipids in the types of endocrine therapy were compared at the 3rd, 6th, 12th, and 24th months after the start of endocrine therapy. Generalized Linear Mixed Model (GLMM) was used in analyses

Results: Our data revealed that LDL-C of patients with TAM group in the 6th, 12th, and 24th months was significantly lower than that in the 3rd month, while HDL-C in the 6th, 12th, and 24th months was significantly higher than that in the 3rd month, indicating that blood lipid levels generally improved with time. While in TAM plus OFS group, HDL-C in the 24th month was significantly higher than that in the 3rd month, TC in the 24th month was significantly higher than that in the 6th month. The lipid profiles of OFS plus AI group did not show significant differences at any time point but were significantly higher than those of the other two groups.

Conclusions: TAM group tended to have lower serum lipid levels. With longer follow-up, no statistically significant difference in values at various time points was observed between TAM and TAM plus OFS groups. Compared with the other two groups, OFS plus AI group presented an increasing trend toward LDL-C and TC. The risk of dyslipidemia requires further investigation using a large sample size.

Keywords: breast cancer; aromatase inhibitors; serum lipids; ovarian function suppression

Background

The International Agency for Research on Cancer（IARC）recently released the latest global cancer burden data for 2020[1]. Breast cancer (BC) now accounts for nearly 2.26 million new cases worldwide, surpassing lung cancer to become the most common cancer in the world. The incidence and mortality rate of breast cancer both rank the first in female malignant tumors in China [2], and hormone receptor-positive (HR+) breast carcinoma is the most common subtype accounting for 60% of all breast cancers [3]. Adjuvant endocrine therapy should be used in patients with HR+ BC to reduce the risk of disease progression and recurrence[4]. Endocrine therapy for premenopausal breast cancer patients, including tamoxifen, ovarian function suppression, and aromatase inhibitors, are based on lowering circulating estrogen levels. However, previous research indicates that oestrogens possess a cardiovascular protective effect [5]. Reduced oestrogen levels may result in dyslipidemia, which increases the risk of cardiovascular disease, and atherosclerotic cardiovascular disease (ASCVD) incidence increased rapidly concurrently[6]. With the improvement of postoperative survival rate of BC patients, it is critical to pay adequate attention to chronic diseases such as dyslipidemia and cardiovascular disease [7]. Cardiovascular disease-related death has become the first cause of death in BC patients, especially in postmenopausal women[8]. Some hormone receptor-positive postmenopausal BC patients receive aromatase inhibitors (AIs) as endocrine therapy[9]. Numerous studies have demonstrated that postmenopausal breast cancer women treated with aromatase inhibitors had an increased risk of heart failure and cardiovascular events through elevated serum lipids [10]. There is evidence that

hypercholesterolemia during AIs treatment may reduce the desired outcome of AIs [11]. Also, the primary metabolite of cholesterol can regulate estrogen receptor activity [12]. However, no large-scale study has been conducted on the impact of endocrine therapy (especially OFS) on blood lipids in premenopausal BC patients [13]. This study retrospectively analyzed lipid profiles of premenopausal BC patients who received different endocrine therapies in eastern China.

Material and Methods

Study Participants and Design

We retrospectively analyzed premenopausal women with early-stage breast cancer who started endocrine therapy in the Second Affiliated Hospital of Zhejiang University from January 1, 2013, to December 31, 2017. Eligible patients were premenopausal, had hormone receptor-positive early-stage breast cancer, and received tamoxifen (TAM), ovarian function suppression (OFS) with TAM or OFS with an aromatase inhibitor (AI) as initial adjuvant endocrine therapy (Fig 1). Exclusion criteria included patients who suffered from another malignancy or tumor recurrence [14], patients with dyslipidemia, certain cardiovascular disease (including coronary artery disease, stroke, and hypertensive heart disease), diabetes mellitus combined with target organ damage, and chronic kidney disease, smokers, and patients taking lipid-altering drugs. Patients were excluded from this lipid analysis if the lipid profile data were unavailable for any time points, including 3, 6, 12, and 24 months after

endocrine treatment initiation.

Patients were stratified based on which type of endocrine therapy they were taking during a 2-year follow-up, including TAM, tamoxifen plus ovarian suppression (OFS plus TAM), and aromatase inhibitor plus ovarian suppression (OFS plus AI). For each patient at baseline, we obtained medication history, disease history, physical examinations, laboratory test results, pathological results, and immunohistochemistry results (Table 1). We then collected blood lipid indexes tested in the Second Affiliated Hospital of Zhejiang University. Following that, we analyzed the levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) at the four times. Researchers recommended that participants with sharply elevated blood lipid levels seek clinical consultation from the cardiovascular department during follow-up (3, 6, 12, and 24 months after initiation of endocrine treatment). Patients were excluded if they had apparent dyslipidemia or other symptoms requiring treatment during follow-up, and we would advise them to seek medical attention in a timely manner.

