EFFECTS OF BREAST CANCER HORMONE TREATMENT ON LIPIDS AND SUBSEQUENT CARDIOVASCULAR DISEASES

by

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ABSTRACT

Selective estrogen receptor modulators (SERMs), the earliest breast cancer (BC) hormone treatment, improve survival of hormone positive (HR+) BC patients. Aromatase inhibitors (AIs) further prolong disease free survival (DFS) for postmenopausal HR+ BC patients, but their benefits in overall survival (OS) are inconclusive. An important factor that impacts OS but not DFS is non-BC death, and cardiovascular disease (CVD) is one of the major contributors. In addition to its high prevalence in the aging population, CVD may be associated with BC cancer treatment. BC hormone treatment influences serum estrogen concentration, which is related to the occurrence of CVD; therefore, it is critical to investigate the impact of BC hormone treatment on CVD, especially in the era when prolonged hormone treatment is increasingly popular in BC care.

This dissertation consists of 3 projects: 1) enhancement of an existing Bayesian Network Meta-analysis (NMA) method by allowing more reporting formats, so more studies may be included and expanding an existing consistency check of direct and indirect evidence for a NMA to include longitudinal data; 2) a Bayesian NMA exploring the effects of BC hormone drugs on changes of lipid profiles during hormone treatment; and 3) a study examining the effects of hormone treatment on dyslipidemia/coronary heart disease (CHD) throughout the whole course of BC treatment using electronic medical records.

The result from the second study showed that patients on SERMs had better lipid profiles and tended to reduce the risk of dyslipidemia/CHD. The third study revealed that the beneficial effects disappeared after discontinuing SERMs. NMA demonstrated that individual AIs impact changes of lipid profiles differently. However, the third study combining AIs as a whole did not reveal the significant impact on risk of dyslipidemia/CHD, which may be caused by mixed effects of individual AIs and insufficient statistical power due to few outcome events. The public health significance of this dissertation is to provide methods promoting applicability of NMA for longitudinal data, and to show the effects of BC hormone treatment on lipids and CHD. BC patients with pre-existing risk factors of CVD should be monitored more frequently when they are on hormone treatment.

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1.0 INTRODUCTION

Breast cancer (BC) is the most prevalent form of cancer in American women, with estimated 252,710 new cases and about 40,610 death to BC women in 2017[1,2]. While recent advances in cancer therapy have improved survival and quality of life, BC survivors now face long term effects of cancer treatments, especially when these coincide or accelerate chronic diseases of aging. This dissertation looks at the effects of BC treatment, selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs), on the long term cardiovascular health of post-menopausal BC survivors.

Coronary heart disease (CHD) is the most common type of cardiovascular disease (CVD) and is the leading cause of death in both men and women. The mortality rate is significantly lower in women before menopause, but the rate for post-menopausal women is close to men[3]. Menopause, with the drastic reduction in female sex hormones, corresponds to changes in CVD risk factors and may play an important role in the development and prognosis of CVDs[4]. Hormone receptor positive (HR+) BC is the major type of BC diagnosed in post-menopausal women and hormone therapy, interrupting either function or production of female sex hormones, is the most important long-term adjuvant treatment. Hormone therapy may impact levels of female sex hormones in post-menopausal BC patients and further deteriorate CVD risk factors.

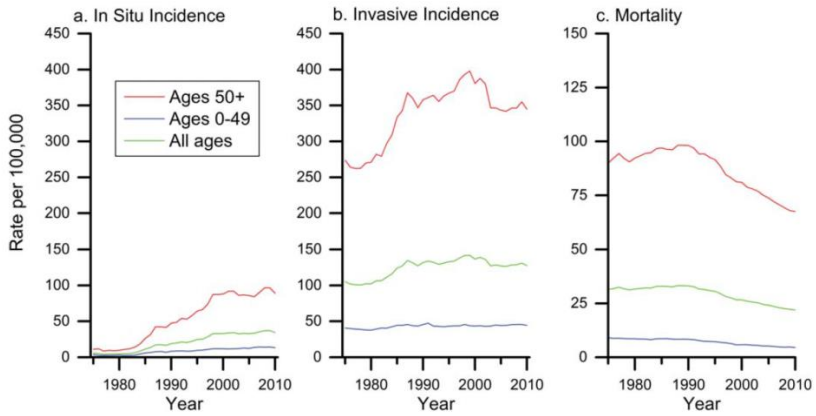
AIs are the main hormone therapies for HR+ breast cancer in post-menopausal patients and act by reducing production of estrogen. An alternate type of hormone therapy, SERM, blocks the function of estrogen on cancer cell proliferation. Several large-scale international clinical trials have shown that AIs improved disease free survival (DFS) in patients with early stage HR+ BC compared to the effect of SERMs; however, overall survival (OS) was not significantly improved by AIs[5]. These results imply more non-BC relapse mortality, or equivalently, higher mortality from non-BC causes in AI verses SERM treated BC survivors. Among the non-BC causes of mortality, CVD is one of the major non-BC recurrence cause of death in randomized clinical trials (RCT)[6]. Additionally, higher incidence of cardiovascular events in AI treated BC patients compared to those taking tamoxifen (a SERM drug) was reported in a meta-analysis study published in 2011[7]. One reason may be due to the association of estrogen and the worsening of lipid profiles[8,9], one of the risk factors of CVDs[10]. The major effect of AIs is to reduce serum estrogen level, and this depletion of estrogen may impact the cardiovascular system similar to menopause.

This dissertation includes the following: Chapter 1: Literature review of BC and CHDs; Chapter 2: The statistcal method that converts values at follow-up visits into changes from baseline; Chapter 3: Bayesian network meta-analysis of effects of BC hormone drugs on changes of lipid profiles during hormone treatment using the method proposed in Chapter 2; Chapter 4: Time-dependent BC hormone treatment on risk of subsequent CHDs in a hospital cohort. The overall goal of this dissertation is to compare differential effects of BC hormone drugs on lipid profiles and CHDs in long-term BC survivors.

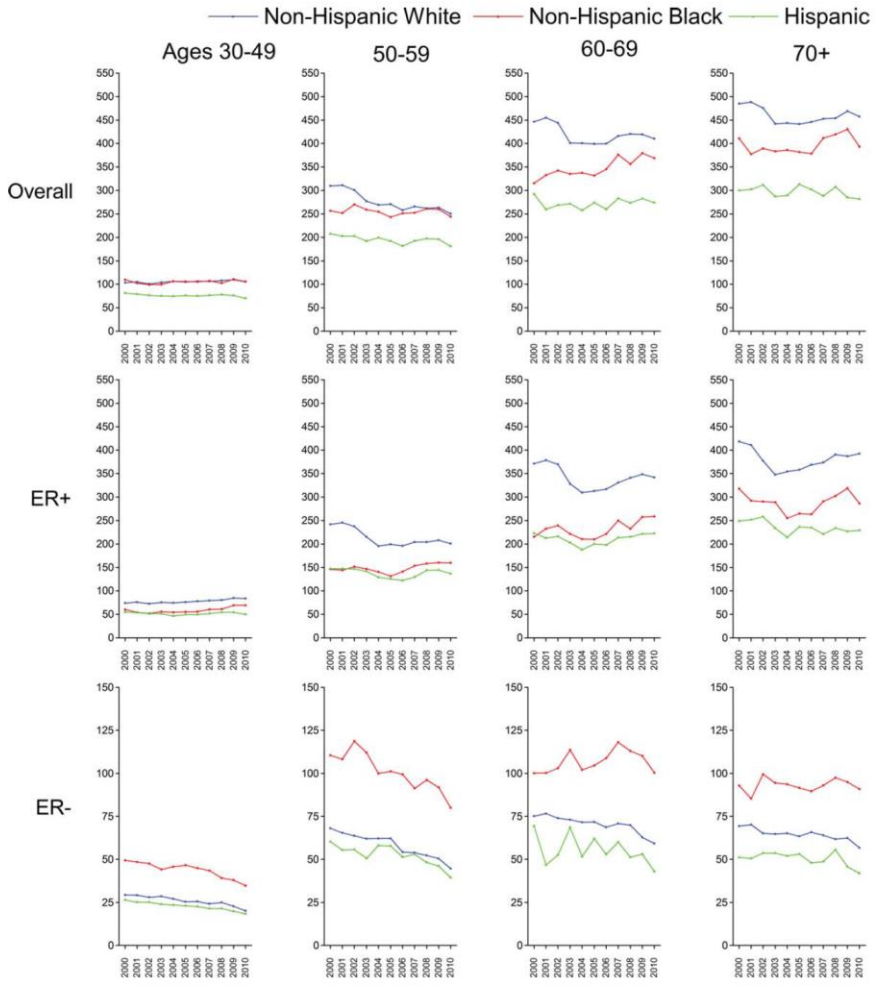
1.1 BREAST CANCER (BC)

1.1.1 Incidence, Mortality and Prevalence

It is estimated that approximately 252,710 new invasive BC cases and 40,610 BC deaths will occur in 2017[11]. Incidence rates of invasive BC increased between 1975 and 2000 in women who were over 50 years old, but incidence of in situ and invasive BC continued increasing since 1980 for all age groups (Figure 1 A, panel a, b). The rates increased rapidly in the 1980s due to popularity of mammography screening; more patients were diagnosed with early stage BC [12]. The incidence rate decreased about 7% between 2002 and 2003, which is believed to be related to discontinuing hormone replacement therapy (HRT) after the Women's Health Initiative randomized trial failed to prove benefits of HRT on preventing CVDs. The change in patterns of BC occurrence in the past 4 decades was mainly observed in women over 50 years old with estrogen receptor positive (ER+) breast cancer while the incidence of estrogen receptor negative (ER-) BC has been decreasing or relatively stable in the past decades, especially for non-Hispanic White women (Figure 1 B)[13–15].



(A) Incidence and mortality rates of female breast cancer by age, United States, 1975 to 2010



(B) Trends in female breast cancer incidence rates by age, race/ethnicity, 2000 to 2010

From DeSantis C, et al. CA Cancer J Clin (2014)[12]

Figure 1. Incidence, mortality, and trends of female breast cancer

Age and race are associated with incidence and subtypes of BC (Figure 1 B). Incidence rates of BC were significantly higher in women over 50 years old compared to women 30-49. In the last decade, non-Hispanic White women over 50 years old had the highest incidence rate compared to non-Hispanic Black and Hispanic women. In all age groups, the incidences of ER+ BC was highest in non-Hispanic White women. However, the incidence rate of ER- breast cancer was highest in non-Hispanic Black women. The incidence rate of ER- breast cancer decreased between 2000 and 2010, especialy for women 50-59 years of age. The incidence rates of ER+ and ER- breast cancers were similar in young women, ages between 30 and 49 years old[12].

During 1990 and 2010, the mortality rate was higher in women aged 50 years old and over compared to the younger population. The mortality rate in the elder population decreased across time (Figure 1 A, panel c). The annual mortality rate was similar in White and non-Hispanic Black women who were younger than 50 years old, but the mortality rate declined more in the white women aged 50 years old and over compared to the black women in the same age group [16]. Though the incidence rates of BC have been stable in the past decade, the mortality rates were continuously decreasing. The prevalence of BC has increased due to more BC survivors in the population [16].

1.1.2 Subtypes

Subtypes of BC are determined by characteristics of the cancer cells, and are closely associated with therapeutic options and survival outcomes. Previously, BC diagnosis mainly depended on histological features of breast cancer tissues (BC cell differentiation) and immunochemical tests (intensity of hormone receptor expression on cell surfaces) to predict prognosis and determine therapeutic strategies. Current technologies are able to identify mechanisms of BC carcinogenesis and molecular characteristics within BC cells, so the modern subtypes of BC are determined by the immunochemical features and expressions of specific genes, which provide information to determine the most effective treatment of BC and to predict prognoses[17].

The modern subtype classification of breast cancer is based on cellular expression of ER, Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2), and Ki-67 (Table 1).

Table 1. Subtypes of breast cancer (BC)

Subtype	Characteristics	Prevalence among BC cases (approximate)
Luminal A	ER+ and/or PR+ HER2 – Low Ki-67	30-70%
Luminal B	ER+ and/or PR+ HER2 + (or HER2- with high Ki-67)	10-20%
Triple negative/basal-like	ER- PR- HER2-	15-20%
HER2 type	ER- PR- HER2+	5-15%

ER: Estrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receptor 2

Adapted from articles of Voduc KD, et al.[18]; Howlader N, et al.[19]

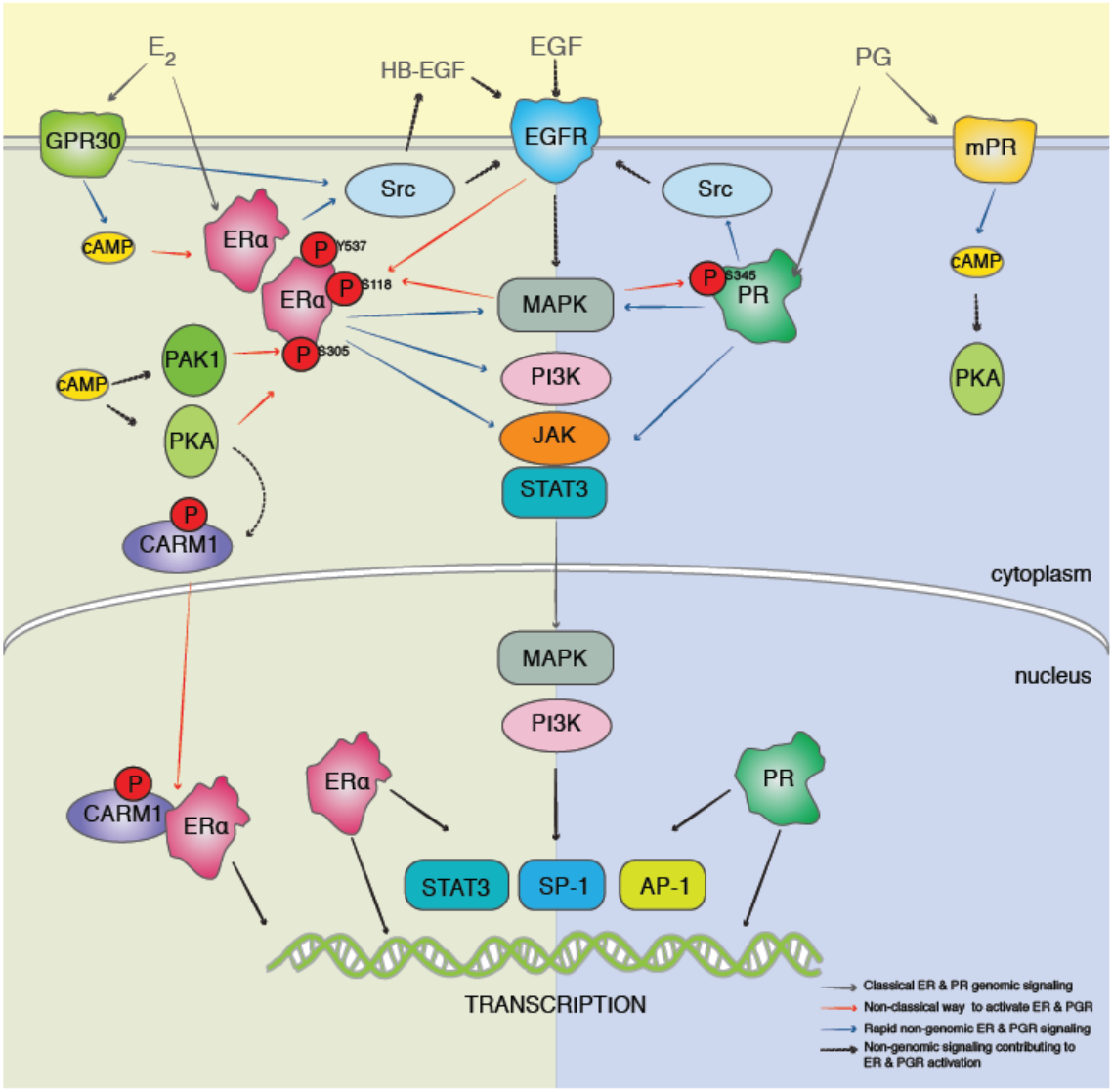
1.1.3 Estrogen Receptor (ER) and Progesterone Receptor (PR)

Estrogen controls cell proliferation via estrogen receptors (ER) in breast tissue. There are two types of ERs, ERα and ERβ. Compared to ERβ, ERα is the predominant form in breast tissue, especially ER+ BC, and is regulated by the distal promotor of ERα mRNA [20–22]. An *in vitro* study showed that ERα can stimulate cell proliferation in an autocrine manner for ERα+ breast cancer cell lines, which cannot be observed in normal mammary epithelial cells[23]. In addition, the proportion of ERα expression is higher in the dividing BC cells compared to the normal breast epithelial cells[24]. This overexpression of ERα in BC cells may be caused by upregulation of ERα via gene amplification or blocking degradation of ERα[25–27].

Transcription of PR genes can be generated by estrogen regulated promoters, leading ER and PR to be commonly expressed in the same cells; however, PR can still be independently expressed in human breast cells[24,28,29]. After being stimulated by progesterone, PR+ breast cells proliferate via a direct Cyclin D1-dependent mechanism (cell intrinsic signaling), and activate receptor activator of $Nf_{\kappa}B$ ligand (RANKL), which induces proliferation of neighboring PR- cells in a paracine manner[30–32]. Therefore, proliferation of the breast cell without PR can still be promoted by progesterone via PR+ cells.

ERα and PR can bind to deoxyribonucleic acid (DNA) of BC cells directly or indirectly by working with the other transcription factors and recruiting coactivators to impact transcription of the BC cell DNA[33–37]. The genomic action (classic pathway) requires ERα receptors to interact with an estrogen response element in the target genes. Genome-wide studies identified more than 5,000 target genes and the majority of the ER binding sites are located at distant regulatory elements and only 4% of them are in the promotor regions[38,39]. ERα/PR can also

induce DNA transcription via influencing signal pathways trigered by growth factor receptors and G-protein-coupled receptors (non-genomic signaling), e.g. Epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2)[40–47](Figure 2). ER/PR expression is the first identified feature that was used to determine BC prognosis and therapeutic strategies.



From Tanos et al. Breast Cancer Research (2012)[47]

Estrogen receptor (ER) and progesterone receptor (PR) can bind directly to DNA-specific sequences or indirectly by binding to other transcription factors. In addition, ERα and PR are able to activate several signaling pathways (mitogen-activated protein kinases (MAPKs),, JAK/STAT, SRC or phosphatidylinositol-3-kinase (PI3K)) (blue arrows). In parallel, epidermal growth factor receptor (EGFR) activation by epidermal growth factor (EGF) or mediated by ERα activates MAPKs, which in turn can phosphorylate and probably activate ERα or PR. Protein kinase A (PKA) and PAK phosphorylate and activate ERα (red arrows). cAMP is involved in the activation of both ERα and PR receptors and can be induced by membrane receptors such as GPR30 or mPR. Besides, coactivators can participate in ERα activation by cross talk with other signling pathways; the coactivator coactivator-associated arginine methyltransferase-1 (CARM1) activates ERα by cAMP signaling, leading to ERα phosphorylation. Once phosphorylated, ER and CARM1 interact and can bind to the DNA to regulate target genes. E2, 17β-estradiol; HB, heparin-binding; PG, progesterone.

Figure 2. Integration of genomic and non-genomic estrogen receptor and progesterone receptor signaling pathways

Risk factors of breast cancer related to estrogen exposure, such as parity and age at menarche[48,49], are closely associated with ER+ breast cancer. Furthermore, ER overexpression is closely related to expression of PR, cyclin-dependent kinase inhibitors p21 and p27, cyclin D1, and apoptosis inhibitor bcl-2 [50–52]. ER expression is closely related to outcomes of BC patients. Based on a report in 2003, only considering the impact of hormone thearpy on BC survival, the estimated 5-year survival for patients with ER+ breast cancer was 90% compared to 77% for the patients with ER- breast cancer [53].

Characteristics of breast cancer are different between pre- and post-menopausal patients. Though the incidence rate of invasive breast cancer is low in pre-menopausal women, the overall survival and recurrence-free survival are markedly poor compared to the post-menopausal patients. The evidence suggests that the clinical features of pre-menopausal breast cancer are biologically distinct from those of post-menopausal breast cancer. Pre-menopausal BCs are more aggressive, and 38-64% of BCs diagnosed in patients younger than 40 years old have high grade histological features (poorly differentiated BC cells) compared to 17-38% in patients aged 60 years old and above [54]. Approximately 54-58% of BCs in pre-menopausal patients are ER+ while 80-83% of post-menopausal breast cancers are ER+. Also, pre-menopausal BCs more often exhibit high Ki-67 expression compared to post-menopausal BCs (48% vs. 26%) [55]. HER2 and p53 are commonly overexpressed in the pre-menopausal breast cancer [55,56]. Furthermore, pre-menopausal breast cancers have a basal-like molecular phenotype and are more likely to be involved in gene mutation, especially associated with BRCA1 mutations [55,57–60]. The specific features of pre-menopausal breast cancer are associated with a poor prognosis. Based on the SEER data between 1988 and 2001, 5-year survival rates for women diagnosed of BC before 40

years old are 78-84% compared to >90% among female patients who were diagnosed at ages of 60 years and older [61].

1.1.4 Therapeutic Strategies

Therapeutic strategies for breast cancer are based on characteristics of breast cancer cells, clinical stage (determined by tumor size and involvement of organs), and organ functions (including heart, lung, liver and kidney) of the patients. The National Comprehensive Cancer Network (NCCN) regularly publishes guidelines of cancer treatment according to updates of clinical trials and expert opinions[17].

The main characteristics of breast cancer cells include hormone receptor status, HER2 expression, and histological grading. The features determine specific chemotherapeutic agents and target therapies. Stages of breast cancer are based on the results from preoperational examination and pathological findings after any surgery, which are based on the size of breast tumor, involvement of nearby tissues and lymph nodes, as well as involvement of vital organs. Radiotherapy focuses on local control of the tumor sites, so it is usually recommended for patients with modified surgical methods to preserve breasts, large breast cancer lesions, or inadequate surgical margins in which potential micro-tumor invasions are possible at the surgical margins. Chemotherapy focuses on systemic disease control, which is usually used in patients with advanced disease even though the local lesions are removed completely. Responses of breast cancer cells to chemotherapeutic agents depend on molecular characteristics of the cells. The major function of chemotherapy is to disturb proliferation of the cancer cells, but it also impacts normal cells with proliferative entities, such as hair, mucosa, and blood cells. These are the sites where patients experience adverse effects during chemotherapy[17].

Targeted therapies are the modern treatment improving survival of patients with BC cells that have specific molecular features. Hormone therapy is the earliest targeted therapy for breast

cancer. It improves survival of patients with overexpression of estrogen receptors and/or progesterone receptors that can be examined by microscopic immunohistochemistry stain[62,63].

More than 90% of early BC patients (stage I and II, which are BC with/without localized lymph node involvement) survive over 5 years, which is attributed to effective cancer treatment and early disease detection via regular mammography. As a result, some physicians consider breast cancer now a chronic disease, requiring regular monitoring but not acutely life-threatening.

1.1.5 Selective Estrogen Receptor Modulators (SERMs) vs. Aromatase Inhibitors (AIs)

Selective estrogen receptor modulators (SERMs) have a different mechanism of action than AIs. SERMs compete with estradiol for binding to estrogen receptors, so the function of estrogen on proliferation of breast cancer cells is blocked. The physiological estrogen production continues after administering SERMs. On the contrary, AIs block production of estrogen by inhibiting the activity of aromatase enzyme, which converts androgen into estrogen.

Tamoxifen (TAM), the first SERM, itself has low affinity to ERs, but induces a metabolite converted by the liver that has high affinity to ERs and acts as an antagonist in mammary cells[64]. A study showed that the tamoxifen-ER complex recruited co-repressors to ER target promoters in the mammary cells, but recruited co-activators in the endometrial cells[65]. These results are consistent with the clinical observations of reducing risk of breast cancer recurrence and increasing incidence of endometrial cancer for BC patients on adjuvant tamoxifen treatment[66,67]. In order to balance benefit and risk on taking TAM for adjuvant therapy of BC, the current guidelines recommend 5 years of treatment. The BC patients completing TAM may shift their treatment to AIs if they approach menopause, or stop TAM without further hormone therapy. However, longer term use of TAM may continue to reduce risk of BC recurrence and mortality. The results of a clinical trial published in 2013 showed a significant lower mortality rate ratio (RR=0.71, 95% CI, 0.58-0.88) after 10 years of TAM compared to the regular 5-year treatment[63].

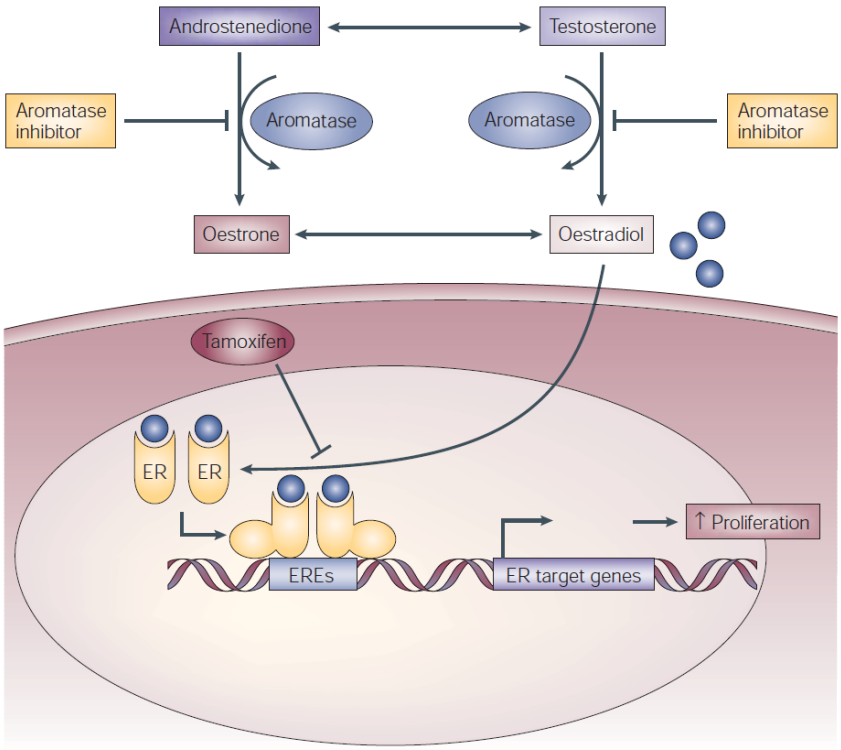
AIs reduce production of estrogen, so the ER-target cells proliferate less due to fewer stimuli of ligand-ER complexes. The effects are more significant in post-menopausal women because their estrogens are mainly derived from peripheral tissues via aromatase activated pathways while pre-menopausal women have more ovaries secreted estrogens.

Figure 3 shows the action of AIs on estrogen production. The major source of estrogen in pre-menopausal women is from the functional ovaries, with other sources coming from subcutaneous fat, breast and bone, via the pathway of converting androgens into estrogens, which requires the aromatase enzyme[68]. After menopause, the ovarian function is lost, so the main source of estrogens is from the other tissues with the action of the aromatase enzyme[69]. In addition, aromatase activity may impact local concentration of estrogen in the peripheral tissues and increase the risk of certain conditions, such as breast cancer. The aromatase gene is located at chromosome 15. Expression of aromatase is higher in breast cancer due to paracrine interaction between malignant epithelial cells and adipose stromal cells. In normal adipose stromal cells, which are undifferentiated adipose fibroblasts, aromatase expression is driven by glucocorticoid dependent promoter. Malignant breast cancer epithelial cells stimulate production of adipose fibroblasts, increasing the amount of aromatase transcription. Furthermore, the cytokines produced by malignant epithelial cells switch aromatase promoters to induce cyclic adenosine monophosphate (cAMP)-dependency which increase aromatase expression[69,70]. Production of estrogens is more efficient on aromatase overexpression status, which increases ligand-bound ERs and leads to proliferation of ER-target cells.

AIs reduce production of estrogen, so the ER-target cells proliferate less due to fewer stimuli of ligand-ER complexes. The effects are more significant in post-menopausal women because their estrogens are mainly derived from peripheral tissues via aromatase activated pathways while pre-menopausal women have more ovaries secreted estrogens.

There are two types of AIs. The steroidal type AIs are analogues of androstenedione, which compete the substrate-binding pocket of aromatase with the natural androstenedione and irreversibly inactivate aromatase enzyme[71]. The non-steroidal type AIs bind to the iron atom in

the heme group of cytochrome P450 in the enzyme, which is reversible[72,73]. The current generation of AIs is able to inhibit aromatase enzyme at more than 95% of specificity[74]. Compared to TAM treatment, post-menopausal BC patients on AIs had significantly lower recurrence and mortality rate after 5 years of treatment[75]. The current breast cancer treatment guidelines, based on National Comprehensive Cancer Network (NCCN) recommendations, suggest switching to AIs after 5 years of TAM if the pre-menopausal patients become post-menopausal or upfront AIs treatment if the patients are post-menopause at diagnosis.



From Johnston SRD, et al. Nature Reviews of Cancer (2003)[76]

Estradiol binds to the estrogen receptor (ER), leading to dimerization, conformational change and binding to estrogen response elements (EREs) upstream of estrogen-responsive genes including those responsible for proliferation. Tamoxifen competes with estradiol for ER binding whereas aromatase inhibitors reduce the synthesis of estrogens from their androgenic precursors.

Figure 3. Mechanism of action of aromatase inhibitors and tamoxifen

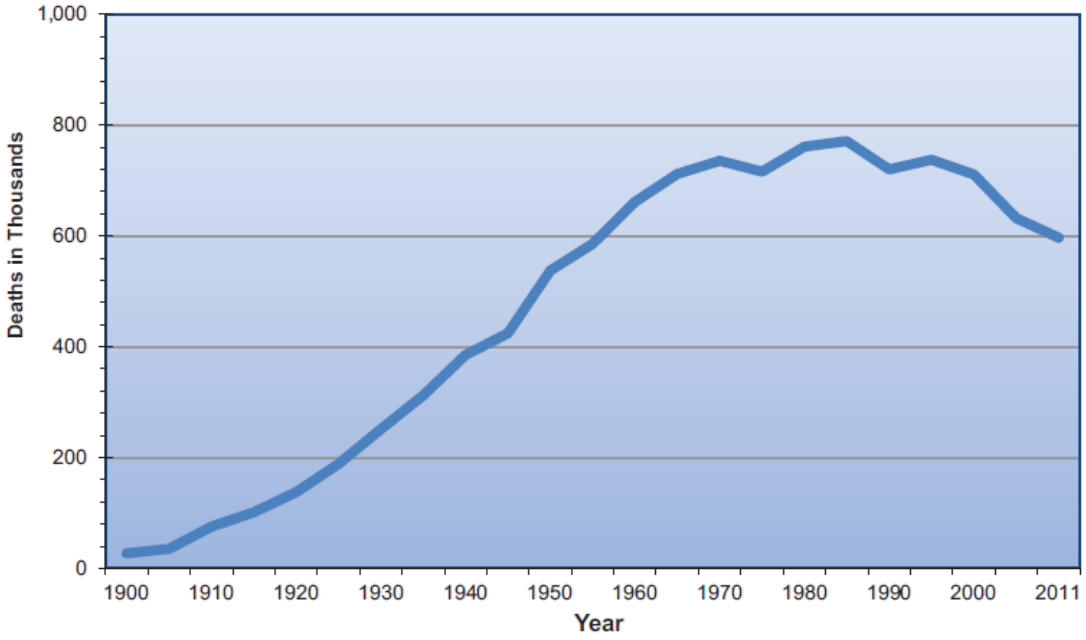
1.2 CARDIOVASCULAR DISEASE (CVD)

1.2.1 Incidence, Mortality and Prevalence

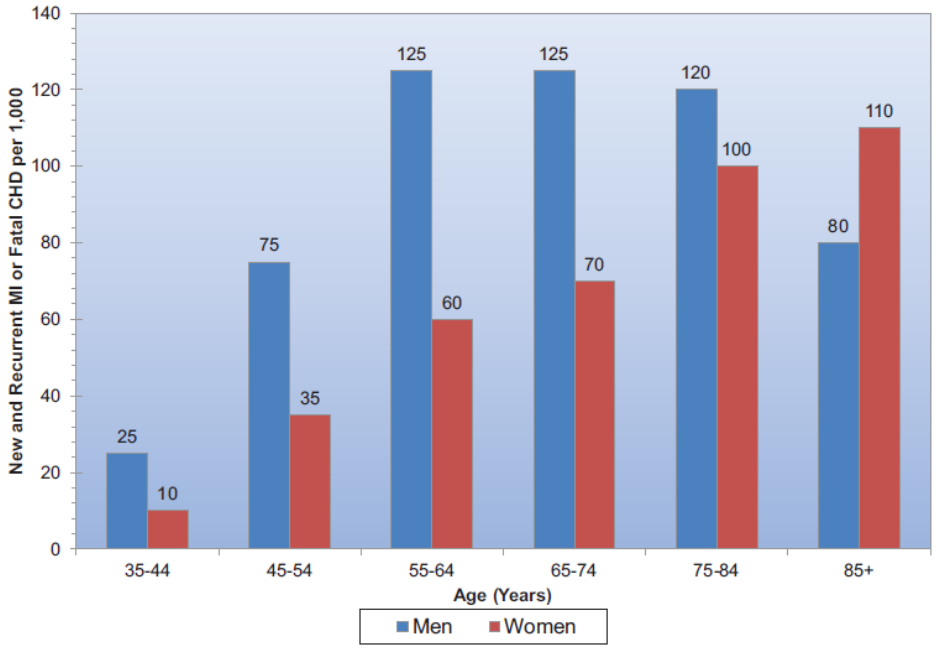
Cardiovascular diseases include diseases in the blood vessels, heart, and brain. Almost 1 in 3 American adults have at least one type of CVD and rises to more than 50% of the population aged 60 years and older. Since beginning of the 20 century, CVD has been the leading cause of death. According to 2013 mortality data, the death rates in men and women were 269.8 and 184.8 per 100,000, respectively. Non-Hispanic men and non-Hispanic women had the highest mortality rate compared to the other racial/ethnic groups[77]. Before age of 60, CVD death rates are higher in men, but the rates are similar in both genders after 60 years old.

Coronary heart disease (CHD), a condition in which the arteries supplying blood to the heart become occluded, is a major type of CVD. Severe CHD can result in a myocardial infarction (MI), the death of heart tissue due to lack of oxygen. In the US, CHD accounted for 18% of CVD events, but almost half of the CVD deaths were associated with CHD. Estimated 550,000 new MI patients were diagnosed in 2016 based on the data from the Atherosclerosis Risk In Communities (ARIC) study[78]. The annual CHD death rate has declined in recent decades (Figure 4A), with 47% of the death rate reduction attributed to improved treatment, including management of CVD risk factors[79,80]. With effective prevention programs, the incidence of MI has also declined significantly. The incidence of CHD varies by race, gender, and age. The annual incidence of MI or fatal coronary heart disease is significantly higher in men among the population under the age of 75; however, the incidence is higher in women among the population older than 85 years old (Figure 4B). The prevalence of CHD is consistently higher in men across all ages (Figure 4C). The phenomenon is partially due to older age of the first MI in

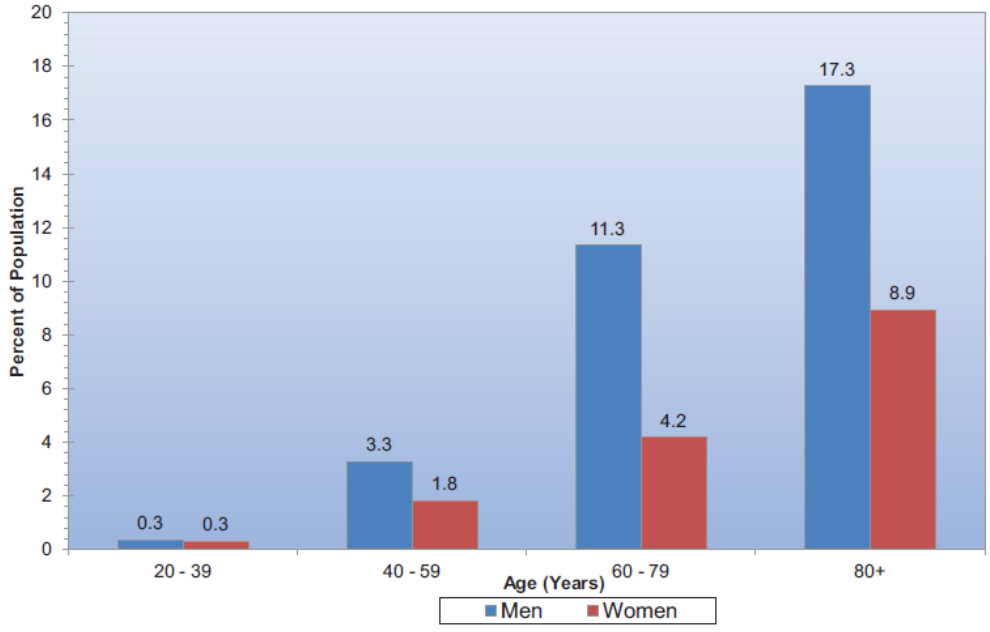
women. In addition, for patients older than 45 years, more women die after the first MI. Subsequently, female patients have a shorter survival time then male patients (5.5 years vs. 8.2 years)[81]. Black males have the highest incidence rate before the age of 85. Non-Hispanic White males have the highest prevalence of CHD. The fact that high incidence of Black males and high prevalence in White males may be reflective of racial disparity in medical access, resulting in more Black male patients who die of CHD than White males.



(A) Death attributable to diseases of heart.



(B) Annual number of adults per 1000 having diagnosed heart attack or fatal coronary heart disease (CHD) by age and sex.



(C) Prevalence of myocardial infarction by age and sex

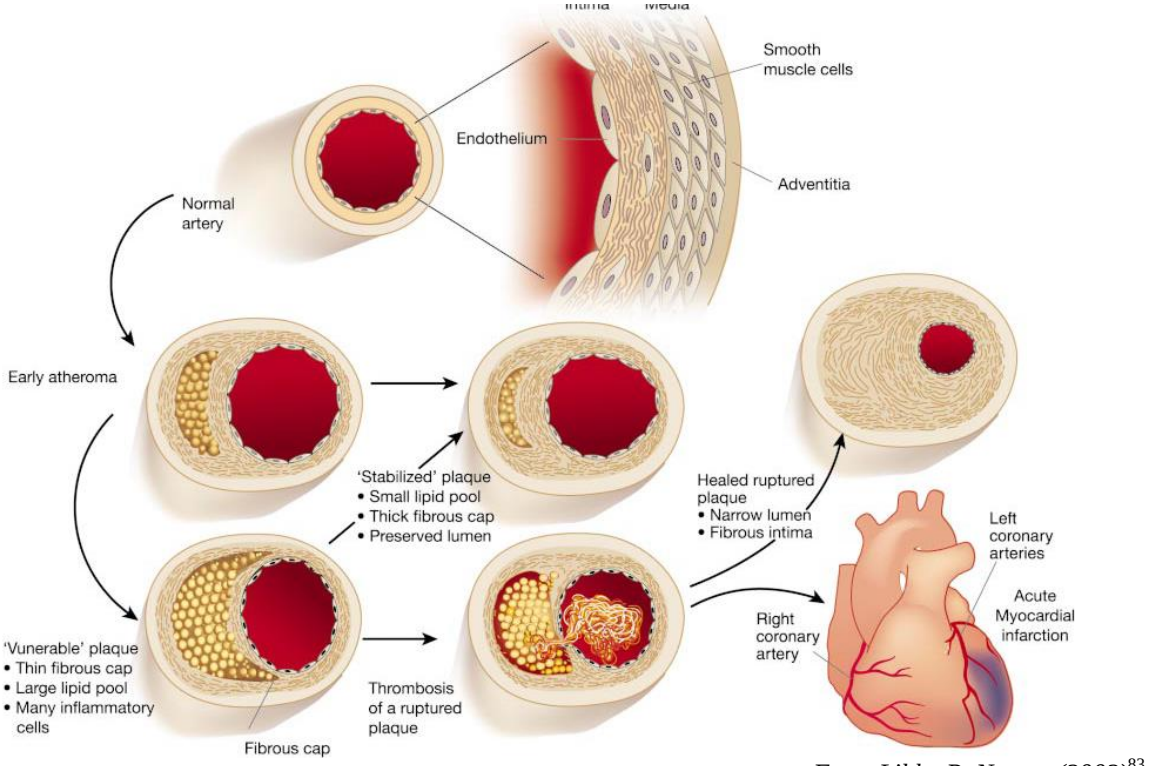
From Mozaffarian et al. Circulation (2015)[81]

Figure 4. Incidence and prevalence of CHD across age groups for men and women

1.2.2 Pathophysiology of Coronary Heart Disease (CHD)

CHD, caused by reduced blood flow due to narrowing of the coronary artery lumen, is the most frequent and fatal CVD. This problem starts in the endothelium of the coronary artery which develops atherosclerosis via a series of inflammatory processes. When infectious agents and/or low-density lipoprotein cholesterol (LDL-C) contact arterial intima and initiate inflammation, endothelial cells are activated and adhesion molecules are expressed. These reactions usually appear at the site of hemodynamic strain. Platelets first arrive at the site and are followed by leukocytes, including monocytes and T cells. These cells migrate to the sub-endothelial space after attaching to the intima. The monocytes are transformed into macrophage via stimulation of cytokines produced by inflammatory intima[82,83]. Therefore, innate immunity is up-regulated. Various molecules and particles are engulfed by macrophages and destroyed. Cholesterol may accumulate in the macrophages, which are then transformed into foam cells if it cannot be removed efficiently. The foam cells secrete pro-inflammatory cytokines and induce local inflammatory reaction of endothelial and smooth muscle cells (SMCs). SMCs move to the intimal layer and proliferate to form an extracellular matrix that is more susceptible to oxidative impact and further facilitates inflammatory responses. Endothelial cells, monocytes and the extracellular matrix secrete matrix metalloproteinases (MMPs) together modulate functions of vascular cells and lead to angiogenesis, destruction, and remodeling of arteries[84]. MMPs can degrade the extracellular matrix, so the strength of plaque's fibrous cap is compromised. Narrowing coronary artery lumen is usually not fatal and spasm of the artery may induce acute coronary artery syndrome (known as angina or chest pain). However, vulnerable plaque rupture and endothelial erosion allow blood entering the plaque core to contact tissue factors, derived from dead lipid-laden macrophages, and then platelets and coagulation are activated for

thrombus formation[85]. Occlusion of the coronary artery blocks blood supply of myocardium and causes myocardial infarction, which is the major cause of acute cardiac death (Figure 5).