Table 1. Patient and Treatment Characteristics

Characteristics	**TAM (N=112)** N(%)	**TAM+OFS (N=37)** N(%)	**OFS+AI (N=11)** N(%)
Age （Median[IQR]）	43[41-47]	38[34-42]	40[37-46]
BMI （Mean±SD）	21.95±2.56	22.15±2.72	21.52±2.97
Surgery			
conserving	56 （50）	14 (37.84)	5 (45.45)
mastectomy	56 （50）	23 (62.16)	6 (54.55)
T(tumor)			
T1	81 (72.32)	24 (64.86)	9 (81.82)
T2	25 (22.32)	13 (35.14)	1 (9.09)
T3	3 （2.68）	0	1 (9.09)
unknown	3 （2.68）	0	0

N(node)			
N0	78 (69.64)	17(45.95)	9 (81.82)
N1	31 (27.68)	19(51.35)	2 (18.18)
N2	0	1(2.70)	0
unknown	3 (2.68)	0	0
HER2			
+	88(78.57)	33(89.19)	10 (90.91)
-	24(21.43)	4(10.81)	1 (9.09)
Radiotherapy			
Yes	72(64.29)	25(67.57)	10 (90.91)
No	40(35.71)	12(32.43)	1 (9.09)
Chemotherapy			
Yes	97(86.61)	37(100)	10(90.91)
No	15(13.39)	0	1 (9.09)

Methods

Direct methods were employed to measure LDL-C and HDL-C levels. Serum TG was detected using glycerol-phosphoric acid oxidase peroxidase method, and TC was detected using cholesterol oxidase method.

Statistical Analyses

Basic descriptive statistics, including mean and standard deviation (SD), were utilized to characterize study participants. Generalized Linear Mixed Model (GLMM) compares lipid level variables with different endocrine therapies at different time points. Statistical analyses were performed using SPSS 25.0 for Windows. $P < 0.05$ was considered statistically significant.

Results

Study Population

Of 631 women enrolled in the study, 160 possessed complete follow-up. The baseline characteristics for individual TAM (n = 112), OFS plus TAM (n = 37), and OFS plus AI (n = 11) groups are presented in Table1. 5-year tamoxifen administration was the first recommendation for adjuvant endocrine treatment of early breast cancer, implying the high number of people in the tamoxifen group.

Lipid Profiles

We analyzed the time point of the third month after starting endocrine therapy, and no significant difference (P>0.05) in the blood lipid profile was observed among the groups. Accordingly, we take the blood lipid at the third month as the baseline to explore long-term change trend. For these three different endocrine treatments, the average and standard deviation of blood lipid spectrum are displayed in Table 2.

During endocrine therapy, the overall TC at the 24th month was significantly higher than that at the other three time points (P<0.05), and the average TC value of OFS plus AI group at the 12th month was 5.10 mmol/L, significantly higher than that of TAM (4.53 mmol/L, P=0.048) and TAM plus OFS (4.45 mmol/L, P=0.041) groups at the same period. Similarly, TC value of OFS plus AI group at the 24th month was 5.36 mmol/L, significantly higher than that of TAM (4.54 mmol/L, P=0.007) and TAM plus OFS (4.60mmol/L, P=0.019) groups. TC value of TAM plus OFS group at the 24th month (4.60 mmol/L) was significantly higher than that at the 6th month (4.39 mmol/L, P=0.043), and TC value of OFS plus AI group at the 24th (5.36 mmol/L) month was significantly higher than that at the 3rd (4.88 mmol/L, P=0.014) and 6th months (4.91 mmol/L, P=0.017).

The average HDL-C value in TAM group at 24th months (1.51mmol/L) was significantly higher

than that at 3rd (1.38mmol/L, P<0.001), 6th (1.40 mmol/L, P<0.001), and 12th months (1.43 mmol/L, P<0.001), and HDL-C value at 12 months was significantly higher than that at 3 months (P=0.018). The average HDL-C of TAM group respectively showed a gradually increasing trend. The average HDL-C value in TAM plus OFS group at the 3rd month (1.42 mmol/L) was significantly lower than that at the 24th month (1.51 mmol/L, P=0.015).

LDL-C values of OFS plus AI group were significantly higher than those of TAM plus OFS (P=0.009) and TAM groups (P=0.007) as a whole. Average LDL-C values of OFS plus AI group demonstrated a gradually increasing trend, while LDL-C values of TAM group at the 3rd month were significantly higher than those at the later observation time points (P<0.05). Different groups revealed an opposite trend (Figure2). LDL-C level remained stable at all time points in OFS plus TAM group.