From Libby P, Nature (2002)[83]

Figure 5. Schematic of the life history of an atheroma

1.2.3 CVDs in Pre- vs. Post-Menopausal Women

Epidemiological data show significantly lower age-specific CVD mortality in women before 50 years old compared to men; however, the advantage disappears when menopause occurs. Though reduced female sex hormones after menopause has been considered a major contributor to losing the advantage in CVD mortality, the increased CVD mortality after midlife of women is not obvious in countries with lower CVD risk factors[86]. Female sex hormone may not be as important as other CVD risk factors for CVD death. Studies show higher incidence of angina pectoris in women compared to men at all age groups, but female CVD mortality rates steadily increase with age, which is contrary to slower increment of mortality rates in males after 45 years old[3,87,88]. More evidence indicates that changes of the CVD risk factors during menopausal transition are also important in addition to changes of female sex hormone levels[89–92].

Many studies have explored physiological changes during the menopausal transition in order to clarify the role of menopause on risk of CVDs. Pre-menopause high body mass index (BMI) and impaired fasting glucose are associated with incidence of post-menopausal metabolic syndrome[93]. Changes of lipids mainly occur at the late peri-menopausal stage. Within 1 year before and after final menstrual period (FMP), total cholesterol, and low density lipoprotein cholesterol (LDL-C) increase significantly. HDL-C also increases at the late peri-menopausal and early post-menopausal stages, but it declines afterwards[94–96]. Subclinical cardiovascular disease (SCD) measures, including carotid intima-media thickness (cIMT) and inter-adventitia diameter (AD) representing remodeling of the carotid artery indicative of vascular aging, deteriorate faster during the late peri-menopausal and post-menopausal stages compared to the pre-menopausal period[97]. The phenomena may be driven partially by changes of endogenous

female sex hormone. HDL-C is inversely related to SCD measures, including aortic calcification (AC) and cIMT, in women at the stages of pre-menopause or early peri-menopause. However, the relationship is reversed or weakens during late peri-menopausal or post-menopausal stages, so the protective effect of HDL-C on CVDs is reduced for post-menopausal women[98]. Physiological metabolism changes during the menopausal transition, which can lead to occurrence of CVDs.

1.2.4 Sex Hormones and CVDs

Estrogen signaling involves two pathways. The first one is a genomic (classic) pathway that requires involvement of ERα and ERβ. The other one is a non-genomic pathway that reacts to stimuli rapidly, which may still use the ERs but is not related to transcription of genes. The rapid non-genomic pathway can directly induce dilatation of normal vessels and inhibit platelet activation via production of nitric oxide (NO) associated with function of ERα[99]. This pathway does not function well in the dysfunctional endothelium because NO production is reduced in the dysfunctional endothelium. The genomic pathway impacts vessels in several ways. It can increase gene expression for vasodilatory enzymes, such as NO synthase[100]. Also, it facilitates endothelial cell growth in response to vascular injury, as well as inhibits migration and growth of smooth muscle cells[101–103]. The systemic effects of estrogen impact levels of lipid, coagulation factors, and the other vasoactive molecules, which influence the cardiovascular system from molecular reactions (e.g. cell growth in response to vascular injury) to physiological vascular mobility (e.g. Vasodilatation)[104]. The overall effects of estrogen protect the cardiovascular system by healing vascular injury faster and dilating vessels (Figure 6).

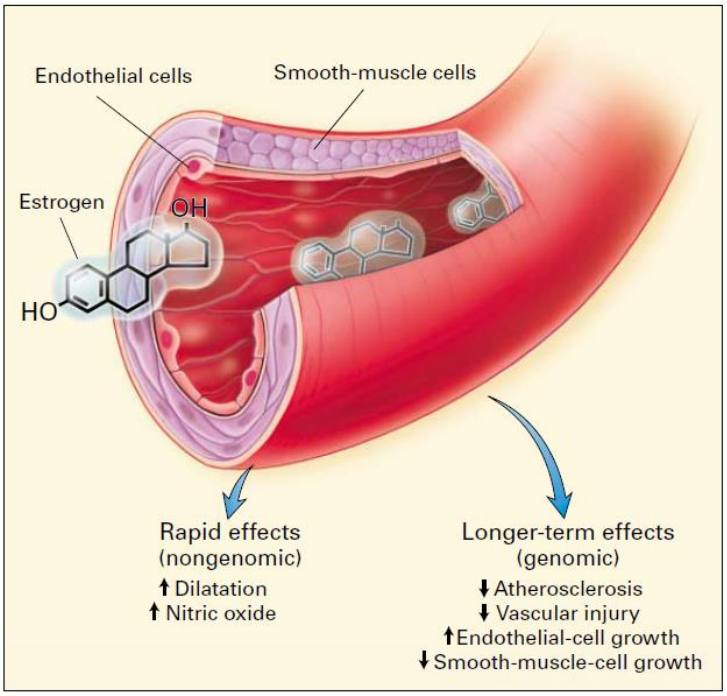


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Figure 6. Direct effects of estrogen on blood vessels

Menopause, either by physiological or surgical removal of the ovaries, is associated with reduced serum estradiol but increased follicle-stimulating hormone (FSH). Leptin, total and LDL cholesterol are higher in post-menopausal women[106]. The relationship between sex hormones and CVDs in post-menopausal women is of interest due to the significant discrepancy of CVD mortality among men, and pre-, and post-menopausal women. However, the results of the relationship between sex hormones and CVDs are inconsistent across studies. Duration of estrogen exposure may be related to risk of CVDs. Women having menarche at very early and late ages have higher risk of ischemic heart diseases in a UK population between 50 and 64 years old[107]. A 20 year cohort study concluded that longer estrogen exposure (more than 18 years in their study) provides a 20% reduction in CV mortality compared to shorter than 13 years of

estrogen exposure in post-menopausal women. The estrogen exposure duration was determined by the menstrual cycles, pregnancy, and oral contraceptive use[108].

The relationship between serum sex hormone levels and CVDs may be non-linear. Extremely low serum estradiol levels and extremely high testosterone levels are independently associated with increased incidence of ischemic heart diseases[109]. During menopausal transition, decreasing sex hormone binding globulin (SHBG) is associated with progression of cIMT while lower estradiol is associated with faster AD progression[110]. Testosterone and SHBG are associated with calcified and non-calcified coronary artery plaque as well as aortic plaque. Androgen but not estrogen level is related to coronary risk factors (Framingham risk score)[111]. In a study of a post-menopausal population, the highest tertile of estradiol was associated with higher risk of CHD, but the association disappeared after adjusting for CVD risk factors[112]. Contrary to this study, higher estradiol was associated with reduced coronary artery calcium score (CACS) in another study[113]. A study indicated changes of estradiol between pre- and post-menopausal stages were inversely related to 10-year CHD risk[114]. Many factors, such as study time (menopausal transition) and study outcomes, may account the inconsistent results of the relationship between sex hormone and CVDs.

Endogenous estrogen, naturally produced female sex hormone, not only impacts the cardiovascular system but also influences lipid metabolism in the liver. Animal studies show that estrogen enhances clearance of LDL-C by increasing LDL-C receptors in hepatocytes and reduces HDL-C catabolism via decreasing HDL-C receptors[115,116]. The clinical experience for relationship of estrogen and lipid profiles is mainly from the studies of hormone replacement therapy (HRT), which increased serum estrogen levels. The results indicated that the current HRT users have lower LDL-C as well as total cholesterol, and higher HDL-C as well as

triglyceride (TG) compared to non-HRT users[117–119]. Specifically, LDL-C responded to HRT earlier than HDL-C[120]. However, association of endogenous sex hormone with lipid profiles is inconsistent across the studies for non-HRT users. A study of peri-menopausal women showed low SHBG and high free androgen index (FAI) were related to unfavorable CV risk factors, including poor lipid profiles. The relationship was weaker for low estradiol levels[121]. Similar results can be found in post-menopausal women[122,123]. However, some studies in post-menopausal women showed that SHBG but not estrogen and androgen independently predicted HDL-C and TG levels[124,125]. Though post-menopausal women tend to have poor lipid profiles, sex hormones cannot fully explain the phenomenon. In brief, the relationship between sex hormones, CVDs, and lipid profiles remains unclear and requires more studies to clarify the mechanisms.

1.3 RATIONALE FOR INVESTIGATING RISK OF CVDS IN BC PATIENTS ON HORMONE TREATMENT

The major function of AIs is reducing the production of estrogen by blocking aromatase function. A study showed that serum estradiol levels decreased and approached a plateau after 6 months of AI treatment for metastatic BC patients[126]. Physiologically, patients taking AIs are in the iatrogenic aromatase deficiency status. Naturally developed aromatase deficiency is very rare in humans. Hypertestosteronemia, hypoestrogenemia, puberty failure, hypercholesterolemia, high LDL-C, and low HDL-C are the common clinical symptoms of aromatase deficiency[127,128]. Studies using animal models have shown that aromatase deficient mice experience the problem of hepatic steatosis and expressed poor lipid profiles. Estrogen replacement can reverse the phenomenon in these mice[129,130]. Current hormone therapeutic strategies for post-menopausal BC include 1) switching from SERMs to AIs after 2-3 years of treatment, 2) upfront AI treatment, and 3) prolonged SERMs therapy, which provide comparable OS. When AIs become the main hormone therapy for post-menopausal BC patient to improve DFS, it is important to understand the major problem that compromises OS. Incidence of CVDs is higher in AI treated BC patients compared to those receiving SERMs[131]. Dyslipidemia is one of the major CVD risk factors, and high risk of CVDs in BC patients may be due to dyslipidemia caused by AIs, which is preventable via appropriate medical intervention.

1.4 SPECIFIC AIMS

The major theme of this dissertation is to investigate the impact of BC hormone therapies on lipid profiles and subsequent cardiovascular events. Starting with developing a statistical method to conduct a Bayesian network meta-analysis in Chapter 2, the network meta-analysis fostered the hypothesis of effects of BC hormone treatment on changes in lipids, which is described in Chapter 3. Based on the results of the meta-analysis, we conducted a cohort study to examine impacts of hormone drugs on risk of cardiovascular diseases in Chapter 4.

Specific Aim 1. Network meta-analysis for correlated longitudinal data with heterogeneous report format using Bayesian statistical methods

Specific Aim 2. Bayesian network meta-analysis of effects of breast cancer hormone therapies on changes of lipid profiles (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride).

Hypothesis: BC patients on AIs have poor lipid profiles compared to those who were on SERMs or not on hormone therapies.

Specific Aim 3. Impact of BC hormone therapy on dyslipidemia and cardiovascular events in a cohort using electronic medical records and time-dependent Cox proportional hazard models.

Hypothesis: Usage of AIs is associated with higher risk of CVDs and dyslipidemia after controlling for important covariates.

2.0 PAPER 1: STATISTICAL METHODS CONVERTING HETEROGENEOUS REPORTING FORMATS INTO A HOMOGENEOUS REPORTING FORMAT AND EXAMINING CONSISTENCY OF ESTIMATES FOR NETWORK META-ANALYSES USING LONGITUDINAL DATA

2.1 ABSTRACT

Traditional meta-analyses combine multiple studies to determine the effect of an intervention to a single comparator on an outcome measured once at the end of a study. Newly developed Bayesian network meta-analysis (NMA) methods expand this to trials with longitudinal repeated outcome measures and to a network of target treatments, including studies that include any subset of the target treatments. However, there exist difficulties regarding the practical implementation of these NMA methods; specifically: 1) heterogeneous reporting, with some studies reporting the mean and variance of the outcome at each follow-up time and others reporting the baseline mean and variance of the outcome and then, at the follow up visits, reporting the mean and variance of the change in the outcome from the baseline, and 2) there are

no consistency checks for longitudinal NMA. In this study, starting with a Bayesian NMA for repeated outcome measures, we incorporated a first-order autoregressive model to convert the variances of the means to the change from baseline variances. We then updated and incorporated a traditional arm-based consistency method to determine whether the direct and indirect effect comparisons of treatments on repeated-measure outcomes were consistent. We illustrate our method with a meta-analysis of the effect of breast cancer hormone therapies on changes in total cholesterol measured multiple times during up to 5 years of follow-up.

2.2 INTRODUCTION

A meta-analysis combines information from multiple published scientific articles that directly compare two treatments for a given condition from results of multiple randomized clinical trials (RCTs) and epidemiologic studies. The analysis increases power by combining study populations and it explores uncertainty of conflicting results. Traditional meta-analysis methods include only the studies with direct treatment comparisons of interest. Some meta-analysis studies may only include RCTs, as the confounding factors within studies are eliminated. However, even if a meta-analysis only includes RCTs, the advantage of within-study randomization does not protect against confounding when combining participants across studies. When increasing the number of studies in the meta-analysis, the treatment arms become complex mixtures of the underlying study populations. The heterogeneous populations and the varying sample sizes of included studies can induce complex biases. Therefore, adjustment for the important confounders, such as specific inclusion criteria of the RCTs, is needed in the meta-analysis.

There are several limitations with the traditional meta-analysis methods. First, meta-analysis uses aggregated data instead of individual data, so investigation of confounders and modifiers cannot occur at the individual level. Second, we can only compare two treatments with studies that contain a direct comparison. Information from RCTs having either one of the target treatments is not used. This limits the RCTs that can be included and reduces the statistical power of meta-analyses, which especially impacts studies for rare diseases. Third, when there are multiple treatment options for a specific disease, not all potential head-to-head comparisons are available from RCTs. RCTs often compare the new drug to the standard therapy or usual care. This reduces the number of treatment comparisons possible in the meta-analysis.

Network meta-analysis (NMA) incorporates indirect comparisons, which use information other than head-to-head comparisons of the target comparators, into meta-analysis by establishing a network of all therapies and allows us to compare one therapy to any other therapy in the network even in the absence of any studies with direct comparisons. In addition to the strong evidence provided by the direct comparison, the indirect comparisons can also provide information regarding the comparison of primary interest. Network meta-analyses are also referred to as mixed treatment comparisons (MTC).

Indirect comparisons are subject to greater bias than direct comparisons. Different from direct comparisons from head-to-head RCTs, indirect comparisons usually use separate RCTs to obtain the same estimate as direct comparisons. Due to the different factors in the separate RCTs such as timing, overall population differences, and the magnitude of the treatment effects, additional biases are introduced to indirect comparisons[132,133]. To preserve the within-study randomization, Bucher et al. recommended that NMA should include all arms in the selected RCTs and the differences between treatments within the RCTs should be modeled.

The main assumption of traditional meta-analysis is that the true difference of treatment effects is constant across trials or the trial specific treatment differences are from a common distribution. In addition, NMA also requires the assumption that the true difference of treatment effects in trials for indirect comparisons would be identical to the true difference of treatment effects in trials for direct comparisons, or at least from the same common distribution. The evidence from indirect comparisons is less precise than the one from direct comparison. Assuming that we have treatments A, B, and C, we are interested in comparing the therapeutic effect between treatment A and treatment B. Denote the estimates of the direct comparisons as $\hat{\theta}_{AB}$, $\hat{\theta}_{AC}$, and $\hat{\theta}_{BC}$. The estimate of the indirect comparison between treatment A and B is

denoted as $\tilde{\theta}_{AB}$. The indirect estimate $\tilde{\theta}_{AB} = \hat{\theta}_{AC} - \hat{\theta}_{BC}$, has a variance of the sum of the variances of $\hat{\theta}_{AC}$ and $\hat{\theta}_{BC}$ minus a correlation term. This variance is usually greater than the variance of a direct estimate $\hat{\theta}_{AB}$. Consistency of the point estimates from direct and indirect evidence must be examined to verify the assumptions of the model for NMA.

The concept of NMA is very attractive and can be applied to clinical questions, especially for diseases having multiple therapeutic options. Most existing NMA models focuse on the final treatment effects, and do not consider longitudinal trajectories. However, RCTs often report multiple interim outcomes before the final results. The longitudinal data provide information regarding the drug effects across time. Models using only the final results ignore the patterns of the therapeutic effects during treatment. In order to solve the problem, several methods were proposed[134–136]. Ding's method focuses on continuous outcome changes from multiple follow-up times using baseline values[134], while Lu's method analyzes binary outcomes over multiple follow-up times[136]. Jansen proposed a more generalized model to manage both longitudinal continuous and binary outcomes[135]. In this study, we focus on Ding's method and address potential problems when applying this method to real world applications.

Ding's method specifically focuses on the drug effects which require time to achieve their maximal effects. The integrated two-component prediction (ITP) model estimates the drug effects and their shapes across time at the individual level data[137]. Ding combines the ITP model with the concept of NMA and developed the Bayesian evidence synthesis techniques-ITP (BEST-ITP) model.

First, we encountered two main challenges when using the BEST-ITP model. The published RCTs reported their results in heterogeneous formats. Some articles report follow-up measures as outcome change from baseline values. However, others provide outcome

measurements at each follow-up time point, which the variances reported do not take correlation among the series of follow-up measurements into account. Second, there are no appropriate consistency tests for the specific NMA method that compare indirect and indirect longitudinal outcome changes from the baseline values. Verifying this assumption is essential to validate the model. To solve the challenges, we propose methods to obtain a uniform reporting format and to examine consistency of the estimates from direct and indirect evidence.

The article is organized as follows. In Section 2.3.1, we outline the Ding's NMA model that estimates longitudinal follow-up outcome changes from baseline values. Section 2.3.2 expands Abram's method for converting heterogeneous reporting formats into a homogeneous format to a longitudinal setting. The method in Section 2.3.3 expands Hong's consistency test of direct and indirect estimates to a longitudinal setting. In Section 2.4, we present simulation data to verify the performance of the proposed methods.

2.3 METHODS

2.3.1 Network Meta-Analysis

Comparison networks were proposed by Thomas Lumley in 2002[138]. His method combines information from available two-arm RCTs for diseases with multiple treatment options; allowing treatment effects without head-to-head RCTs can be compared. Lumley indicated that it is straightforward to estimate treatment difference by taking differences of the individual estimates, and he further focused on detecting and estimating inconsistency of treatment effects across trials.

$$Y_{ijk} \sim N(y_{ijk}, \sigma_{ijk}^2)$$

$$y_{ijk} = \delta_{ij} + \eta_{ik} + \eta_{jk} + \xi_{ij}$$

$$\delta_{ij} = \mu_i - \mu_j$$

$$\eta_{ik} \sim N(0, \tau^2), \quad \eta_{jk} \sim N(0, \tau^2)$$

$$\xi_{ij} \sim N(0, \omega^2)$$

Y_{ijk}: the treatment difference estimate from the *k*th RCT comparing treatment *i* and *j*
y_{ijk}: the mean treatment difference estimate of the *k*th RCT comparing treatment *i* and *j*
σ_{ijk}^2: estimated variance
μ_i & μ_j: true average effects of treatment *i* and *j*
δ_{ij}: the true difference between treatment *i* and *j*
η_{ik} & η_{jk}: random effects from the normal distribution with a common mean, 0, and variance, τ^2, representing the difference between the pooled average effect and the effect in *k*th trial
ξ_{ij}: random effect from the normal distribution with a common mean, 0, and variance, ω^2, representing a change in the effect of treatment *i* when comparing to treatment *j*

Lumley's model includes variations of average effects of two treatments (*i* and *j*) in the individual trials, η_{ik} and η_{jk}, and inconsistency of the specific pair of treatments (ξ_{ij}) into

consideration. If ξ_{ij} is too large, inconsistency of the estimates occurs and network meta-analysis may not be appropriate. The model proposed by Lumley restricts its application to two-arm clinical trials.

In order to include trials that have more than two arms in the NMA, Lu and Ades proposed a hierarchical Bayesian model for K-comparisons[139]. This method is an extension of the Smith, Spiegelhalter and Thomas (SST) model, which uses the full Bayesian approach to estimate treatment effects for traditional meta-analysis focusing on the 2-arm clinical trials[140].

2.3.1.1 K-Comparison Extended from SST Model by Lu and Andes

The k-comparison model[139] estimates the *k*th treatment effect, θ_{ik}, on a binomial outcome from N trials. By choosing treatment 1 as the reference treatment in the *i*th trial with *k* treatment groups, the model can be written as follows:

$$r_{ik} \sim bin(p_{ik}, n_{ik}), \qquad k = 2, \cdots, K$$

$$logit(p_{i1}) = \alpha_i - {\delta_{i2}}/{K} - {\delta_{i3}}/{K} - \cdots - {\delta_{iK}}/{K}$$

$$logit(p_{i2}) = \alpha_i + (K-1)\,{\delta_{i2}}/{K} - {\delta_{i3}}/{K} - \cdots - {\delta_{iK}}/{K}$$

$$\vdots$$

$$logit(p_{iK}) = \alpha_i - {\delta_{i2}}/{K} - {\delta_{i3}}/{K} - \cdots + (K-1)\,{\delta_{iK}}/{K}$$

$$\delta_i^T = (\delta_{i2}, \cdots, \delta_{iK})^T \sim N(\delta, \Sigma)$$

$$\alpha_i = \sum_k {logit(p_{ik})}/{K}$$

$$\delta_{ik} = logit(p_{ik}) - logit(p_{i1}), k = 2, \cdots, K$$

Prior distribution for α_i, δ, and Σ

r_{ik}: the number of events in the *k*th treatment group in trial *i*.
n_{ik}: the number of participants in the *k*th treatment group in trial *i*.
p_{ik}: the probability of events in the *k*th treatment group in trial *i*.
δ_{ik}: effect of the *k*th treatment compared to the reference in trial *i*
α_i: the average event rate (on the logit scale) in the *i*th trial, and a nuisance parameter that will be changed to the reference after reparameterization.
δ: the population mean treatment effects relative to the reference treatment; the (*K*-1)-dimensional hyperparameter
Σ: the (*K*-1)×(*K*-1) variance-covariance matrix for δ

All δ_i's are from the common normal distribution with mean δ and variance Σ. This model structure expands upon the original SST model, which focuses only on two arm clinical trials, by replacing the single variance parameter with the variance-covariance matrix Σ.

Let X be a K×K matrix.

$$X = \begin{bmatrix} 1 & -1/K & -1/K & \cdots & -1/K \\ 1 & (K-1)/K & -1/K & \cdots & -1/K \\ 1 & -1/K & (K-1)/K & \cdots & -1/K \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1 & -1/K & -1/K & \cdots & (K-1)/K \end{bmatrix} \equiv \begin{bmatrix} X_1^T \\ X_2^T \\ X_3^T \\ \vdots \\ X_K^T \end{bmatrix}$$

The outcome estimate, Y_{ik}, can be written as a logit function of p_{ik}.

$$Y_i = (Y_{i1}, Y_{i2}, \dots, Y_{ik})^T = (logit(p_{i1}), logit(p_{i2}), \dots, logit(p_{ik}))^T.$$

The parameters can be described as

$$\Theta_i = (\alpha_i, \delta_{i2}, \dots, \delta_{ik})^T,$$

and then the k-comparison model can be rewritten in the matrix form

$$Y_i = X\Theta_i, \quad i = 1, \dots, N$$

or

$$logit(p_{ik}) = X_k^T \Theta_i.$$

α_i is the average event rate of the *i*th trial, a nuisance parameter, and not a parameter of interest. Therefore, the equation can be reparameterized as follows:

$$logit(p_{ik}) = \phi_i + \theta_{ik}$$

$$\theta_{i1} = 0$$

$$(\theta_{i2}, \cdots, \theta_{iK})^T \sim N(\theta, \Sigma_\theta)$$

$$\phi_i \sim N(\mu_\phi, \tau_\phi^2)$$

ϕ_i: the reference effect from trial *i*
θ_{ik}: the difference between the *k*th treatment and the reference treatment in trial *i*
μ_ϕ : the treatment effect from reference treatment
θ : a hyperparameter with (*K*-1) dimensions, which represents the treatment effects relative to the reference treatment.
Σ_θ: the (*K*-1)×(*K*-1) variance-covariance matrix.

This reparameterization facilitates expansion of the model. Continuous outcomes can be similarly modelled by changing the logit link to the identity link[141].

2.3.1.2 Integrated Two-Component Prediction (ITP) Model

The Integrated Two-component Prediction (ITP) model specifically focusing on longitudinal repeated outcomes from RCTs investigating drug effects should be described. The RCTs often collect outcome measures throughout the study. The treatment effects can vary across time. The therapeutic effect of a drug can gradually accumulate and then achieve a plateau. In general, the meaningful drug effects may be observed after a certain period of time and the early responses may not completely reflect the final results. Fu and Manner developed

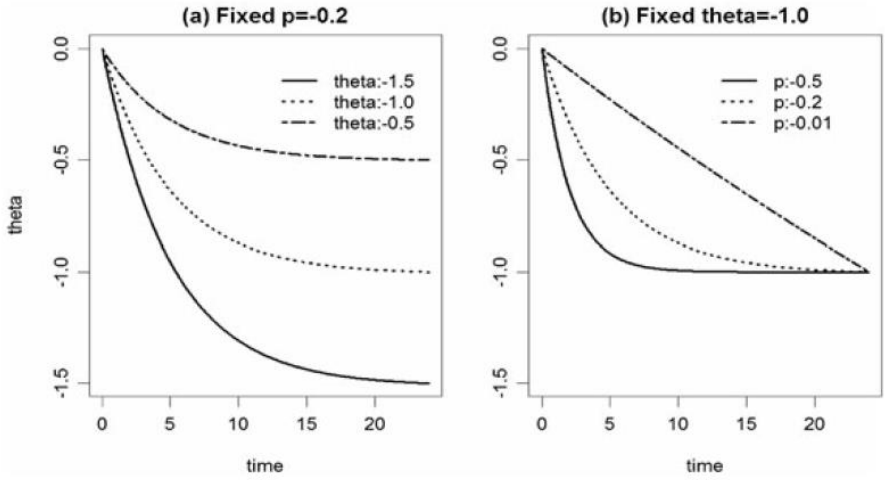
the ITP model to represent a time course of drug effects[137]. The model assumes the drug effects accumulate across the therapeutic course with the concave pattern that achieves plateau during treatment.

The ITP model focuses on continuous outcome measures and estimates the final mean treatment effect, θ_k, from repeated measurement across the whole treatment course at the individual level. Different from the models described above, this model also considers the time variable. Later, this model is expanded to meta-analyses from aggregated data reported in published articles regarding the similar patterns of drug effects.

$$Y_{kjl} = (\theta_k + s_{kj} + \epsilon_{kjl}) \frac{1 - e^{p_k t_{kjl}}}{1 - e^{p_k d}}$$

Y_{kjl}: the observation (change from baseline) from the subject *j* on treatment *k* at time *l*.
θ_k : the mean effect of the *k*th treatment by the end of time *d*, the total treatment duration.
p_k: the shape of the *k*th treatment throughout the treatment duration
t_{kjl}: the time points for the interim observations for subject *j* on treatment *k*, $t_{kjl} \leq d$.
s_{kj}: the random effect accounting for the correlations of the within-subject measurements.
ϵ_{kjl}: is the residual error for the subject *j* on treatment *k* at time *l*.

This model expresses the increased variation of the treatment effects when time increases, which is often observed during drug therapies. The first component of the equation, $\theta_k + s_{kj} + \epsilon_{kjl}$, is a traditional mixed-effect ANOVA model and the second component, $\frac{1-e^{p_k t_{kjl}}}{1-e^{p_k d}}$, models changes in time. The baseline values are incorporated because the model estimates the responses as changes from baseline. When p is fixed and θ_k varies, the trends of the drug effects are the same but the final drug effects are different, depending on the values of θ_k. When θ_k is fixed and p varies, the trends of the drug effects are different but the final drug effects are toward to the same end point (Figure **7**).



(a) fixed p= -0.2 for θ= -1.5, -1.0, -0.5, respectively; (b) fixed θ = -1.0 for p= -0.5, -0.2, -0.01, respectively.

From Ding & Fu, Statistics in Medicine, (2013)[134]

Figure 7. The treatment effect, θ, and shape parameter, p, from the ITP model.

2.3.1.3 Bayesian Evidence Synthesis Techniques-ITP (BEST-ITP) Model

Ding and Fu further proposed a Bayesian evidence synthesis techniques –ITP (BEST-ITP) model[134] by combining the K-comparison extended from SST model with the ITP model, enabling NMA to estimate longitudinal drug effects from available RCTs. Instead of using individual level data in the ITP model, the study summary level data are used in the BEST-ITP model. The main available data are $\bar{Y}_{ikl}$, s_{ikl}, n_{ikl}, d_i, and t_{ikl}. $\bar{Y}_{ikl}$ is the observed outcome change from baseline for treatment k at time l in trial i. s_{ikl} is the corresponding observed standard deviation, and n_{ikl} is the numbers of the participants for the kth treatment at time l in trial i. d_i is the treatment duration for trial i and t_{ikl} is the interim follow-up duration of

treatment k at time l in trial i with $t_{ikl} \leq d_i$. The model assumes that the trial and treatment effects are additive. The BEST-ITP model is as follows:

$$\bar{Y}_{ikl} \sim N(\mu_{ikl}, \sigma_{ikl}^2)$$

$$\frac{S_{ikl}^2(n_{ikl}-1)}{\sigma^2}\left(\frac{1-e^{p_k d_i}}{1-e^{p_k t_{ikl}}}\right)^2 \sim \Gamma\left\{\frac{(n_{ikl}-1)}{2}, \quad 2\right\}$$

$$\mu_{ikl} = (\phi_i + \theta_k)\left(\frac{1-e^{p_k t_{ikl}}}{1-e^{p_k d_i}}\right)$$

$$\sigma_{ikl}^2 = \frac{\sigma^2}{n_{ikl}}\left(\frac{1-e^{p_k t_{ikl}}}{1-e^{p_k d_i}}\right)^2$$

$$\theta_0 = 0$$

$$\bar{Y}_{ikl} = \left(\phi_i + \theta_k + \frac{\epsilon_{ikl}}{\sqrt{n_{ikl}}}\right)\frac{1-e^{p_k t_{ikl}}}{1-e^{p_k d_i}}, \qquad Var(\epsilon_{ikl}) = \sigma^2$$

The non-informative priors can be chosen for the following parameters.

$$\begin{cases} \theta_k \propto 1, \quad k = 2, \ldots, K \\ p_k \propto 1, \quad k = 2, \ldots, K \\ \phi_i \sim N(\mu_\phi, \tau_\phi^2) \\ \mu_\phi \propto 1 \\ \log(\tau_\phi^2) \propto 1 \\ \epsilon_{ikl} \sim N(0, \sigma^2) \\ \log(\sigma^2) \propto 1 \end{cases}$$

μ_{ikl} is the hyperparameter mean of the observed outcome changes from baseline for the *k*th treatment at time *l* in trial *i*. σ_{ikl} is the corresponding hyperparameter standard deviation. ϕ_i is the *i*th trial-specific effect, which has a normal distribution with mean μ_ϕ and standard deviation τ_ϕ. θ_k is the *k*th treatment effect relative to the reference treatment. p_k is the change pattern within therapeutic duration for the *k*th treatment. ϵ_{ikl} is the residual error.

This is a fixed-effect (FE) model for θ_k, but it can be extended to a random-effect (RE) model by replacing θ_k with θ_{ik}, with a multivariate normal distribution:

$(\theta_{i2}, \cdots, \theta_{iK})^T \sim N(\theta, \Sigma_\theta)$. Ding recommended a FE model for many reasons. First, the clinical trials are usually designed with inclusion and exclusion criteria for specific groups of patients where a RE model assumes subjects from different trials are randomly chosen from the same population. In addition, sample sizes may differ significantly among trials and they often indicate the strength of evidence from the trials. Therefore, it is more reasonable to put more weight to the trials with large sample sizes (the FE model) than to treat all trials as equally important (the RE model). Finally, each treatment combination in the NMA usually contains fewer trials than the overall meta-analysis which includes all trials, so the between-trial variability may not be precisely estimated by the RE model. Alternatively, if the data sets from RCTs have similar study designs and sample populations, it is reasonable to assume that the estimates from trials are drawn from a common distribution and a RE model can serve as a primary analysis. Ding recommended that both models can be examined with one model as a sensitivity analysis to the other.

2.3.2 Assessing Change from Baseline for Heterogeneously Reported Trials

Clinical trials often use a variety of formats when publishing their results, including 1) mean changes and standard deviation (SD) from baseline, and 2) observed mean values and SD at follow-up time points. The first format is consistent with the BEST-ITP model, but the second format is not and specifically lacks the variance of the change since baseline, which requires the correlation between measurements from the same person.

The heterogeneous reporting formats may reduce the number of the included studies in meta-analysis as statistical methods often focus on one reporting format. For example, the BEST-ITP model uses baseline and changes (and SD) from baseline values. When experiencing heterogeneous reports of the primary effect measures for meta-analysis, there are three options: (i) use the studies with the format that is consistent with the model and eliminating the others, (ii) assume a value for the correlation between baseline and follow-up, based on the prior knowledge, for the within-subject correlation, and use that to impute values[142], and (iii) use a fully Bayesian approach to estimate a distribution of the correlation, which requires at least one study to report observed follow-up values and changes from baseline at all time points[143,144]. The first option reduces the number of studies included. Several correlation values may need to be examined for sensitivity analyses in the second option. We further examined option iii.

Abrams et al. proposed a fully Bayesian method to estimate the within-arm correlation from external evidence for the trials without appropriate reporting format in the meta-analysis[145]. Distribution of correlation, ρ, is skewed but ρ can be converted using the Fisher transformations, S, via the form, $S = \frac{1}{2}\ln\left(\frac{1+\rho}{1-\rho}\right)$. Different from ρ, the Fisher transformation is normally distributed. We use Bayesian methods to estimate the Fisher transformations from studies that

provide both follow-up and change values and then use the overall pooled mean of the Fisher transformations to estimate ρ. For the *I* trials that contain both follow-up and change values, we have the equations as follows:

$$S_i \sim N(\eta_i, \nu_i)$$

$$\eta_i \sim N(\delta, \omega^2), \quad i = 1, \ldots, I$$

$$\delta \sim N(0, 10000) \text{ and } \omega^{-2} \sim Gamma(0.001, 0.001)$$

$$\rho = \frac{e^{2\delta} - 1}{e^{2\delta} + 1}$$

S_i: observed Fisher transformation in the *i*th trial
η_i & ν_i : the underlying Fisher transformation and variance in the *i*th trial
δ: overall pooled mean of the Fisher transformation
ω^2: between-study variance

The estimated ρ can be applied to the below equation to calculate the variances of changes from baseline for the *J* trials only reporting values at all time points:

$$V(d_{jk}) = V(y_{jk1}) + V(y_{jk2}) - 2\rho\sqrt{V(y_{jk1})V(y_{jk2})}, \quad j = 1, \ldots, J$$

d_{jk}: value change from baseline to follow-up in the *k*th group of the *j*th trial
y_{jk1}: baseline measurement in the *k*th group of the *j*th trial
y_{jk2}: follow-up measurements in the *k*th group of the *j*th trial
ρ: the within-subject correlation

Inspired by the above models to estimate ρ for one follow-up measurement, we estimate ρ for the trials with multiple follow-up measurements by assuming a first-order autoregression model, AR(1), for correlation of a series of outcomes measured at different time points. For a series of measurements,$y_1, \ldots, y_{t-1}, y_t, y_{t+1}$, ..., recorded at time 1,…, *t-1*, *t*, *t+1*,… with a fixed time interval, the correlation of measurements are interval apart (y_{t-1} and y_t, or y_t and y_{t+1}, for

example) is ρ. The correlation of two observations t time periods apart is ρ^t. For example, cor(y_0, y_t)= ρ^t. The correlation matrix is as follows:

$$\begin{array}{c} \\ y_0 \\ y_1 \\ y_2 \\ y_3 \end{array} \begin{array}{c} \begin{array}{cccc} y_0 & y_1 & y_2 & y_3 \end{array} \\ \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \rho^3 & \rho^2 & \rho & 1 \end{bmatrix} \end{array}$$

By using information from the trials that report longitudinal outcomes with both changes from baseline and values for all follow-up time points, we can obtain observed within-trial correlation and then calculate the observed trial-specific correlation, ρ_i, by assuming AR(1) correlation. The corresponding Fisher transformation, S_i, can be obtained from ρ_i. Next, we can estimate the trial-specific Fisher transformation, η_i, and then the overall pooled mean Fisher transformation, δ. The overall correlation, ρ, can be estimated by δ, and then is applied to the trials which only report follow-up values. The mean and variance of the changes from baseline can be obtained by the ρ. For the studies focusing on treatment effects, we mainly use the published studies with follow-up and change measures in the placebo arms. The estimated ρ represents the natural correlation of the series of the outcome measures without intervention of drug effects.

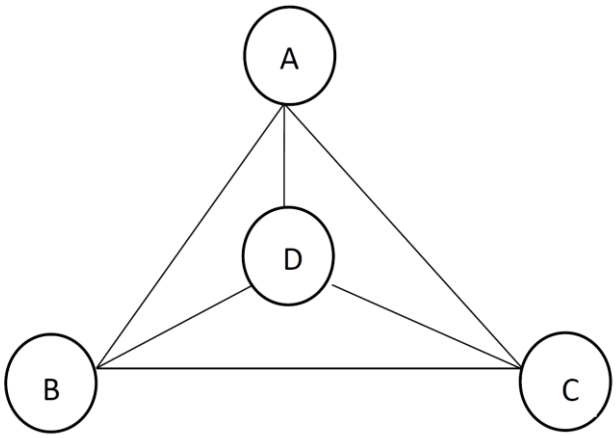
2.3.3 Treatment Comparison Inconsistency

NMA produces a set of contrast estimates of any treatment relative to any other in the established network, under the major assumption of consistent evidence between direct and indirect comparisons. Dias et al. presented several methods to detect inconsistency of evidence in networks[146].

Bucher et al. introduced a 2-stage method for a loop with three treatments and three head-to-head comparisons[147]. First, the estimates from RCTs with head-to-head comparisons and from RCTs without head-to-head comparisons are separately synthesized in each pairwise contrast. Second, the estimates from direct and indirect evidence are compared to detect conflicting results by using a z-score to examine the null hypothesis of no inconsistency. This method can be used in the network involving more than 3 edges of the loop. An indirect estimate of any edge can be obtained from the other edges, and its variance of the inconsistency term is the sum of the variances of all the direct comparisons forming the indirect estimate. Therefore, the increased number of edges in the loop increases the variance of the inconsistency estimate hence reducing the probability of detecting inconsistency.

Dias et al. proposed an unrelated mean effects (UME) model for general networks by using Bayesian statistical methods[146]. The UME model separately estimates each of the direct effect contrasts from available evidence. The results are then compared to the estimates from NMA to examine consistency by using their residual deviance and deviance information criterion (DIC). The posterior mean deviance of individual trials can be obtained from the MCMC samples in each of UME and NMA models, which can be used to identify the trials that contribute inconsistency of the meta-analysis if they are significantly different.

Lu and Ades proposed a model to check loop-based inconsistency by adding one parameter, inconsistency factor (ICF), *w*, to the consistency equations for every loop in the network[148]. For example, suppose we compare four treatment effects, including treatment A, B, C, and D. Taking treatment A as the reference treatment, we add an ICF for each loop to model inconsistency. The models are as follows (Figure 8):



$$d_{BC} = d_{AC} - d_{AB} + w_{ABC},$$

$$d_{BD} = d_{AD} - d_{AB} + w_{ABD},$$

$$d_{CD} = d_{AD} - d_{AC} + w_{ACD}.$$

d_{ij}: difference in treatment effect between treatment *i* and *j*.

Figure 8. Loop-based inconsistency test for NMA comparing treatment A, B, C, and D

All ICFs are from the same distribution, $N(0, \sigma_w^2)$. It is recommended to allow the posterior probability that the overall variance of the ICFs, σ_w^2, to be greater than the between-trial variance, σ^2, given the observed data. The greater posterior probability indicates potential inconsistency.