In addition, no significant difference in the absolute value of TG was observed between the three groups at each evaluation point and among different regiments, but all fluctuated within a small range.

Discussion

Tamoxifen has been the gold standard of adjuvant endocrine therapy for premenopausal BC patients with relatively low risk of recurrence [15]. As known, it has been confirmed that LDL-C is independently associated with CVD risk [16]. Our data reveal that LDL-C of patients with TAM group in the 6th, 12th, and 24th months is significantly lower than that in the 3rd month, and HDL-C in the 6th, 12th, and 24th months is significantly higher than that in the 3rd month.

Generally, the overall blood lipid level improves over time with tamoxifen treatment， which is in accordance with previous reports. Numerous studies have demonstrated that TAM improves lipoprotein metabolism [17]. Tamoxifen use has been associated with decreased LDL-C and TC levels and an increase in the relative amount of HDL-C. Vehmanen L et al. stated that adjuvant tamoxifen therapy initiated following chemotherapy decreased the increased TC and LDL-C concentrations to pre-chemotherapy levels, whereas TC and LDL-C remained elevated in the control group (no endocrine or other therapy) [18]. Additionally, EBCTCG data indicated that adjuvant tamoxifen reduced non-breast cancer mortality by 12%± 6%probably due to tamoxifen's effects in preserving bone mineral density and reducing TC levels and cardiovascular events. The lipid profile changes associated with tamoxifen use may significantly reduce mortality from coronary artery disease [19]. According to data from Scottish adjuvant tamoxifen trial, tamoxifen may reduce the incidence of fatal myocardial infarction in postmenopausal women compared with control patients， as well as a significant reduction in the incidence of hospital admissions for cardiac disease in postmenopausal women treated with tamoxifen compared with controls [20]. Similarly, another clinical study demonstrated that toremifene might be beneficial in reducing cardiovascular risk [21]. At the Royal Marsden Hospital, a blinded randomized study comparing tamoxifen 20 mg daily to placebo in 200 healthy women demonstrated that tamoxifen significantly reduced serum TC and LDL-C in premenopausal women [22]. These studies corroborate our findings. Although only a few patients used toremifene as an endocrine drug, some studies indicate that tamoxifen and toremifene appear to have the opposite effect on LDL-C and TC[23].

With a longer follow-up, no statistically significant difference in values at various time points was observed between the TAM group and TAM plus OFS group. A clinical trial has revealed no statistically significant differences in blood lipid levels between TAM-alone and goserelin plus TAM groups [24]. That is in accordance with our data. We conjecture that the positive effects of TAM compensated for adverse effects of OFS.

What is more, we are much more concerned on changes in lipid profiles in OFS plus AI group. During follow-up of long-term endocrine therapy (24 months), there were no significant differences in the lipid profiles of the OFS plus AI group at any time point, but LDL-C values exhibited with an upward trends . Serum TC and LDL-C were significantly higher in patients treated with OFS plus AI than the other two groups (TAM group and TAM plus OFS group), implying a potential risk of dyslipidemia. The large-scale phase III prospective study SOFT trial reveals that 66% of premenopausal patients treated with exemestane plus triptorelin exhibited a profound, persistent reduction in E2 levels during the first 12 months of treatment, significantly greater than in tamoxifen plus triptorelin group at all time points [25]. This could be a contributing factor to dyslipidemia. However, the number of enrolled patients in OFS plus AI group was small, influencing the statistical conclusions.

Compared with tamoxifen, AI use was associated with an increased cumulative risk of cardiovascular disease [26]. ITA and ACTC trials demonstrated that hypercholesterolemia was significantly more prevalent in anastrozole group over tamoxifen group among postmenopausal patients [27], although the latter did not indicate an increased incidence of

cardiovascular events [28]. However, no significant difference in the rate of cardiovascular events was observed between letrozole and placebo groups, and no drug-related hypercholesterolemia was reported [29]. In some animal and clinical studies, exemestane has shown minimal adverse effects among AIs on lipid metabolism [30]. Premenopausal women will not benefit from these clinical trial findings because their hormone levels are higher than postmenopausal women [31]. Using AIs could theoretically increase the risk of dyslipidemia in premenopausal women whose hormones have reached menopausal levels following OFS therapy. Our study observed increased lipid levels in this group compared with the other two groups and at each observation point. However, the absence of a significant difference at each time point in OFS plus AI group could be explained by the fact that this group consisted of only too small samples. On the other hand, different AIs may have varying effects on blood lipids [32] and other safety concerns [33]. According to some studies, anastrozole is less toxic than exemestane and letrozole, consistent with previous reports [34]. AIs are associated with more CVD risk than tamoxifen [35].