Node-splitting is more complicated than the previous methods, which a node indicates a specific pair comparison[149]. This method is displayed by a directed acyclic graph (DAG). The main concept is to split different sources of information for each node of interest in a DAG to examine potential conflict between the inferences derived from different sources. A node of

interest, the *k*th treatment vs. reference (d_{bk}), in the network has two posterior distributions generated from independent sources: trials that direct compare two treatments and trials that do not. We can detect conflict between these sources via comparing the two distributions. For treatment A and B, there are two posterior distributions for the mean treatment effect, d_{AB}: d_{AB}^{Dir} is from the trials directly comparing A and B, and d_{AB}^{Ind} is from trials providing indirect evidence, from a NMA that does not include trials directly compare treatment A and B. The trial specific treatment effects for treatment A and B (direct evidence) in the *i*th trial are drawn from a normal distribution with mean d_{AB}^{Dir} and variance σ^2, $\delta_{iAB} \sim N(d_{AB}^{Dir}, \sigma^2)$. The indirect evidence from the other trials is used to estimate d_{AB}^{Ind} via consistency equations. The inconsistency parameter $\omega_{AB} = d_{AB}^{Dir} - d_{AB}^{Ind}$ is used to test the hypothesis that the direct and indirect estimates are equal. Inconsistency for each pair of treatments should be checked separately.

The above methods are contrast-based (CB) models that estimate treatment effects comparing to the reference treatment. Hong et al. proposed an arm-based (AB) model that estimates the magnitude of each treatment effect. There are different assumptions between AB and CB models. The AB model assumes exchangeability of treatment arms across trials. The assumption for CB model is exchangeability of the relative treatment effects compared to the reference treatment across trials. The assumptions of studies at random and effects at random were assumed by the AB and CB models, respectively, in meta-analysis[150].

Taking binary data as an example, the CB model estimates the logit response with nuisance trial-specific mean effect, α_i, and trial-specific relative treatment effect, δ_{ik}, representing *k*th treatment vs. reference in trial *i*.

$$logit(p_{ik}) = \alpha_i + \delta_{ik}$$

Instead, the AB random effect model estimates the logit response probability as follows:

$$logit(p_{ik}) = \theta_k + \eta_{ik}$$

θ_k: the fixed effect representing the mean effect of treatment *k*
η_{ik}: the random effect for treatment *k* in trial *i*.

The random effects $\vec{\eta}_i$ for trial *i* are from a multivariate normal distribution:

$$\vec{\eta}_i = (\eta_{i1}, \dots, \eta_{iK})^T \sim MVN(0, \Sigma)$$

Σ: an $K \times K$ unstructured covariance matrix representing correlation between treatment arms in each trial. A non-informative Wishart prior on Σ_k^{-1}.

Expanding application of the AB model from the cross-sectional data to the longitudinal data, we incorporated the functional form of the BEST-ITP model with the AB model to obtain:

$$\mu_{ikl} = (\theta_k)\left(\frac{1 - e^{p_k t_{ikl}}}{1 - e^{p_k d_i}}\right) + \eta_{ik}$$

$$\bar{Y}_{ikl} \sim N(\mu_{ikl}, \sigma_{ikl}^2)$$

$$\frac{S_{ikl}^2 (n_{ikl} - 1)}{\sigma^2} \left(\frac{1 - e^{p_k d_i}}{1 - e^{p_k t_{ikl}}}\right)^2 \sim \Gamma\left\{\frac{(n_{ikl} - 1)}{2}, \qquad 2\right\}$$

$$\sigma_{ikl}^2 = \frac{\sigma^2}{n_{ikl}}\left(\frac{1 - e^{p_k t_{ikl}}}{1 - e^{p_k d_i}}\right)^2$$

$$\bar{Y}_{ikl} = \left(\theta_k + \frac{\epsilon_{ikl}}{\sqrt{n_{ikl}}}\right)\frac{1 - e^{p_k t_{ikl}}}{1 - e^{p_k d_i}} + \eta_{ik}, \qquad Var(\epsilon_{ikl}) = \sigma^2$$

θ_k: the fixed mean outcome change from baseline of the *k*th treatment at the end of the treatment.
μ_{ikl}: the hyperparameter mean of the observed outcome changes from baseline for the *k*th treatment at time *l* in trial *i*.
$\bar{Y}_{ikl}$: the observed outcome change from baseline for treatment *k* at time *l* in trial *i*.
s_{ikl}: the corresponding observed standard deviation
n_{ikl}: the numbers of the participants for the *k*th treatment at time *l* in trial *i*.
d_i: the treatment duration for trial *i*

t_{ikl}: the interim follow-up duration of treatment k at time l in trial i with $t_{ikl} \leq d_i$.
σ_{ikl}: the corresponding hyperparameter standard deviation.
p_k: the change pattern within therapeutic duration for the kth treatment.
ϵ_{ikl}: the residual error.
We are interested in the contrast of any two treatments, which is $\theta_k - \theta_{k\prime}$, where $k \neq k'$.

To detect the discrepancy of direct and indirect evidence for comparing two treatments (e.g. A and B), the trials can be categorized into 4 groups:

(i) trials including both A and B,

(ii) trials including A but not B,

(iii) trials including B but not A, and

(iv) trials including neither A nor B.

The fixed effects for treatment A and B in group (i) are denoted as $\theta_A^{(i)}$ and $\theta_B^{(i)}$, and the effects in the other groups have the similar notations. The discrepancy between A and B can be tested by the posterior distribution of the discrepancy factor $\Delta_{AB} = \left(\theta_A^{(i)} - \theta_B^{(i)}\right) - \left(\theta_A^{(ii)} - \theta_B^{(iii)}\right)$, which is the difference of treatment effects in trials with direct evidence minus the difference in trials with indirect evidence. If zero is in the far tail of the posterior distribution, we conclude that inconsistency happens. Borrowing the concept of the node-splitting method that only defines the sources of evidence as direct and indirect comparisons, the trials in group (ii), (iii), and (iv) can be combined as group (ii) which represents indirect comparisons. The discrepancy factor is $\Delta_{AB} = \left(\theta_A^{(i)} - \theta_B^{(i)}\right) - \left(\theta_A^{(ii)} - \theta_B^{(ii)}\right)$. When inconsistency is detected, the random effects η_{iA} and η_{iB} can be used to identify the trials with extreme variations, which provide information of treatment A and/or B. Afterwards, we can refit the model excluding the

identified trials with extreme variations, and examine improvement of the model fit by using deviance information criterion (DIC).

2.4 SIMULATION

2.4.1 Design

We conducted simulations to evaluate performance of combining the proposed methods for longitudinal repeated outcome NMA. One set of simulations tested heterogeneous reporting and another set tested consistency verification.

For the both simulations, we generated data using the BEST-ITP and AR(1) correlation models. The primary data set was simulated using the known parameter values and comprised of baseline, changes from baseline, and follow-up values at all time points. The changes from baseline represent the treatment effects which are the main interest of the study. Each generated data set consists of 24 trials and each trial compared two of the three treatments (placebo, treatment A and treatment B) with two follow-up visits at 3 and 6 months, respectively. We generated 1000 data sets from the BEST-ITP model and AR(1) correlation between the baseline and the follow-up values with the parameter values similar to Ding's paper:

$$\begin{cases} \phi_i \sim (\mu_\phi, \tau_\phi^2), & \mu_\phi = -3, \tau_\phi^2 = 1, i = 1, \dots, 24 \text{ trials} \\ p_1 = -0.10, & p_2 = -0.15, \quad p_3 = -0.20 \\ \theta_1 = 0, & \theta_2 = -1.0, \quad \theta_3 = -1.5 \\ \sigma^2 = 9 & \\ \eta_i \sim N(\delta, \omega^2), & \delta = 0.5, \omega = 0.15, i = 1, \dots, 24 \text{ trials} \\ \overline{B_i} \sim (\mu_b, \sigma_b^2), & \mu_b = 15, \sigma_b = 0.3, i = 1, \dots, 24 \text{ trials} \end{cases}$$

ϕ_i is the trial-specific mean effect, which is normally distributed with mean, μ_ϕ, and standard deviation, τ_ϕ, for the *i*th trial. p's and θ's are the target parameters, which represent the change patterns and the mean treatment effects at the end of treatment. η_i is the Fisher transformation for the *i*th trial. δ is the pooled mean Fisher transformation and ω is the

corresponding standard deviation. B_i is the mean baseline value for the ith trial, which is normally distributed with mean, μ_b, and standard deviation, σ_b. The sample sizes, n_{ikl}, for the *i*th trial and *k*th treatment at time *l* ranges from 20 to 50 without loss of follow-up for all visits and the sample sizes of the two arms are balanced in each study.

The primary simulated data were modified to examine the performance of the proposed methods according to the following scenarios:

(1) The data sets examine the Fisher transformation with AR(1) correlation model for longitudinal repeated values: Two trials consisting of the placebo arm reported baseline, changes from baseline, and follow-up values. Two trials only reported baseline and follow-values and the rest trials reported baseline and changes from baseline.

(2) Three separate scenarios examine the AB model for longitudinal repeated values:

   a. Four trials (trial 3, 6, 9, and 12) consisting of the treatment 3 arm reported changes from baseline with $\theta_3 = -6$ instead of -1.5.

   b. Four trials (trial 3, 6, 9, and 12) consisting of the treatment 3 arm reported changes from baseline with $\theta_3 = -7.5$ instead of -1.5.

   c. Four trials (trial 3, 6, 9, and 12) consisting of the treatment 3 arm reported changes from baseline with $\theta_3 = -9$ instead of -1.5.

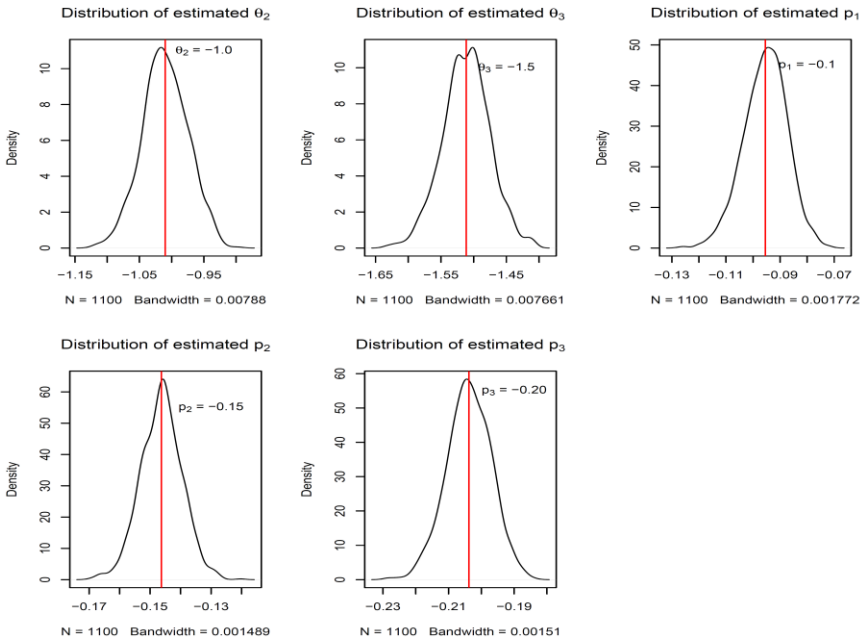
2.4.2 Statistical Software

The Bayesian statistical methods were conducted by using WinBUGS v1.4.3, JAGS 4.3.0, "R2WinBUGS", and "RJAGS" package in R program v3.2.3. The numbers of iteration, burn-in, and thinning to obtain the MCMC sampling was determined by the results of the convergence diagnostics, including tracing plots, autocorrelation function plots, and Geweke.

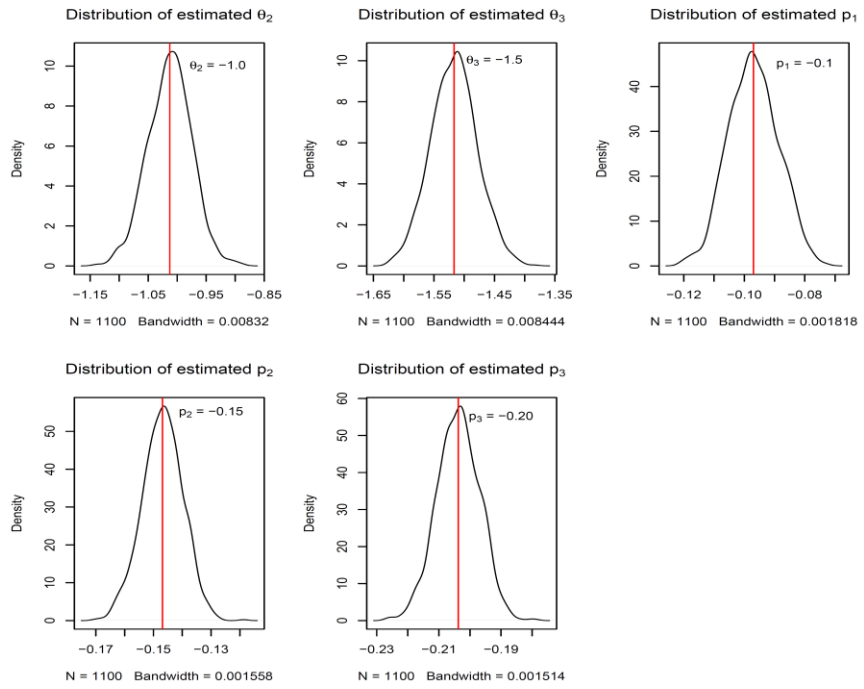
2.4.3 Results

The first scenario examined performance of the Fisher transformation and AR(1) correlation models. The placebo arms from the two trials reporting baseline, changes from baseline, and follow-up values were used to estimate Fisher transformation using the full Bayesian statistical method. The pooled Fisher transformation value was converted to correlation, ρ. The variances of changes from baseline for the trials that reported baseline and follow-up values were obtained using ρ, and the new data sets were available for further analyses. The target parameters, θ's and p's, are estimated from the primary and the new data sets using the BEST-ITP model.

Figure 9 displayed the density curves of the posterior samples for each of the parameters, θ's and p's, from both the original and the modified data set. The true values are printed on each plots and the vertical lines represent the mean of the parameter in the 1000 posterior samples. The estimated mean value of each parameter is close to the true value, which indicates that the proposed model performs well in estimating parameters. We apply the proposed model in all 1000 data sets and summarize the estimated parameter values from the 1000 data sets by presenting the estimated bias, standard deviation, and mean squared error (MSE) (Table 2). The results indicate that AR(1) model and Fisher transformation can appropriately estimate the final treatment effects.



(A) Original



(B) Modified

Figure 9. Plot of posterior distribution from the model for one simulated data set (original and modified)

Table 2. Bias and MSE of estimates from the primary and the modified data sets

Parameter	θ_2			θ_3			p_1		
	Bias	SD	MSE	Bias	SD	MSE	Bias	SD	MSE
Primary	0.002	0.071	0.005	-0.001	0.074	0.005	0.001	0.016	0.000
Fisher	0.001	0.071	0.005	-0.001	0.074	0.005	0.002	0.016	0.000

Parameter	p_2			p_3		
	Bias	SD	MSE	Bias	SD	MSE
Primary	0.000	0.014	0.000	0.050	0.014	0.003
Fisher	0.000	0.014	0.000	0.050	0.014	0.003

The data sets examining performance of the AB model on detecting the inconsistent estimates from direct and indirect evidence were generated based on three separate scenarios. Table 3 shows the discrepancies of the estimates from the direct and the indirect evidence in each scenario. The table shows the mean discrepancy values for individual contrast pairs from all 1000 simulations and their 95% credible interval. The % inconsistent is the percentage of the estimated discrepancy values outside of the 95% credible interval among 1000 simulations. For the data with consistent parameter values, the mean discrepancy values in individual contrast pairs are very small. For the data with inconsistent parameter values in the three trials, the discrepancies are significantly away from zero in the contrast estimates of treatment 2 vs. 3 and treatment 3 vs. 1. Taking the data including four trials with θ_3= {-1.5, -6} as an example, the direct contrast estimate of treatment 1 and treatment 3 is -3.75, but the indirect contrast estimate is -1.5. The discrepancy between direct and indirect contrast estimates of treatment 1 vs. treatment 3 is 2.25, which is close to our simulation result of 2.35. The direct contrast estimate of treatment 2 and treatment 3 is -0.5, but the indirect estimate is -2.75. The discrepancy between

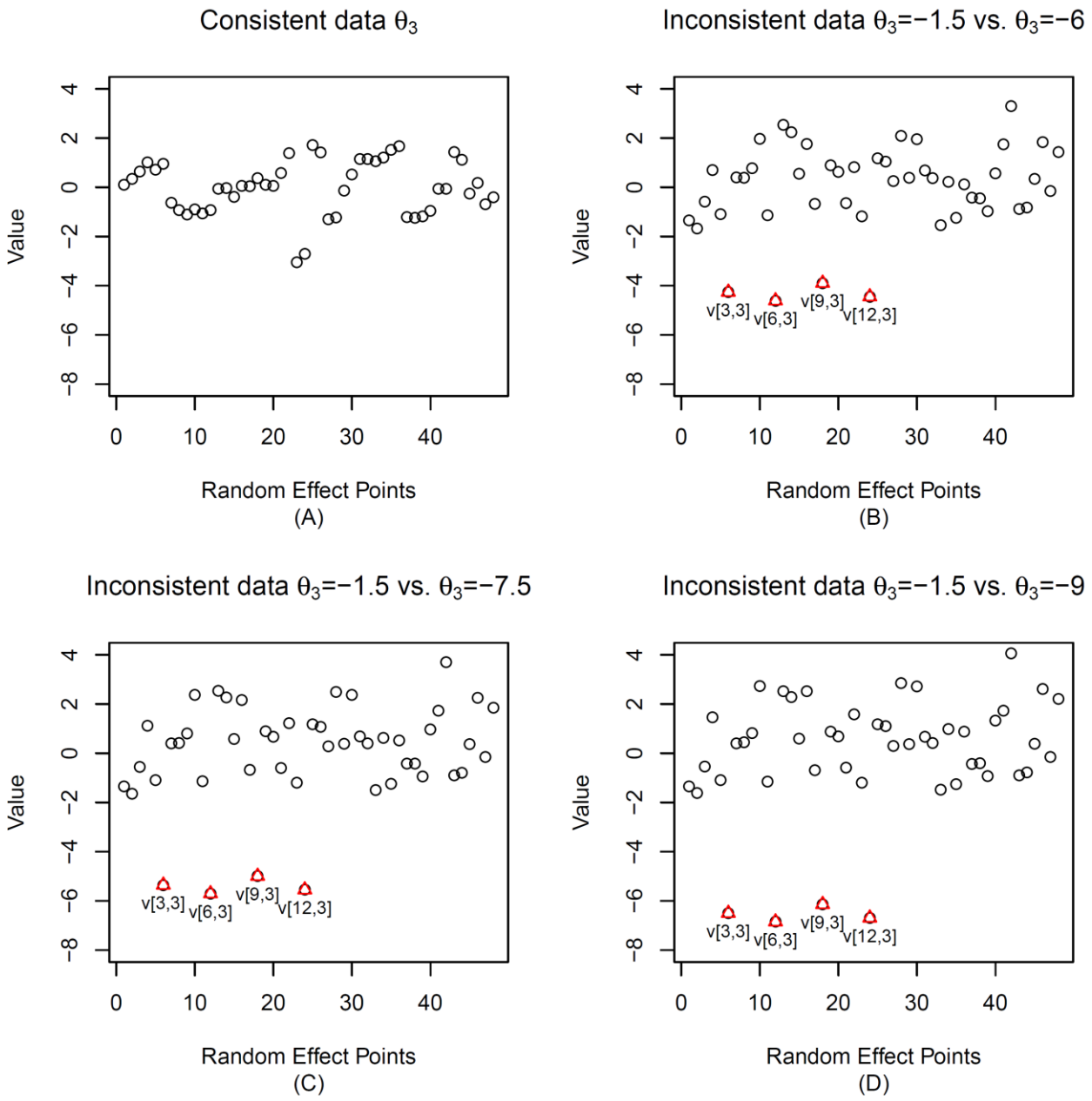
direct and indirect contrast estimates of treatment 2 vs. treatment 3 is -2.25, which is also close to the simulation result. The treatment estimates of the treatment 3 are inconsistent from the two evidence sources. The power of the AB model to detect inconsistency grows as the effect size increases.

To identify the trials that induce the inconsistent results, we examined the random effects that express variation of treatment effects within trials. When the treatment effects are consistent across trials, the random effects should be multivariate normally distributed around the mean zero. The random effect values representing the trials with inconsistent treatment B effects are significantly different from the random effect values for the trials with consistent treatment effects. Figure 10 shows the random effect values estimated by the AB model in one data set. The red dots indicate the significant different random effect values representing treatment 3 in trial 3, 6, 9, and 12. The result is compatible to our scenarios to demonstrate performance of the AB consistent test.