TAM protects blood lipids during endocrine therapy, probably because its structure is similar to that of estrogen. It can compete with estradiol for estrogen receptor, form a stable complex with estrogen receptor, and perform an estrogenic function. Extensive evidence indicates that estrogen has a positive effect on blood lipids [36], consistent with existing research results. This introduces a novel concept into clinical decision-making. This was a prospective clinical study comparing effects with exemestane plus ovarian suppression versus tamoxifen plus ovarian suppression, and dyslipidemia or CVD were not listed in adverse events of grade 3 or

4 [37]. However, if a patient possesses a high risk of cardiovascular diseases, such as smoking, hypertension, hyperglycemia [38], and obesity, clinicians may consider TAM an endocrine therapy when the risk of recurrence is similar. Estrogen receptor genotyping may help predict which premenopausal women would benefit more from tamoxifen [39]. When BC patients experience significant weight gain or are diagnosed with abnormal lipid metabolism during adjuvant endocrine treatment, short-term interventions such as behavior improvement (diet/exercise) can benefit BMI and blood lipids[40]. Even using long-term statin can improve OS and DFS. Although a high lipid level may be a favorable prognostic factor, the increased risk of CVD was detrimental[41].

Conclusions:

For premenopausal hormone receptor-positive BC patients, TAM endocrine therapy demonstrated significant short- and long-term protective effects on serum lipids, as evidenced by a gradual decrease in LDL-C and increased HDL-C with prolonged medication time. No statistically significant difference in lipid profiles was observed between follow-up time points with OFS plus TAM treatment. OFS plus AI group revealed significantly higher TC and LDL-C levels at almost all time points compared with the above two treatments, suggesting that the combined treatment had a detrimental effect and may increase the risk of cardiovascular events. Different endocrine drugs and standard combinations will affect serum lipids, providing us with a starting point for further investigation.

The sample size remains small, highlighting the need for its expansion for further assessment,

such as a comparison among OFS plus different AIs. Steroidal and non-steroidal AIs differ in chemical structure and mechanism, which may affect blood lipids[42]. As a result, randomized controlled trials are required to verify existing findings[43]. Generally, long-term management and follow-up are necessary to improve survival[44].

Abbreviations:

HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
GLMM	Generalized Linear Mixed Model
TAM	tamoxifen
TC	cholesterol
HR+	hormone receptor-positive
TG	triglyceride
AI	aromatase inhibitor
OFS	ovarian function suppression
BC	breast cancer
IARC	The International Agency for Research on Cancer
ASCVD	atherosclerotic cardiovascular disease

Declarations:

Ethics approval and consent to participate

The institutional review board of the Second Affiliated Hospital of Zhejiang University approved the study. All procedures performed in studies involving human participants were in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Authors' contributions

WT and KW contributed equally to this work. SZ and WT came up with the idea, KW and LS analyzed most of the data. KW drafted the manuscript. YW was a contributor in organizing the database and study. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset analyzed in this study can be reasonably obtained from the corresponding author.

Consent for publication

All authors agree to publish this article in the Journal of Lipids in Health and Disease.

Competing interests

The authors declare that they have no conflict of interest.

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1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: **Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.** *CA Cancer J Clin* 2021, **71:**209-249.

2. Liu T, Song S, Wang X, Hao J: **Small-molecule inhibitors of breast cancer-related**

targets: Potential therapeutic agents for breast cancer. *Eur J Med Chem* 2021, **210:**112954.

3. Roberto M, Astone A, Botticelli A, Carbognin L, Cassano A, D'Auria G, Fabbri A, Fabi A, Gamucci T, Krasniqi E, et al: **CDK4/6 Inhibitor Treatments in Patients with Hormone Receptor Positive, Her2 Negative Advanced Breast Cancer: Potential Molecular Mechanisms, Clinical Implications and Future Perspectives.** *Cancers (Basel)* 2021, **13**.

4. Collin LJ, Cronin-Fenton D, Ahern TP, Goodman M, McCullough LE, Waller LA, Kjaersgaard A, Damkier P, Christiansen PM, Ejlertsen B, et al: **Early discontinuation of endocrine therapy and recurrence of breast cancer among premenopausal women.** *Clin Cancer Res* 2020.

5. Ouyang P, Michos ED, Karas RH: **Hormone replacement therapy and the cardiovascular system lessons learned and unanswered questions.** *J Am Coll Cardiol* 2006, **47:**1741-1753.

6. Akyol M, Alacacioglu A, Demir L, Kucukzeybek Y, Yildiz Y, Gumus Z, Kara M, Salman T, Varol U, Taskaynatan H, et al: **The alterations of serum FGF-21 levels, metabolic and body composition in early breast cancer patients receiving adjuvant endocrine therapy.** *Cancer Biomark* 2017, **18:**441-449.

7. He T, Yang W, Zhang X, Li P, Yang D, Wu Y, Fan Y, Xiang M, Huang Q, Chen J, et al: **Comparative effectiveness of tamoxifen, toremifene, letrozole, anastrozole, and exemestane on lipid profiles in breast cancer patients: A network meta-analysis.** *Medicine (Baltimore)* 2020, **99:**e18550.

8. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD: **Cardiovascular disease**

competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Res* 2011, **13:**R64.

9. Anagnostis P, Bitzer J, Cano A, Ceausu I, Chedraui P, Durmusoglu F, Erkkola R, Goulis DG, Hirschberg AL, Kiesel L, et al: **Menopause symptom management in women with dyslipidemias: An EMAS clinical guide.** *Maturitas* 2020, **135:**82-88.

10. Franchi M, Tritto R, Tarantini L, Navazio A, Corrao G: **Adjuvant Hormonotherapy and Cardiovascular Risk in Post-Menopausal Women with Breast Cancer: A Large Population-Based Cohort Study.** *Cancers (Basel)* 2021, **13**.

11. Borgquist S, Giobbie-Hurder A, Ahern TP, Garber JE, Colleoni M, Lang I, Debled M, Ejlertsen B, von Moos R, Smith I, et al: **Cholesterol, Cholesterol-Lowering Medication Use, and Breast Cancer Outcome in the BIG 1-98 Study.** *J Clin Oncol* 2017, **35:**1179-1188.

12. Nelson ER: **The significance of cholesterol and its metabolite, 27-hydroxycholesterol in breast cancer.** *Mol Cell Endocrinol* 2018, **466:**73-80.

13. Lintermans A, Neven P: **Safety of aromatase inhibitor therapy in breast cancer.** *Expert Opin Drug Saf* 2015, **14:**1201-1211.

14. Li X, Liu ZL, Wu YT, Wu H, Dai W, Arshad B, Xu Z, Li H, Wu KN, Kong LQ: **Status of lipid and lipoprotein in female breast cancer patients at initial diagnosis and during chemotherapy.** *Lipids Health Dis* 2018, **17:**91.

15. Montemurro F, Perrone F, Geuna E: **Adjuvant ovarian suppression in premenopausal breast cancer.** *N Engl J Med* 2015, **372:**1672-1673.

16. Verbeek R, Hoogeveen RM, Langsted A, Stiekema LCA, Verweij SL, Hovingh GK, Wareham NJ, Khaw KT, Boekholdt SM, Nordestgaard BG, Stroes ESG: **Cardiovascular disease risk associated with elevated lipoprotein(a) attenuates at low low-density lipoprotein cholesterol levels in a primary prevention setting.** *Eur Heart J* 2018, **39:**2589-2596.

17. Gaibar M, Fernandez G, Romero-Lorca A, Novillo A, Tejerina A, Bandres F, Fernandez-Santander A: **Tamoxifen therapy in breast cancer: do apolipoprotein E genotype and menopausal state affect plasma lipid changes induced by the drug?** *Int J Biol Markers* 2013, **28:**e371-376.

18. Vehmanen L, Saarto T, Blomqvist C, Taskinen MR, Elomaa I: **Tamoxifen treatment reverses the adverse effects of chemotherapy-induced ovarian failure on serum lipids.** *Br J Cancer* 2004, **91:**476-481.

19. Janni W, Hepp P: **Adjuvant aromatase inhibitor therapy: outcomes and safety.** *Cancer Treat Rev* 2010, **36:**249-261.

20. Jaiyesimi IA, Buzdar AU, Decker DA, Hortobagyi GN: **Use of Tamoxifen for Breast-Cancer - 28 Years Later.** *Journal of Clinical Oncology* 1995, **13:**513-529.

21. Erkkola R, Mattila L, Powles T, Heikkinen J, Toivola B, Korhonen P, Mustonen M: **Bone mineral density and lipid changes during 5 years of follow-up in a study of prevention of breast cancer with toremifene in healthy, high-risk pre- and post-menopausal women.** *Breast Cancer Res Treat* 2005, **93:**277-287.

22. Powles TJ, Jones AL, Ashley SE, O'Brien ME, Tidy VA, Treleavan J, Cosgrove D, Nash AG, Sacks N, Baum M, et al.: **The Royal Marsden Hospital pilot tamoxifen chemoprevention trial.** *Breast Cancer Res Treat* 1994, **31:**73-82.