Table 3.Discrepancy of estimates from direct and indirect evidence

Occurrence of inconsistent treatment 3 in trials comparing to treatment 1		Discrepancy		
		Treatment 1 vs. Treatment 2	Treatment 1 vs. Treatment 3	Treatment 2 vs. Treatment 3
Treatment 3, all trials: -1.5	Mean	-0.00	0.00	-0.01
	95% CI	(-1.03, 1.02)	(-0.99, 1.00)	(-1.00, 0.98)
	% inconsistent	1%	0.60%	0.20%
Treatment 3 4 trials: -1.5 4 trials: -6	Mean	0.04	2.35	-2.25
	95% CI	(-0.98, 1.05)	(1.16, 3.52)	(-3.29, -1.21)
	Power	0%	49.20%	74.40%
Treatment 3 4 trials: -1.5 4 trials: -7.5	Mean	0.04	3.01	-3.00
	95% CI	(-0.97, 1.05)	(2.02, 4.01)	(-4.00, -1.97)
	% inconsistent	0%	62.10%	91.70%
Treatment 3 4 trials: -1.5 4 trials: -9	Mean	0.04	3.76	-3.74
	95% CI	(-0.99, 1.07)	(2.76, 4.77)	(-4.78, -2.71)
	% inconsistent	0%	76.70%	98.60%

(A) all trials with θ_3= -1.5; (B) 4 trials of θ_3= -1.5, 4 trials of θ_3= -6; (C) 4 trials of θ_3= -1.5, 4 trials of θ_3= -7.5; (D) 4 trials of θ_3= -1.5, 4 trials of θ_3= -9



v[3,3]: Treatment 3 in Trial 3, v[6,3]: Treatment 3 in Trial 6, v[9,3]: Treatment 3 in Trial 9, v[12,3]: Treatment 3 in Trial 12
Red dots: extreme random effect values

Figure 10. Random effects from consistent data and inconsistent data.

2.5 DISCUSSION

Our proposed method expands applications of the Ding's longitudinal BEST-ITP NMA model in two ways for 1) incorporating articles with different reporting formats, and 2) testing inconsistency of estimates from direct and indirect evidence.

The existing NMA studies use the final outcomes from published articles. As repeated measurements are available, new NMA techniques are required to analyze such data and Ding's BEST-ITP model specifically focuses on estimating cumulated drug effects throughout the treatment course. This method estimates treatment effects reported as changes from baseline. Some studies that report follow-up values may be excluded, reducing the number of studies included. In addition, the inconsistency tests have not been developed for this method. Prior to this study, the assumption of consistency between direct and indirect effects in a longitudinal NMA could not be examined, which limited the application of Ding's model in the real-world data. Our proposed methods expand Abram's method to convert multiple follow-up values into changes from baseline by appropriately estimating the variances of changes from baseline values. This allows more studies to be included in a NMA. This can have a large impact, especially for studies on rare diseases as they usually have fewer RCTs with small sample sizes. By expanding Hong's AB model to test inconsistency of estimates from direct and indirect evidence from Ding's model, the assumption of NMA, and hence the results from Ding's model, can be verified.

Our simulation demonstrated using Bayesian approach and AR(1) model to estimate Fisher transformation and to obtain variances of changes from baseline performs well. The results showed that the estimated treatment effect and shape parameters are very close to the true values with small biases and MSEs. The simulation results demonstrated efficiency of Ding's

method in estimating treatment and shape parameters using the primary data sets and the modified data sets that used the Bayesian approach and AR(1) model to convert follow-up values into changes from baseline.

The three separate scenarios were used to demonstrate effectiveness of the AB model on detecting discrepancy of estimates from direct and indirect evidence. The power of the AB model to test inconsistency of the estimates from direct and indirect evidences depends on magnitude of the discrepancy between the estimates from the two information sources. The larger different the direct and indirect evidences are, the more power the AB model has to detect inconsistency. The values of the random effects that represent variation of the treatment effects across trials effectively identify the treatment and trials that have inconsistent estimates. We showed that AB model can effectively test the assumption of NMA by identifying treatments and trials that provide inconsistent information.

The method proposed in this study has several strengths. First, our method takes the correlation of the longitudinal data into consideration and converts the heterogeneous reporting formats into the homogenous reporting formats. When we want to convert the follow-up values into changes from baseline, the mean estimates can be calculated straight forward by taking difference between the follow-up value and the baseline; however, the variances must take correlations between the follow-up value and the baseline into consideration. Our method can appropriately estimate correlation between the follow-up value and the baseline. The estimates are closer to the true values if more data are available using the Bayesian approach. Second, more published results can be included in the NMAs using the BEST-ITP model. By efficiently obtaining the homogeneous reporting format, we can increase the sample sizes of the NMAs by including more trials. Third, we can examine the assumption of NMA, consistency of estimates

from direct and indirect evidence, for the BEST-ITP model. The previously proposed inconsistent methods only focus on cross sectional data. Incorporating the BEST-ITP model with the AB model can effectively detect inconsistency of estimates from direct and indirect evidence and identify the trials and the treatment that cause inconsistency for longitudinal data.

Our methods have some limitations. We may underestimate variability of the treatment impacted outcomes by assuming the correlation between the baseline and follow-up values is the same in placebo arm and the treatment arm. The assumption ignores variation of outcomes impacted by treatment effects. If more data, studies reporting both follow-up and changes from baseline, for the treatment impacted outcomes are available, we can simply use the available information to estimate the corresponding correlation, ρ, for individual treatment impacted outcomes. However, using the data representing the natural course of the outcome over time may be more appropriate than using the data with mixture of the outcomes impacted by different treatments if the individual treatment impacted outcome data are unavailable. The variations of the correlation, ρ, may be large in the data with outcomes impacted by different treatments, and the model may not converge if the available data are scarce. Using AR(1) structure for correlations may be naïve. However, assuming unstructured relationship requires more data for the model to converge. The requirement is hard to achieve for the studies focus on rare diseases. We can use different correlation structures as the sensitivity tests to test if we can obtain robust estimates.

My future work will develop a robust method to account for correlation of follow-up and baseline values. In addition to reporting follow-up values, some studies report median, lower limit, and upper limit of the follow-up values. Appropriate statistical methods are needed to convert such report format into the format reporting changes from baseline. Though the AB

model performs adequately in the simulation, the method requires reasonable number of included trials to avoid unstable estimates of the random effects. We will work on methods to detect inconsistency in NMA with small sample sizes.

3.0 PAPER 2: BAYESIAN NETWORK META-ANALYSIS OF BREAST CANCER HORMONE THERAPIES ON CHANGES OF LIPIDS

3.1 ABSTRACT

Background: Aromatase inhibitors (AIs) improve disease free survival (DFS) for postmenopausal hormone receptor positive breast cancer (BC) patients compared to selective estrogen receptor modulators (SERMs). As BC patients survive longer, they are more likely to develop chronic diseases, with cardiovascular diseases (CVDs) being the critical one that threatens survival. One meta-analysis showed that AIs increase the risk of CVDs compared to a SERM, tamoxifen. However, it is uncertain whether the risk of CVDs for AI users is higher than BC patients without hormone treatment. Dyslipidemia is a CVD risk factor. We used dyslipidemia as an early risk factor of CVDs and applied Bayesian network meta-analysis to examine the effects of specific hormone treatment on changes of lipid profiles in hormone receptor positive breast cancer survivors.

Methods: Randomized clinical trials (RCTs) investigating effects of all types of adjuvant hormone treatment (tamoxifen, toremifene, anastrozole, letrozole, and exemestane, and placebo) on lipids were searched from two online databases, PubMed and EMBASE. The RCTs recruiting

post-menopausal BC patients without residual cancer after primary treatment were eligible for our meta-analysis. The articles that did not report results from all intervention arms in the study were excluded. The studies reporting lipid values at each follow-up visit were converted to changes from baseline. Bayesian network meta-analysis for longitudinal data evaluated the drug effects on lipid profiles. Age of participants, baseline lipid values, and prior usage of tamoxifen were examined to determine heterogeneity of the treatment effects. Consistency of the estimates derived from direct and indirect evidence was examined using the arm-based method.

Results: Toremifene is the best therapeutic option among all hormone drugs for the lipid profiles. Tamoxifen improves cholesterol, but worsens triglycerides. Most AIs do not significantly impact lipids, except exemestane decreasing HDL-c and anastrozole decreasing TGs. Compared to tamoxifen, AIs worsen most lipids, except triglycerides. Age, baseline lipid value, and prior usage of tamoxifen modify the treatment effects in most lipids. However, ranking the drugs based on their benefit for each lipid value produces similar result after accounting for effect modification.

Conclusions: SERMs are beneficial to most lipid profiles, but AIs do not have consistent impacts on lipids. Tailoring hormone drug prescriptions based on medical conditions of BC patients is recommended.

3.2 INTRODUCTION

Selective estrogen receptor modulators (SERMs), especially tamoxifen, have demonstrated improved disease free survival (DFS) and overall survival (OS) for hormone receptor positive breast cancer (BC) patients[151,152]. Five-year of tamoxifen use provides better event-free survival (EFS) and OS compared to only 1-2 years of treatment[153]. For early stage breast cancer, adjuvant 5-year tamoxifen can reduce the 15-year recurrence and mortality rate by 11.8% and 9.2%, respectively compared to the patients without adjuvant hormone therapies[62]. The ATLAS trial compared 10-year and 5-year tamoxifen usage and reported significantly reduced recurrence (18% vs. 20.8%, p=0.002) and breast cancer mortality (9.7% vs. 11.4%, p=0.01) with the longer duration of treatment. It also revealed that longer use of tamoxifen increases risk of endometrial cancer (RR=1.74, p=0.0002) and pulmonary embolism (RR=1.87, p=0.01), but reduces incidence of ischemic heart disease (RR=0.76, p=0.02)[63].

Aromatase inhibitors (AIs) restrict production of estrogen from the peripheral tissue, which is recommended for postmenopausal hormone positive BC patients. AIs compared to tamoxifen-only treatment provide longer DFS[154–168]. However, OS benefits were not consistent in clinical trials. Compared to tamoxifen treatment, some studies showed improved OS after 1-3 years of AI usage[162,163]. A larger number of studies revealed comparable OS in both AI and tamoxifen arms within 2 to 10 years of follow-up [156,158,165,167,168]. The fact that better DFS does not reflect better OS may be related more non-recurrence BC deaths in the AI treatment group[161,165,166].

Among the non-recurrence BC deaths, cardiovascular diseases (CVDs) are important complications to monitor partly because of cardiotoxicity from BC treatment and partly because of significant increased CVD risk after transition from pre-menopause to post-menopause. A

meta-analysis analyzed 7 trials with 30,023 patients and showed that longer duration of AI usage was associated with higher risk of CVDs, but not significantly related to non-BC deaths[7]. A cohort study showed that extremely low concentration of estradiol is associated higher risk of ischemic heart disease (IHD) and increased total cholesterol, but not related to HDL serum levels[109]. Therefore, AIs, which block production of estrogen for postmenopausal women, can induce extremely low levels of estradiol and then may increase the risk of dyslipidemia and CVDs for postmenopausal BC patients on AIs.

Though the meta-analysis revealed higher odds of CVDs for AI users compared to those who taking tamoxifen, the results do not indicate that AI increases the CVD risk. Several studies have already shown cardiac protection from tamoxifen[169–174]. Also, the meta-analysis aggregated non-steroidal and steroidal AIs and only used the final outcomes of the trials, ignoring the patterns of CV incidence across time. We hypothesize that changes in lipid profiles are different among hormone therapies across time. Network meta-analysis allows us to disentangle these relationships.

3.3 METHODS

3.3.1 Search Strategy and Selection Criteria

Published articles were searched using PUBMED and EMBASE (host: OVID) for records up to January 31st, 2016. Gray literature was searched for abstracts from two conferences: American Society of Clinical Oncology Annual Meetings and San Antonio Breast Cancer Symposium Annual Meetings, from 2000 to 2015. Only English language articles were included. The search algorithm was described in the supplementary material (Table S 1 & Table S 2). We excluded studies that did not focus on human subjects, were not randomized clinical trials, and were not investigating adjuvant hormonal therapies. The studies only reporting mean values of lipid profiles without standard deviation (SD) were excluded. The studies that did not report results of all arms were excluded.

3.3.2 Study Selection and Data Extraction

Data on lipid values (follow-up and/or baseline) were extracted by HH. Discrepancies were resolved by consensus of the author HH and MB. The lipid profiles studied included total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and triglycerides (TG). The aromatase inhibitors included both non-steroidal (anastrozole and letrozole) and steroidal (exemestane) types. The selective estrogen receptor modulators include tamoxifen and toremifene.

3.3.3 Outcomes

Serum values of lipid profiles, including TC, HDL-C, LDL-C, and TG, during and after hormone therapies are the major outcome of this meta-analysis. The results from different articles but the same clinical trials were pooled together. Four reporting formats of the outcome values were included: 1) mean and standard deviation (SD) of changes from baseline values and/or measurements at all follow-up time points; 2) median and ranges of the changes from baseline values and/or measurements at all follow-up time points; 3) mean and SD of the percent change from baseline at all follow-up time points; and 4) median and ranges of the percent change from baseline at all follow-up time points.

3.3.4 Quality Assessment – Risk of Bias

Quality of the studies were evaluated using the Cochrane Collaboration's tool to assess risk of bias, including selection, performance, detection, attrition, and reporting biases[175]. The assessment of each article was judged and recorded in a standard form by HH.

3.3.5 Statistical Analysis

The aim of this study is to estimate the mean effect of hormone therapy on changes of lipid profiles throughout the therapeutic period. We developed a data set consisting of the format reporting mean and SD of changes from baseline values at all follow-up time points, conducted

network meta-analysis for the longitudinal data, and examined consistency of the estimates using the methods proposed (manuscript in progress). The statistical approaches included three steps. The first step is to convert all reported formats into a baseline and change from baseline and associated SD's. The second step is the network meta-analysis using the BEST-ITP model. The third step examines the consistency assumption of the network meta-analysis and heterogeneity of the included trials.

For step one, we converted the reported measurements at all follow-up time points into changes from baseline, using the information from the articles that reported both changes from baseline values and measurements at all follow-up time points. Only the data from the placebo arm in these articles were used to estimate correlation, ρ, between the baseline value and the follow-up measurements. We assumed autoregression model of order 1, AR(1), for correlation between baseline and the measurement at the 6-month intervals from the placebo. The Fisher transformation was applied to the observed correlations. By using the fully Bayesian approach proposed by Abrams et al.[145] and expanded by HH, we estimated the pooled Fisher transformation, and then obtained the overall correlation, ρ, between measurements which are observed 6 months apart. The process was performed separately for each lipid type. The SDs of the changes from baseline was calculated using the estimated ρ, and the SDs of the baseline value and the follow-up measurement for the articles only reporting measurements at all follow-up time points. For the articles that reported the median, lower, and upper range of the changes from baseline, we assumed that they are equivalent to the mean, lower and upper limits of the 95% confident intervals. The percentages of changes from baseline and the corresponding SD's were multiplied by the baseline mean values.

The second step uses network meta-analysis to estimate the treatment effects on changes of lipid profiles. Our data comprise longitudinal records of lipid changes, so we used the model proposed by Ding and Fu[134] to account for the trends of the treatment effects over time. The method assumes the magnitude of the treatment effects may gradually change monotonically over time and then achieve a plateau. The speed to achieve the maximal treatment effect is different among all drugs, so the early responses may not strongly predict the final treatment effects. Bayesian statistical methods were used to estimate the parameters of interests, including the final treatment effects at the end of the therapeutic duration and the patterns of the treatment effects throughout the therapeutic duration. The Markov Chain Monte Carlo (MCMC) sampling output was used to obtain relevant statistics from the posterior distributions. We computed all pairwise drug comparisons for each lipid, the probabilities of the ranks for individual drugs, and the surface under the cumulative ranking curve (SUCRA) of each drug. The estimated mean effects of individual drugs over time were graphed to visualize the patterns of lipid value changes over time.

The third step examines the assumption of consistent estimates from the direct and indirect evidence. The arm-based (AB) model proposed by Zhao et al. was used to detect inconsistency of estimates from the direct and the indirect evidence for each pairwise treatment comparison[176]. When inconsistent contrast estimates were detected, we identified studies produced the inconsistent evidence. We re-ran the model to check for consistency after excluding the inconsistent trials to ensure final consistency. Heterogeneity of the trial results due to key demographics was examined using metaregressors (median ages, baseline values, or prior usage of tamoxifen)[177].

Sensitivity analyses were performed by removing studies reporting median changes of lipids and comparing the fixed-effect BEST-ITP model with the random-effect BEST-ITP models. We used R version 3.2.3 with "R2WinBUGS" package to incorporate WinBUGS software version 1.4.3 to perform the Bayesian statistical methods via MCMC simulations for all analyses.

3.4 RESULTS

We identified 114 articles by reviewing the titles and abstracts. Ninety-seven articles were excluded for the following reasons: duplication (n=27), no available data (n=7), no appropriate lipid data (n=34), and inappropriate study design and report (n=29). Total 17 articles from 13 individual clinical trials were included in our meta-analysis (Figure 11 & Table S 3). Five of the included studies reported sub-cohorts of the randomized clinical trials. All studies are 2-arm randomized design and were published between 1990 and 2012. The number of enrolled subjects in each trial ranged from 48 to 411. The 13 trials included a total of 1,913 subjects, who were randomized to 6 therapeutic arms: placebo (n= 508), tamoxifen (n= 344), toremifene (n= 120), letrozole (n= 312), anastrozole (n= 57), and exemestane (n= 572). At least 2 trials contributed to each node in the therapeutic network. (Figure 12). The major problems in the bias assessment included lacking reporting for methods of randomization and allocation concealment of participants (Table S **4**).