23. Vogel CL, Johnston MA, Capers C, Braccia D: **Toremifene for breast cancer: a review of 20 years of data.** *Clin Breast Cancer* 2014, **14:**1-9.

24. Yang H, Zong X, Yu Y, Shao G, Zhang L, Qian C, Bian Y, Xu X, Sun W, Meng X, et al: **Combined effects of goserelin and tamoxifen on estradiol level, breast density, and endometrial thickness in premenopausal and perimenopausal women with early-stage hormone receptor-positive breast cancer: a randomised controlled clinical trial.** *Br J Cancer* 2013, **109:**582-588.

25. Bellet M, Gray KP, Francis PA, Lang I, Ciruelos E, Lluch A, Climent MA, Catalan G, Avella A, Bohn U, et al: **Twelve-Month Estrogen Levels in Premenopausal Women With Hormone Receptor-Positive Breast Cancer Receiving Adjuvant Triptorelin Plus Exemestane or Tamoxifen in the Suppression of Ovarian Function Trial (SOFT): The SOFT-EST Substudy.** *J Clin Oncol* 2016, **34:**1584-1593.

26. Ramchand SK, Lim E, Grossmann M: **Adjuvant endocrine therapy in women with oestrogen-receptor-positive breast cancer: how should the skeletal and vascular side effects be assessed and managed?** *Clin Endocrinol (Oxf)* 2016, **85:**689-693.

27. Boccardo F, Rubagotti A, Guglielmini P, Fini A, Paladini G, Mesiti M, Rinaldini M, Scali S, Porpiglia M, Benedetto C, et al: **Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial.** *Ann Oncol* 2006, **17 Suppl 7:**vii10-14.

28. Williams N: **Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial.** *Lancet Oncology* 2008, **9:**45-53.

29. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Tu D,

Shepherd LE, Pritchard KI, et al: **A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Engl J Med* 2003, **349:**1793-1802.

30. Carpenter R, Miller WR: **Role of aromatase inhibitors in breast cancer.** *Br J Cancer* 2005, **93 Suppl 1:**S1-5.

31. Kawase T, Matsuo K, Suzuki T, Hirose K, Hosono S, Watanabe M, Inagaki M, Iwata H, Tanaka H, Tajima K: **Association between vitamin D and calcium intake and breast cancer risk according to menopausal status and receptor status in Japan.** *Cancer Sci* 2010, **101:**1234-1240.

32. McCloskey EV, Hannon RA, Lakner G, Fraser WD, Clack G, Miyamoto A, Finkelman RD, Eastell R: **Effects of third generation aromatase inhibitors on bone health and other safety parameters: results of an open, randomised, multi-centre study of letrozole, exemestane and anastrozole in healthy postmenopausal women.** *Eur J Cancer* 2007, **43:**2523-2531.

33. Smith I, Yardley D, Burris H, De Boer R, Amadori D, McIntyre K, Ejlertsen B, Gnant M, Jonat W, Pritchard KI, et al: **Comparative Efficacy and Safety of Adjuvant Letrozole Versus Anastrozole in Postmenopausal Patients With Hormone Receptor-Positive, Node-Positive Early Breast Cancer: Final Results of the Randomized Phase III Femara Versus Anastrozole Clinical Evaluation (FACE) Trial.** *J Clin Oncol* 2017, **35:**1041-1048.

34. Tian W, Wu M, Deng Y: **Comparison of Changes in the Lipid Profiles of Eastern Chinese Postmenopausal Women With Early-Stage Breast Cancer Treated With Different Aromatase Inhibitors: A Retrospective Study.** *Clin Pharmacol Drug Dev* 2018, **7:**837-

843.

35. Zhao X, Liu L, Li K, Li W, Zhao L, Zou H: **Comparative study on individual aromatase inhibitors on cardiovascular safety profile: a network meta-analysis.** *Onco Targets Ther* 2015, **8:**2721-2730.

36. Dnistrian AM, Schwartz MK, Greenberg EJ, Smith CA, Schwartz DC: **Effect of tamoxifen on serum cholesterol and lipoproteins during chemohormonal therapy.** *Clin Chim Acta* 1993, **223:**43-52.

37. Pagani O, Regan MM, Walley BA, Fleming GF, Colleoni M, Lang I, Gomez HL, Tondini C, Burstein HJ, Perez EA, et al: **Adjuvant exemestane with ovarian suppression in premenopausal breast cancer.** *N Engl J Med* 2014, **371:**107-118.

38. Chia CW, Egan JM, Ferrucci L: **Age-Related Changes in Glucose Metabolism, Hyperglycemia, and Cardiovascular Risk.** *Circ Res* 2018, **123:**886-904.

39. Ntukidem NI, Nguyen AT, Stearns V, Rehman M, Schott A, Skaar T, Jin Y, Blanche P, Li L, Lemler S, et al: **Estrogen receptor genotypes, menopausal status, and the lipid effects of tamoxifen.** *Clin Pharmacol Ther* 2008, **83:**702-710.

40. Suzuki H, Seki A, Hosaka T, Matsumoto N, Tomita M, Takahashi M, Yamauchi H: **Effects of a structured group intervention on obesity among breast cancer survivors.** *Breast Cancer* 2020, **27:**236-242.

41. Jung SM, Kang D, Guallar E, Yu J, Lee JE, Kim SW, Nam SJ, Cho J, Lee SK: **Impact of Serum Lipid on Breast Cancer Recurrence.** *J Clin Med* 2020, **9**.

42. Wang X, Zhu A, Wang J, Ma F, Liu J, Fan Y, Luo Y, Zhang P, Li Q, Xu B, Yuan P: **Steroidal aromatase inhibitors have a more favorable effect on lipid profiles than nonsteroidal**

aromatase inhibitors in postmenopausal women with early breast cancer: a prospective cohort study. *Ther Adv Med Oncol* 2020, **12:**1758835920925991.

43. Santa-Maria CA, Blackford A, Nguyen AT, Skaar TC, Philips S, Oesterreich S, Rae JM, Desta Z, Robarge J, Henry NL, et al: **Association of Variants in Candidate Genes with Lipid Profiles in Women with Early Breast Cancer on Adjuvant Aromatase Inhibitor Therapy.** *Clin Cancer Res* 2016, **22:**1395-1402.

44. Yeo W, Mo FKF, Pang E, Suen JJS, Koh J, Loong HHF, Yip CCH, Ng RYW, Yip CHW, Tang NLS, Liem GS: **Profiles of lipids, blood pressure and weight changes among premenopausal Chinese breast cancer patients after adjuvant chemotherapy.** *BMC Womens Health* 2017, **17:**55.

File name: Additional file 1.png

Title: Fig 1. Review the process of grouping.

File name: Additional file 2.png

Title: Fig 2. Low-Density Lipoprotein Cholesterol (LDL-C) levels Over Time

File name: Additional file 3.xls

Title: Table 2. Changes in Lipid Levels (Mean and Standard Deviation) From the Third Month to Each Time Point Among Patients with Different Endocrine Therapies