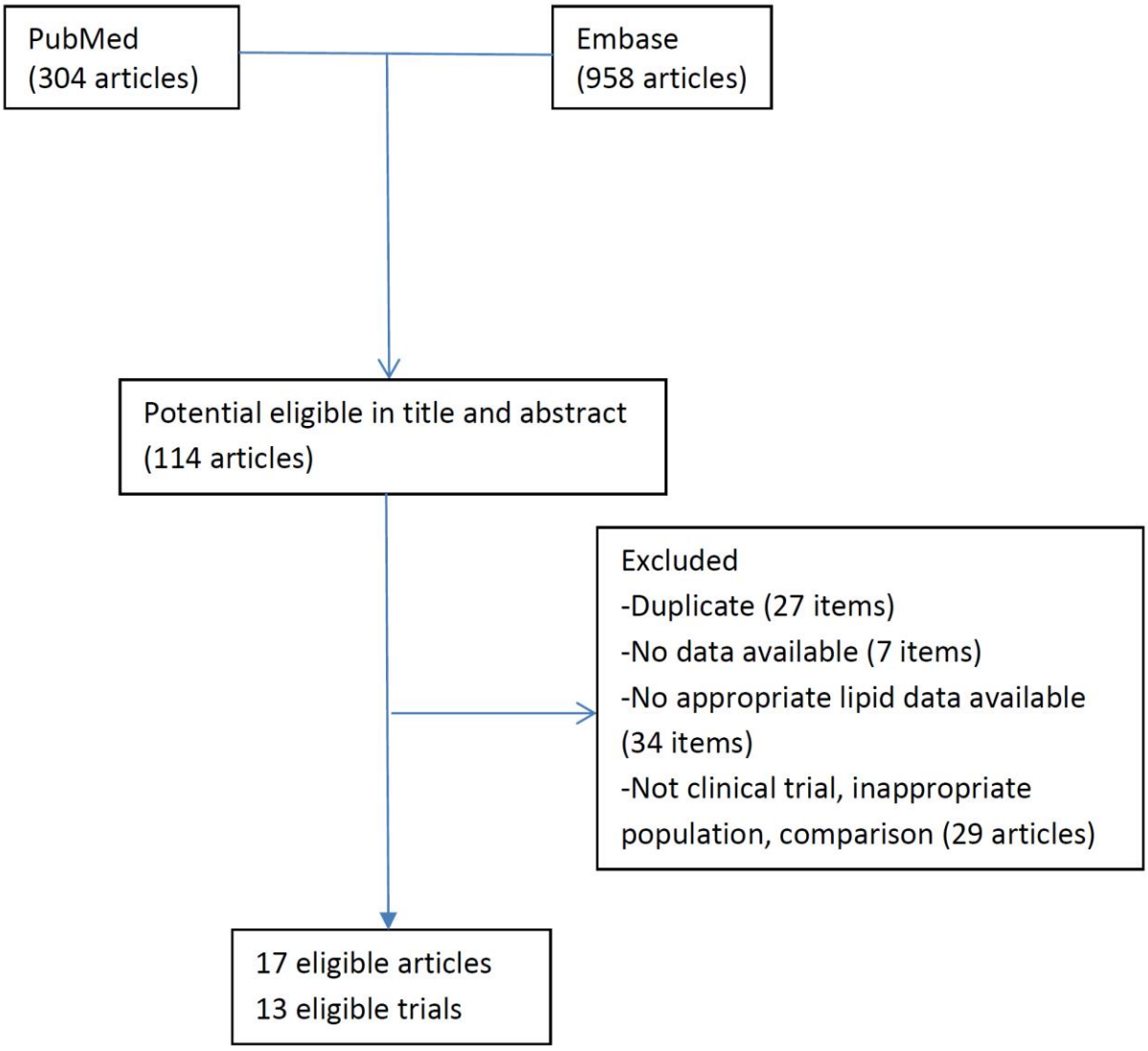
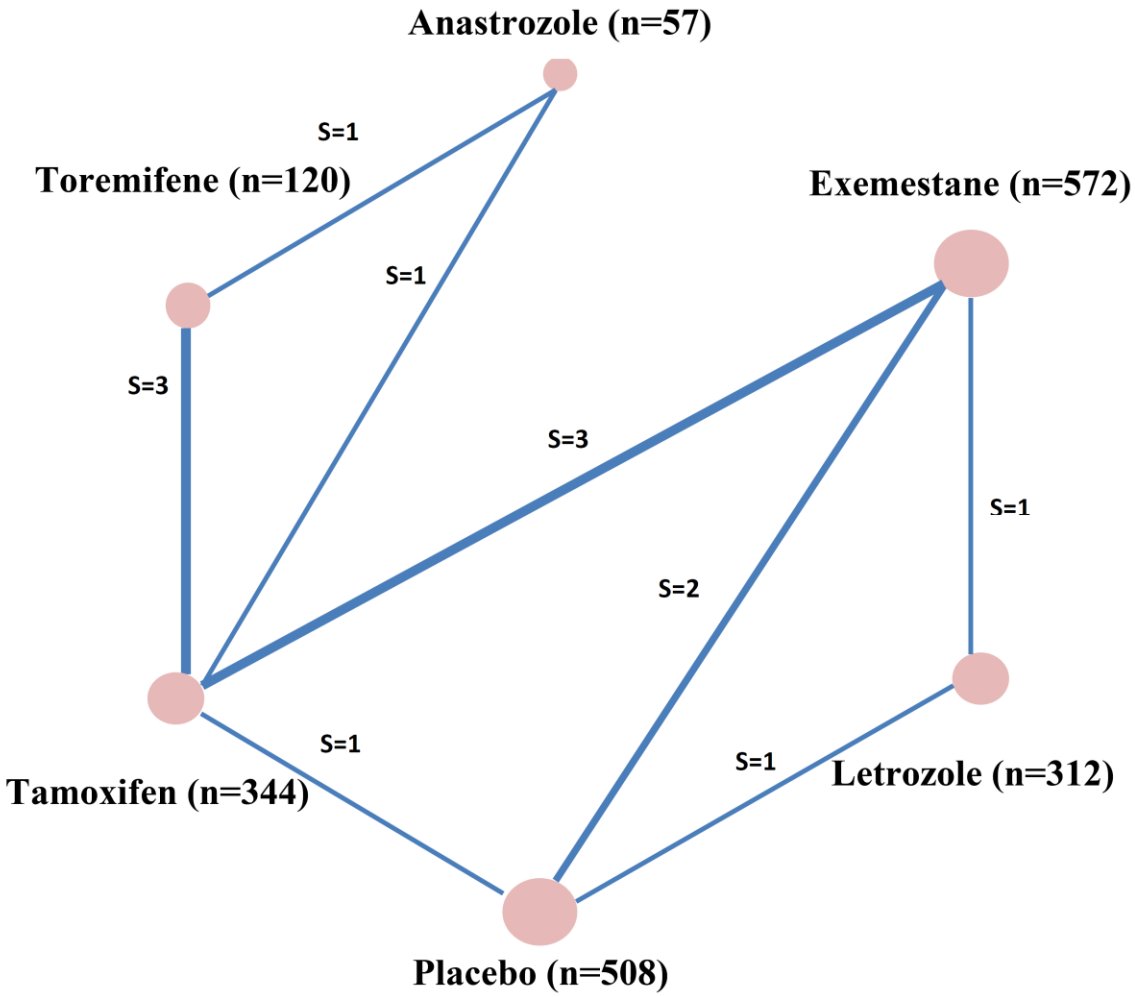


Figure 11. Flow chart of literature search and selection



n: number of participants; S: number of studies

Figure 12. Network graph of breast cancer hormone drugs in the available studies

The mean age of the participants in the included trials ranged from 57 to 65 years old (Table S **5**). The sample sizes for each arm ranged from 23 to 211. Participants in 5 of the 13 trials accepted tamoxifen treatment prior to enrolling to the trials. Eight of the 13 trials provided information regarding weight, height, and body mass index (BMI), and more than half of them with subjects having mean BMI ≥25, classified as overweight. The overall follow-up duration

ranged from 3 month to 60 months for the included trials. The trials regularly measured the lipid values and the intervals between measurements ranged from 2 month to 12 months.

The effects of hormone therapies on changes from baseline for the lipid profiles were listed in Table 4. Toremifene significantly improved all lipid profiles (increasing HDL-C, but reducing TC, LDL-C, and TG). Tamoxifen significantly reduces TC and LDL-C, but increase TG. Anastrozole significantly reduced TG. Exemestane significantly decreased serum levels of HDL-C. All other effects of drugs on lipids were not significant.

Table 4. Estimated 5-year effects of hormone therapy on changes from baseline for lipid profiles

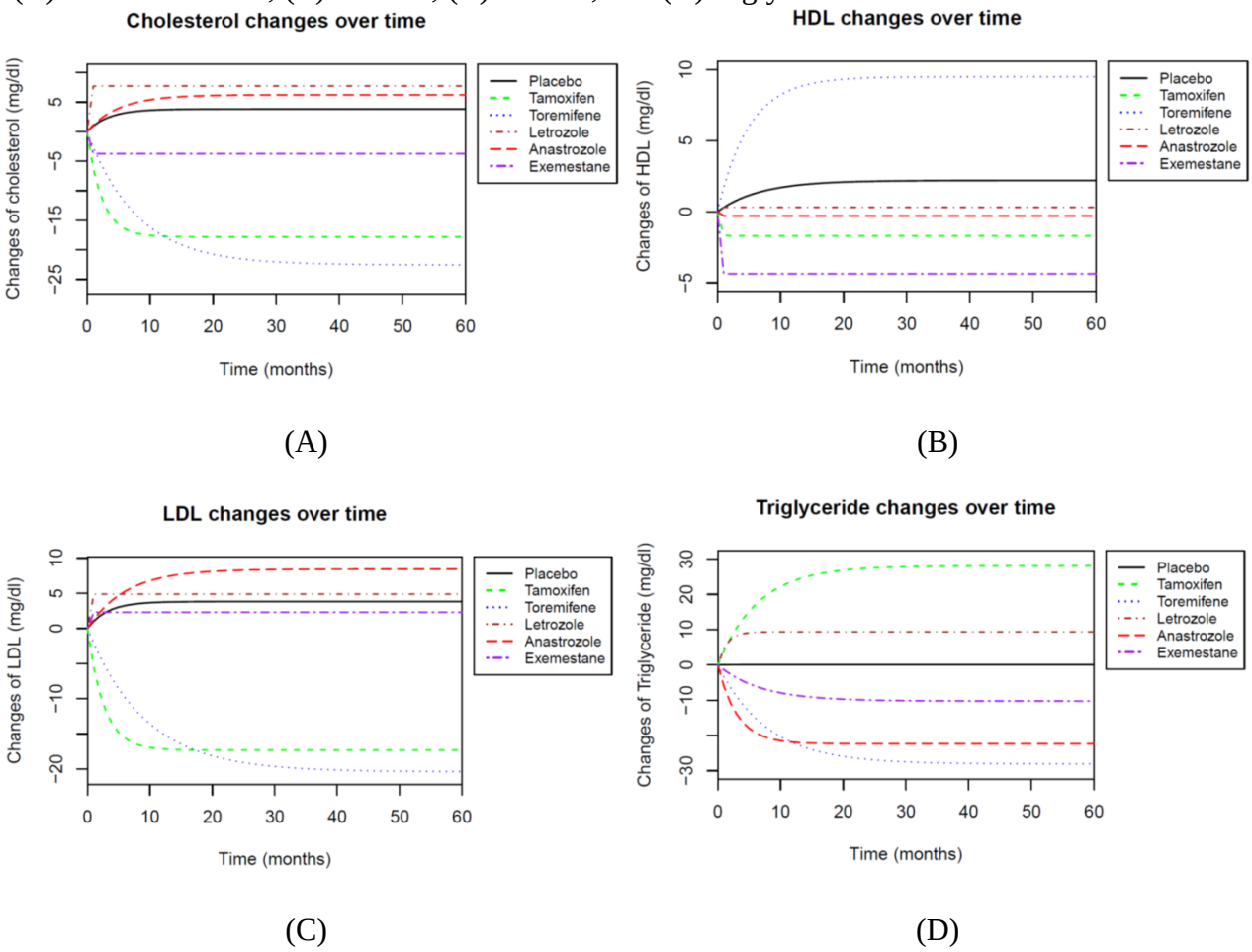
		TC (mg/dl)	**HDL-C(mg/dl)**	**LDL-C(mg/dl)**	**TG(mg/dl)**
		Mean (95 % Credible interval)			
	Placebo	3.81 (-3.27, 11.82)	**2.20 (0.46, 4.23)**	3.81 (-5.62, 12.58)	0.06 (-11.30, 11.86)
SERMs	**Tamoxifen**	**-17.81 (-24.95, -10.06)**	-1.70 (-3.49, 0.17)	**-17.31 (-26.25, -8.13)**	**28.08 (16.81, 39.23)**
	Toremifene	**-22.56 (-31.47, -13.92)**	**9.50 (7.19, 11.88)**	**-20.37 (-31.02, -10.69)**	**-28.06 (-42.95, -13.51)**
AIs	**Letrozole**	7.71 (-0.44, 15.51)	0.31 (-1.77, 2.38)	4.88 (-4.63, 14.25)	9.36 (-4.00, 22.90)
	Anastrozole	6.22 (-3.55, 16.42)	-0.30 (-3.10, 2.64)	8.43 (-3.06, 19.08)	**-22.34 (-43.98, -1.45)**
	Exemestane	-3.74 (-10.90, 3.89)	**-4.37 (-6.12, -2.45)**	2.29 (-7.13, 10.93)	-10.25 (-21.49, 1.32)

TC: Total Cholesterol; TG: Triglyceride; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; SERMs: Selective Estrogen Receptor Modulators; AIs: Aromatase Inhibitors
Bold: $p<0.05$

Figure 13 showed the predicted changes of lipid profiles over time for each therapeutic option. Letrozole increases TC faster than the other drugs, but toremifene slowly decreases TC to the greatest magnitude after about 3 years of treatment. On the contrary, toremifene increases HDL-C faster and more than the other drugs, and achieves its plateau at about 1.5 years of

treatment. Exemestane reduces HDL-C faster than the other AIs. Both tamoxifen and toremifene reduce LDL-C, but toremifene impacts LDL-C more slowly. Tamoxifen slowly increases TG and achieves plateau after about 2 years of treatment.

(A) total cholesterol; (B) HDL-C; (C) LDL-C; and (D) triglyceride



(A) (B)

(C) (D)

Figure 13. Changes of lipid profiles for each hormone therapeutic option during 5 years of treatment

We compared all therapeutic options based on their beneficial effects on lipid changes. The first rank indicates the best choice accounting for the changes of the lipid profiles, and the last rank indicates that the drug either improves the least or worsens the most for a given lipid profiles. SUCRA indicates the cumulative rank probabilities. The larger SUCRA implies the better rank among all therapeutic options for the individual treatment with regard to the outcome. Across all lipid profiles, toremifene is the best therapeutic option. The other hormone drugs have various effects regarding lipid types. For TC, toremifene is ranked the best option in 93% of the MCMC samples (Table S **6**). Tamoxifen is ranked the best option in only 7% of the MCMC samples, but ranked the second best option in 93% of the MCMC samples. Exemestane is the best choice among the AIs, which is ranked the third among all hormone drugs (Figure S 1). Tamoxifen is not a good choice regarding HDL-C and TG because it ranks 5^{th} and 6^{th}, respectively. Among all AI drugs, Exemestane is the better option, except for HDL-C (Table S **7**, Table S **8**, Table S **9**, Figure S 2, Figure S 3, & Figure S 4).

In addition to the changes of lipids for each hormone therapeutic drug, all possible treatment pairwise comparisons were made for each lipid profile. SERMs and exemestane reduce more TC serum levels compared to placebo. Patients taking AIs had significantly increased TC compared to those who taking SERMs. The two SERMs have compatible effects on TC and LDL-C. However, only toremifene increases more HDL-C than placebo, and the other drugs do not benefit patients regarding HDL-C. Compared to placebo, tamoxifen and letrozole significantly increase TG, but toremifene, anastrozole, and exemestane reduce TG. Among all hormone therapeutic drugs, tamoxifen performs worst for TG profile changes (Table 5).

Table 5. Pair-wise (comparator vs. reference) comparisons of hormone therapeutic effects on changes in lipids

TC(mg/dl)							
	Reference / Comparator	Placebo	Tamoxifen	Toremifene	Letrozole	Anastrozole	Exemestane
	Mean (95% Credible Interval)						
	Placebo	0					
SERM	Tamoxifen	**-21.62 (-24.17, -19.12)**	0				
	Toremifene	**-26.37 (-33.04, -19.7)**	-4.77 (-10.89, 1.36)	0			
AI	Letrozole	**3.89 (0.83, 6.97)**	**25.49 (21.65, 29.34)**	**30.26 (23.06, 37.46)**	0		
	Anastrozole	2.40 (-5.90, 10.81)	**24.04 (16.00, 32.09)**	**28.81 (21.69, 35.93)**	-1.45 (-10.31, 7.41)	0	
	Exemestane	**-7.55 (-9.53, -5.58)**	**14.06 (11.79, 16.34)**	**18.83 (12.33, 25.33)**	**-11.43 (-14.84, -8.02)**	**-9.98 (-18.30, -1.66)**	0

HDL-C(mg/dl)							
	Reference / Comparator	Placebo	Tamoxifen	Toremifene	Letrozole	Anastrozole	Exemestane
	Mean (95% Credible Interval)						
	Placebo	0					
SERM	Tamoxifen	**-3.90 (-4.73, 3.08)**	0				
	Toremifene	**7.30 (5.23, 9.35)**	**11.20 (9.30, 13.10)**	0			
AI	Letrozole	**-1.89 (-2.91, -0.87)**	**2.013 (0.75, 3.27)**	**-9.19 (-11.42, -6.96)**	0		
	Anastrozole	-2.50 (-5.18, 0.17)	1.44 (-1.10, 3.98)	**-9.76 (-12.11, -7.42)**	-0.57 (-3.37, 2.22)	0	
	Exemestane	**-6.57 (-7.24, -5.90)**	**-2.67 (-3.43, -1.92)**	**-13.87 (-15.87, -11.87)**	**-4.68 (-5.82, -3.55)**	**-4.11 (-6.72, -1.50)**	0

Table 5. (cont.)

LDL-C(mg/dl)

	Reference / Comparator	Placebo	Tamoxifen	Toremifene	Letrozole	Anastrozole	Exemestane
		Mean (95% Credible Interval)					
SERM	Placebo	0					
	Tamoxifen	**-21.11 (-23.62, -18.65)**	0				
AI	Toremifene	**-24.17 (-30.56, -17.90)**	-3.08 (-9.00, 2.83)	0			
	Letrozole	1.07 (-1.96, 4.12)	**22.15 (18.42, 25.88)**	**25.24 (18.30, 32.17)**	0		
	Anastrozole	4.62 (-3.54, 12.72)	**25.70 (17.79, 33.61)**	**28.78 (21.76, 35.81)**	3.55 (-5.16, 12.25)	0	
	Exemestane	-1.52 (-3.50, 0.49)	**19.62 (17.37, 21.86)**	**22.70 (16.42, 28.98)**	-2.54 (-5.81, 0.74)	-6.08 (-14.23, 2.06)	0

TG(mg/dl)

	Reference / Comparator	Placebo	Tamoxifen	Toremifene	Letrozole	Anastrozole	Exemestane
		Mean (95% Credible Interval)					
	Placebo	0					
SERM	Tamoxifen	**28.02 (21.51, 34.51)**	0				
	Toremifene	**-28.12 (-43.08, -13.46)**	**-56.15 (-69.88, -42.42)**	0			
AI	Letrozole	**9.30 (1.5, 17.11)**	**-18.74 (-28.29, -9.19)**	**37.41 (21.06, 53.76)**	0		
	Anastrozole	**-22.41 (-44.30, -1.06)**	**-50.33 (-71.65, -29.01)**	5.82 (-11.76, 23.40)	**-31.59 (-54.62, -8.56)**	0	
	Exemestane	**-10.31 (-15.45, -5.19)**	**-38.33 (-44.43, -32.23)**	**17.82 (3.29, 32.35)**	**-19.59 (-28.17, -11.01)**	12.00 (-9.79, 33.79)	0

TC: Total Cholesterol; TG: Triglyceride; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol

Bold: $p<0.05$

Heterogeneity of the trials was examined by including metaregressors in the models. For TC, age, baseline lipid values and prior tamoxifen use modified the effects of hormone therapies on lipid changes. For example, the effect of tamoxifen on reduction of TC is more for young

patients than the older patients. The effect size is 1.51 mg/dl of TC per year increase of age (Table S **10**). The patients taking tamoxifen prior to the new hormone therapies have less reduction of TC compared to those who were not exposed to tamoxifen previously. After adjusting for the metaregressors, toremifene and tamoxifen still the best two options to reduce TC compared to placebo (Table S **11** & Figure S 5). For HDL-C, baseline HDL-C and prior tamoxifen usage significantly modify the impact of hormone therapies on changes of HDL-C by further reducing the HDL-C levels. Accounting for effect modification, toremifene increases more HDL-C than placebo in either model (Table S **12**, Table S **13**, & Figure S 6). Similar to the impacts on TC, the metaregressors significantly modify the effects of hormone therapies on LDL-C (Table S **14**, Table S **15**, & Figure S 7). Only baseline TG values significantly modify the effects of hormone therapies on changes of TG (Table S **16**, Table S **17**, & Figure S 8).

There are eight comparisons with direct evidence from the available trials. Inconsistency tests are based on differences of the contrast estimates between direct and indirect evidence of the contrast pairs. We detected inconsistent contrast estimates for the pair of tamoxifen and toremifene regarding TC. Two trials providing indirect evidence of tamoxifen have large variations. Inconsistency disappeared after removing the two trials. For the pair of tamoxifen and exemestane, inconsistency was observed regarding TC, LDL-C, and TG. Greater variations of two trials providing indirect evidence of tamoxifen and exemestane, respectively, were identified and inconsistency of the three lipids was solved after removing the two trials (Table S **18**).

Sensitivity analyses were performed for three scenarios, including the original model, the model excluding trials reporting median changes of lipids, and the random-effect model. Comparing the original model to the model excluding trials reporting median changes of lipids, the ranks of the drug effects on lipid changes are not completely the same. Toremifene stayed the

top ranked for HDL-C and TG, ranked second (switched with tamoxifen) in TC and LDL-C. The main effects of the drugs on the lipid profiles are similar in both models. The results of the random-effect model are also similar to the original models regarding to TC, HDL-C, and LDL-C (Table S **19**, Table S **20**, & Table S **21**); however, the results for TG are significantly different from the original model. Anastrozole becomes the first rank while toremifene is the third rank (Table S **22**).

3.5 DISCUSSION

Our Bayesian network meta-analysis demonstrated the effects of hormone drugs on lipids throughout the 5-year therapeutic period. The results showed that SERMs, especially toremifene, improve lipid profiles more than AIs. The only exception is tamoxifen which significantly increases triglyceride levels. Most AIs did not significantly impact changes in lipids. The maximal effects of the drugs on lipids requires at least 6 months of treatment, and some may need at least 20 months to achieve their stable effects. Compared to placebo, toremifene improves all lipid profiles while the other hormone drugs impact lipids inconsistently. Patients' ages, baseline lipid values, and prior usage of tamoxifen modify the effects of hormone therapies on changes in lipid profiles.

Previous meta-analysis showed that BC patients on AIs had higher odds of CVDs compared to those who are on tamoxifen[7]. The major argument of the study is that tamoxifen may reduce the risk of CVDs[178], so we cannot conclude that AIs increase risk of CVDs with the evidence that compares effects of AIs and tamoxifen. Though our study does not directly investigate the effects of BC hormone treatment on CVDs, we examine the well-established CVD risk factor, lipids, instead. Our results support the above argument by showing that AIs does not deteriorate all lipid profiles and AIs perform worse than SERMs because SERMs improve most lipid profiles.

Tamoxifen and toremifene provide beneficial effects on most lipids, but tamoxifen worsens triglyceride in our study. Prior studies showed consistent benefits of tamoxifen on TC and LDL-C, but inconsistent effects on HDL-C and TG[178–181]. These studies mainly reported tamoxifen treatment effect without comparing to the other therapeutic arms. Our results are

similar to the prior reports that tamoxifen itself improves TC, LDL-C, but not HDL-C and TG. We further have comparison of tamoxifen and placebo, and showed that tamoxifen has significantly worse HDL-C and TG changes compared to placebo.