Figures

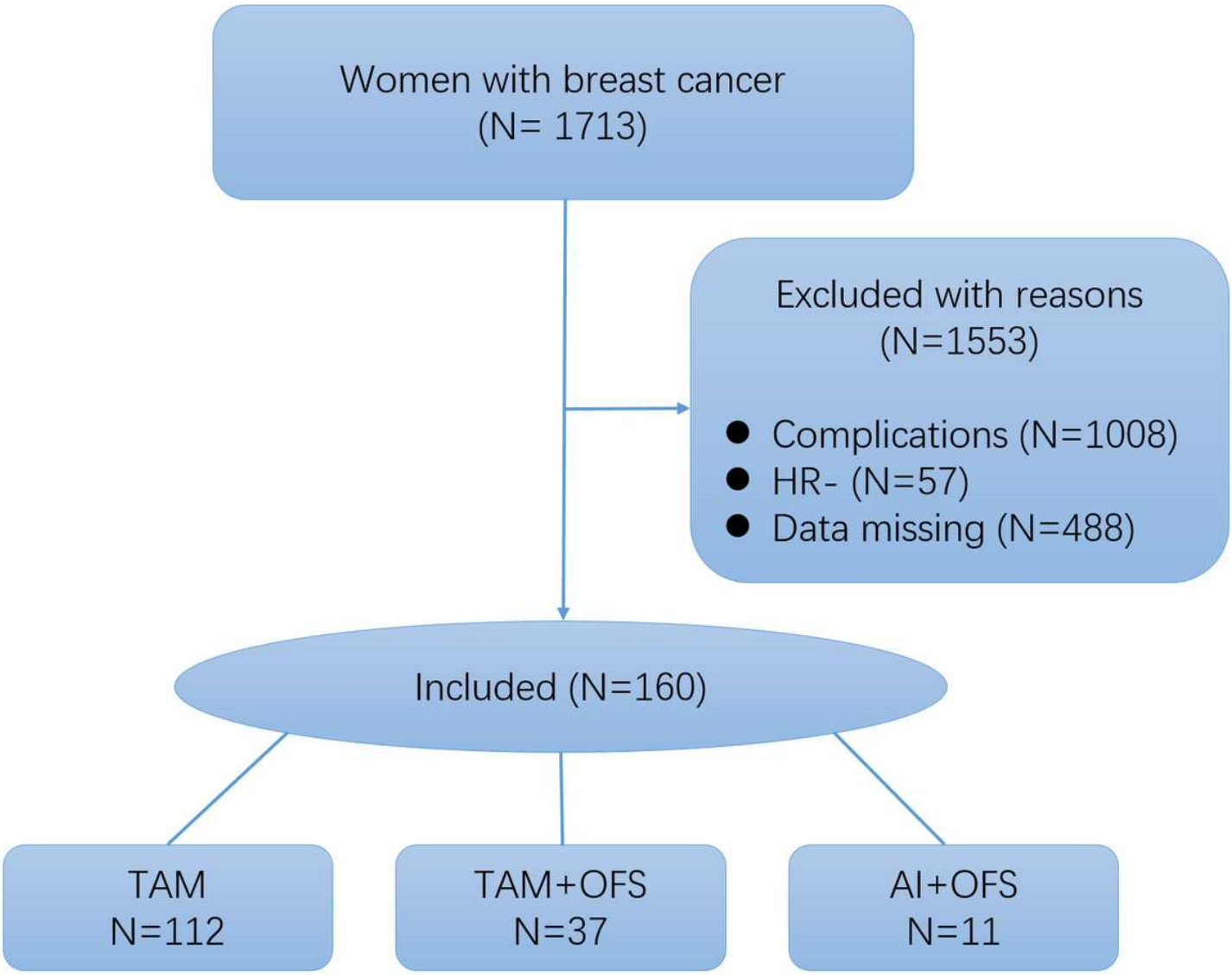

Figure 1

Review the process of grouping.

Figure 2. Low-Density Lipoprotein Cholesterol(LDL-C) levels Over Time

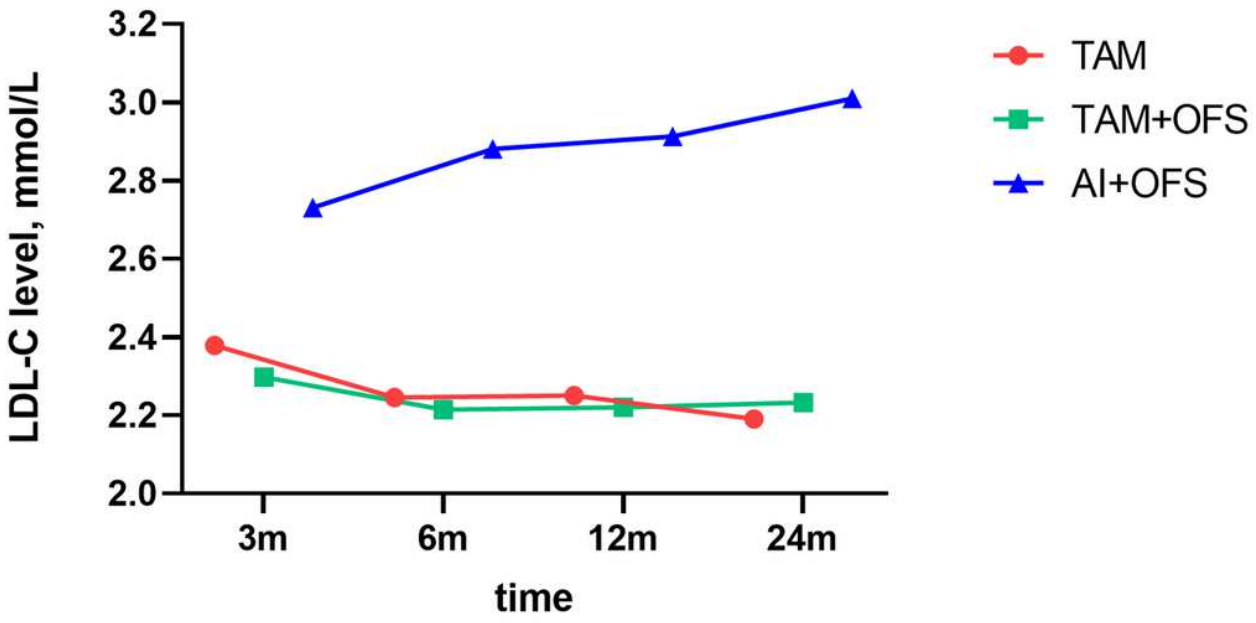

Figure 2

Low-Density Lipoprotein Cholesterol (LDL-C) levels Over Time