AIs do not impact lipids as significantly as SERMs in our study. Anastrozole and exemestane improves TG and worsens HDL-C, respectively. A reviewed study showed inconsistent effects of AIs on lipid changes, which were mainly from small studies[182]. The inconsistent results may be due to various follow-up periods for the included articles; therefore, the result from the article with a short follow-up period cannot reveal the real effects of AIs on lipids throughout the 5-year therapeutic duration. Our studies incorporated longitudinal information to project the potential long term effects of AIs on lipid changes. Some hormone drugs achieved their maximal effects slower than the others in our study; therefore, conclusions drawn from the studies with short follow-up periods may be misleading.

The age when starting BC hormone treatment modifies the effects of hormone drugs on the final TC and LDL-C values. The TC and LDL-C values increase more in older patients than in younger patients. Compared to the unadjusted models, the benefits of tamoxifen and toremifene on TC and LDL-C are slightly reduced, but the benefit of exemestane on TC and LDL-C are increased in the model adjusted for age starting BC hormone treatment. The effect of age on changes of lipid in our study are compatible with the studies showing increased TC with aging in women[183,184]. Even though the effects of hormone therapies on changes of lipids are slightly different after adjusting for ages, our conclusion for the best hormone treatment options does not change.

Prior tamoxifen use worsens most lipid changes in our study. Our results showed that tamoxifen improves most lipid profiles, so the lipid profiles of the patients previously taking

tamoxifen may return to their natural levels once tamoxifen is discontinued. Compared to the unadjusted models, AIs are more beneficial or at least are less harmful to lipids after adjusting for prior tamoxifen use. The results may explain the inconsistent effects of AIs on lipids in the previous studies, which did not account for existing of prior tamoxifen usage.

Inconsistency tests that compare direct information to the indirect information reveal two inconsistent pairs, tamoxifen vs. toremifene and tamoxifen vs. exemestane. The trials causing inconsistency for the pair of tamoxifen and toremifene enrolled patients who previously took tamoxifen for at least 2 years. Therefore, the effects may be overestimated without considering the impact of prior tamoxifen usage. One of the trials that impact the pair of tamoxifen and exemestane only follow-up the patients for 3 months, so it may underestimate the final effect of tamoxifen, which requires at least 6 months to achieve its plateau of the effects on TC, LDL-C, and TG. The trial providing indirect information of exemestane for the pair of tamoxifen and exemestane has older subjects compared to the trials providing direct information. The inconsistent results were solved after removing the trials with large variations.

The results of fixed and random effect models are in TC, HDL-C, and LDL-C. The results may indicate the subjects in trials were randomly selected from the same population. However, the effects of hormone therapy drugs in TG are different between fixed and random effect models. If TG is the only one measurement that contrary to the other measurements about the population, measurement biases are highly suspected. It is possible that participants did not follow the instruction of fasting before blood test. TG is more sensitive to fasting status of the patients on blood tests than lipoprotein cholesterol, so large variations can be observed in TG measurement[185]. Exclusion of trials only reporting median measurements flips the ranks of

tamoxifen and toremifene for TC and LDL-C, but the general conclusion is the same that SERMs benefit lipid changes with respect to TC, HDL-C, and LDL-C.

There are several strengths of our study. First, we are able to incorporate longitudinal information and to compare all hormone therapeutic options in one analysis. The previous meta-analysis and network meta-analysis only focused on the final follow-up results of the selected articles, not the patterns of the changes over time. This analysis does not only estimate the final changes of the outcomes, but also presents the changing patterns across time. Second, we convert the heterogeneous reporting format into a homogeneous format by using Bayesian statistical methods. Therefore, more studies can be included in our analyses. Increasing the number of drugs and participant enhances the power to detect differences. Without appropriate estimation process, we may have to exclude studies without the same reporting format, so the statistical power of the study will be reduced due to much smaller sample size. Third, we showed important factors that can modify the drug effects on lipid changes, which may explain the conflicting results among the previous studies.

We also identified some weaknesses of this study. First, we have small sample size in this study. Some comparison pairs have only one study for direct comparison. Therefore, there are large variances due to limited information. Second, we included articles reporting median of lipid changes instead of mean and standard error. The studies reporting median instead of mean may have skewed data. We may not obtain efficient estimates by including these studies. However, the conclusions are similar for the analyses with and without studies reporting median changes. Therefore, we are still confident of our results. Third, the included articles were published between 1990 and 2012. The health care and treatment of BC and lipids improve over time, as well as, the techniques of lipid measurements and lipid treatment. The changes may

impact the estimates of our study. We mainly focused on lipid changes, so the effects of the different baseline values, which may be induced by techniques, may be reduced. We also examined the impact of the baseline lipid values and revealed that they do not influence the ranks of the best choices among the hormone therapy drugs. Fourth, we only included published articles, so publication bias cannot be avoided.

In conclusion, toremifene benefits all lipid profiles in BC patients. AIs do not significantly impact most lipids. The BC patients taking exemestane need to monitor their HDL-C during treatment. Regularly examining triglyceride may be necessary for patients taking tamoxifen, especially for those who accept extended tamoxifen treatment, which can prolong survival of pre-menopausal BC patients[186], since aging and tamoxifen both deteriorate triglyceride. The results are based on the aggregated data from published articles of RCTs. Further studies on individuals with personal characteristics are necessary to validate the results of our study.

4.0 PAPER 3: RISK OF DYSLIPIDEMIA AND CORONARY HEART DISEASE IN POSTMENOPAUSAL EARLY-STAGE HORMONE RECEPTOR-POSITIVE BREAST CANCER PATIENTS ON HORMONE TREATMENT

4.1 ABSTRACT

Background

Tamoxifen, a selective estrogen receptor modulator (SERM), improves disease free survival (DFS) and overall survival (OS) for hormone receptor positive (HR+) breast cancer (BC) patients. Aromatase inhibitors (AIs), an alternate hormone treatment, further prolong DFS in postmenopausal HR+ BC patients, but their reported benefit in OS is inconsistent. Prior studies reported conflicting results of hormone cancer treatments on risk of cardiovascular diseases and dyslipidemia when patients were on treatment. We investigate the impact of hormone treatment on incidence of dyslipidemia and coronary heart disease (CHD) in HR+ BC patients.

Methods

Electronic medical records from University of Pittsburgh Medical Center (UPMC) were reviewed to extract information on patients aged 50 years and above with stage I/II HR+ BC. For

each patient without a prior history of dyslipidemia or CHD events, we collected information on use and type of hormone treatment, and diagnosis of dyslipidemia and CHD events after cancer diagnosis. Demographic and BC characteristics were extracted from Cancer Registry data. Cox proportional hazard models with time-varying hormone treatment indicators were used to investigate effects of different types of hormone treatment on risk of dyslipidemia and CHD. Hormone treatment was categorized by timing of usage and type of drug.

Results

A total of 968 BC patients were included in this study. We classified participants into four groups describing their trajectory of treatment; AI only (N=725, 75%), SERM only (N=53, 6%), both (either AI then SERM or vice versa, N=108, 11%), or no hormone therapy (N=82, 8%). Age at diagnosis differed significantly across the groups (57.30 years, 63.13 years, 56.26 years, and 64.59 years, $p<0.0001$) for AI only, SERM only, both, and no hormone therapy, respectively. Our population was mostly white (94%) with mean follow up time of 71 months, 74 months, 76 months and 70 months for SERM, AI, both, and no hormone treatment, respectively. Nineteen percent of AI-only users developed dyslipidemia versus 13% of SERM-only users. Incidence of CHD was similar (1% vs. 1%). The time-varying Cox proportional model showed that current SERM users tended to have lower risk of dyslipidemia/CHDs compared to never SERM users (HR: 0.49, 95% CI: 0.19, 1.25, p=0.134). The potential protective effect of current SERM usage disappeared after discontinuing treatment (HR: 0.89, 95% CI: 0.35, 2.28). Current AI users tended to have a higher risk of dyslipidemia/CHDs compared to current SERM users (HR: 2.02, 95% CI: 0.94, 4.33, p=0.071). Patients previously using AIs had similar risk of dyslipidemia/CHD compared to those who previously used SERMs (HR: 1.13, 95% CI: 0.43, 2.93, p=0.809).

Discussion

This study showed a potential protective effect of SERMs on dyslipidemia/CHDs during treatment with the effect disappearing after discontinuing treatment. Though current AI usage increased the risk of dyslipidemia/CHDs compared to current SERM usage, patients had similar risk for dyslipidemia and CHD events after discontinuing either treatments (prior AI vs prior SERM). Future studies should include more subjects and longer follow up of patients.

4.2 INTRODUCTION

Due to the increased use of hormone treatment for breast cancer, survival for hormone receptor positive breast cancer (HR+ BC) patients has improved in recent decades. Tamoxifen, the most popular selective estrogen receptor modulator (SERM), has been shown to improve disease free survival (DFS) and overall survival (OS) in HR+ BC patients compared to those without any hormone treatment[151,152]. Compared to SERMs, aromatase inhibitors (AIs) further prolonged DFS in post-menopausal HR+ BC patients[154,155,159,162]. However, beneficial effects on overall survival (OS) are controversial in the early literature[162,163,165,167,168]. As data on long-term effects of AIs from clinical trials are now available, more recently published articles increasingly report improved long-term OS in patients receiving 5-year AI treatment compared to 5-year tamoxifen treatment[165,205]. In addition, more studies showed that longer use of hormone therapies, both tamoxifen and AIs, benefits survival of HR+ BC patients[186,206]. Since long-term hormone treatment is beneficial to the HR+ BC patients, a good understanding of the adverse effects (AEs) of these drugs during treatment is important to balance benefits and harms of hormone treatment.

In addition to secondary cancers, the most noticeable and severe AEs related to hormone treatment involve cardiovascular diseases (CVDs). CVDs and their risk factors are not only related to hormone treatment, they are also related to the normal aging process. A study showed 37% of the HR+ BC patients had higher 10-year predicted CVD risk than 10-year predicted BC recurrence risk, while only 20% of the recruited patients had higher 10-year predicted BC recurrence risk than 10-year CVD risk, especially those with early stage BC[207]. However, a meta-analysis showed that AI treated patients have higher odds of CVD mortality than those taking tamoxifen[7]. A network meta-analysis (NMA) did not show higher CVD events in AI users

compared to SERM users[208]. In addition to the CVD events, our prior work in investigating hormone therapies on changes in lipids using NMA showed that SERMs improve lipid profiles but that most AIs have a non-significant impact on most lipids compared to placebo (see Chapter 3, Table **4**).

The above-described meta-analyses used self-reported AEs from randomized clinical trials (RCTs) to report their CVD events. There are two disadvantages to this type of ascertainment. First, the self-reported events may not be accurate. Second, the studies using the final reports of the RCTs did not differentiate between events that happened during versus after use of hormone therapy. Most AIs do not permanently inhibit the aromatase enzyme activities, so assuming constant drug effects during and after stopping with treatment may be unreasonable. The cohort study published in 2016 by Haque, et al. estimated cumulated hazard ratios (HRs) of tamoxifen and AIs on all cardiovascular events using time-dependent Cox proportional hazards models to manage changes of treatment throughout the follow-up periods based on electronic medical records. The results showed that AI-only and tamoxifen-only users have a similar risk of cardiac ischemia (HR: 0.97, 95% CI: 0.78-1.22) and stroke (HR: 0.97, 95% CI: 0.70-1.33)[209]. However, the study also did not reveal the possible difference in risk of cardiovascular events during vs after hormone treatment. Our previous NMA only focused on the effects of hormone treatment on lipids during treatment. To understand the complete effects of hormone treatment on risk of dyslipidemia and coronary heart diseases (CHDs) throughout the whole course of BC patient care, we conducted this cohort study using hospital electronic medical records (EMRs) from diagnosis through treatment to off-treatment follow up visits. The main goals of the study are to examine if patients on AIs have higher risk of dyslipidemia/CHD events than those who are on SERMs and whether the risk difference disappears after discontinuing treatment.

4.3 METHODS

4.3.1 Data Sources and Setting

The University of Pittsburgh Medical Center (UPMC) is a health care enterprise that provides healthcare services via community and tertiary hospitals. The service area covers the western/north central Pennsylvania, western New York, and Ohio. Data in the UPMC Cancer Registry include demographic and cancer related information at diagnosis and are updated regularly for vital status and cancer treatment. Our data were provided by two honest brokers who identified the patients and medications from the Electronic Medical Administrative Records (e-MARs) and the Cancer Registry data from UPMC in Pittsburgh. This study was approved by the University of Pittsburgh Institutional Review Board (IRB). We obtained demographics, BC characteristics, and cancer treatment from the Cancer Registry. The e-MARs provided medical records, including medication and outcome events, starting from the date of BC diagnosis to the end of the study period (Figure **14**). The prescription information of hormone treatment was extracted by HHH from the eMARs.

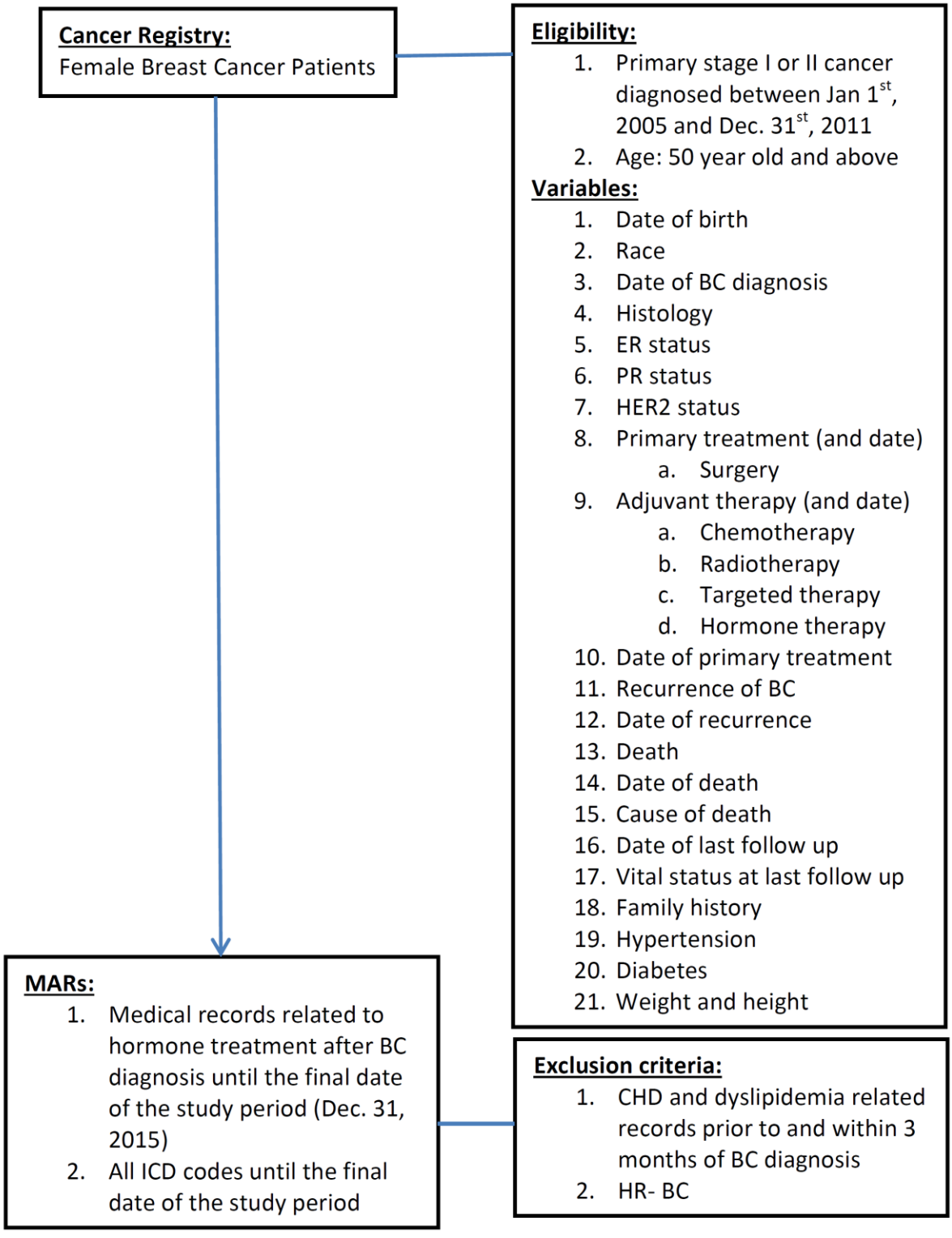


Figure 14. Flow chart for data extraction from Cancer Registry and MARs

4.3.2 Patients and Design

The target population is the group of HR+ BC patients ascertained from the Cancer Registry. Patients diagnosed with primary stage I or stage II BC between Jan. 1st, 2005 and Dec. 31st, 2011 were eligible for this study. We excluded patients younger than 50 years old from the study, as they are likely to not yet be postmenopausal, and patients with HR- or unknown HR status breast cancer. Those who were diagnosed with heart disease or dyslipidemia before or within 3 months after BC diagnosis were also excluded. The medical records of each patient were obtained from eMARs starting from BC diagnosis till the final date of the study, Dec. 31, 2015.

4.3.3 Outcomes

Outcomes included new dyslipidemia and CHD events (myocardial infarction, ischemia, coronary artery disease, and angina pectoris). The CHD events were determined by one of the following three criteria: 1) ICD-9 (410.0-414.9) and ICD-10 (I20.0-I25.9) as appropriate; 2) procedure codes related to CABG (36.10-36.20; 33510-33523, 33533-33536) and PTCA (92982-92984); and 3) elevated Troponin levels. Dyslipidemia was determined based on ICD-9 (272.0-272.5) and ICD-10 codes (E78.5-E78.6). Patients were considered diagnosed with new dyslipidemia or CHD if they met the above criteria at least once for inpatient or twice for outpatient records.

4.3.4 Hormone Treatment Data

Hormone treatment information was recorded longitudinally and categorized by type of hormone drug (AI or SERM) and status of usage (current, prior, or never). The variables representing usage of hormone therapy during the follow-up period, including current usage for SERM, current usage for AI, prior usage for SERM, prior usage for AI, and never usage for SERM and AI, were constructed. For example, a patient started tamoxifen for 6 months, followed by an AI for another 12 months, and then was observed off treatment for 3 months. The first input for this patient would be: duration is 6 months; SERM: current; and AI: never. The second input would be: duration is 12 months; AI: current; and SERM: prior. The final input would be: duration is 3 months; SERM: prior; and AI: prior. We also created a variable to summarize hormone treatment in mutually exclusive categories during the whole study period (i.e., SERM-only, AI-only, both SERM and AI, and no hormone treatment). The example patient above would be categorized as both SERM and AI for this alternate variable. Information on prescriptions of hormone treatment, including start and stop dates, were extracted from eMARs. The hormone treatment information from eMARs was verified to be consistent with the Cancer Registry data.

4.3.5 Covariates

Baseline characteristics of the patients were abstracted from the Cancer Registry data, and included race (White, non-White), weight, height, smoking status (yes, no), alcohol consumption (yes, no), post-menopausal status (yes, no/unknown), BC cancer stage (stage I, stage II), and family history of BC (yes, no). Cancer treatment prior to hormone treatment,

including chemotherapy and radiotherapy, was also extracted from the Cancer Registry data. Pre-existing diabetes and hypertension before BC diagnosis were identified using ICD-9 (250.0-250.93; 401.0-401.9) and ICD-10 (E08-E11.9; I10-I16) code as appropriate. Height and weight were used to calculate body mass index (BMI), which was categorized as: under-/normal weight (BMI < 25), overweight (25 ≤ BMI < 30), obese (BMI ≥ 30), and unknown.

4.3.6 Statistical Analysis

Descriptive statistical analyses were performed to examine differences in baseline characteristics between the 4 mutually exclusive groups of BC patients (i.e., those who received AI-only, SERM-only, both, and no hormone treatment). Continuous variables were tested using one-way analysis of variance (ANOVA) and categorical variables were examined using χ^2 or Fisher exact test as appropriate.

Follow-up time for each patient started at the date of BC diagnosis and ended on the date of the new outcome event, either dyslipidemia or CHD whichever came first. If the patient did not develop any new event, the end of the follow-up time was the last contact date in the Cancer Registry or the last date of the study period, Dec. 31, 2015, whichever came first. Time between BC diagnosis and the date that the first hormone drug was prescribed contributed to the never usage categories. Cox proportional hazards models were used to estimate the hazards of the outcome events for time-varying hormone treatment. We performed three Cox proportional hazard models to investigate the effects of hormone treatment on the outcome events. The first one is an unadjusted model containing only the hormone treatment variables. The second model included demographic characteristics in addition to the treatment variables. The third model added medical history and BC related features to the second model. All variables were selected

based on their clinical importance. The parameter estimates and standard errors of hormone treatment as well as the hazard ratios (HRs), 95% confidence intervals (CIs) and p-values were obtained from the Cox proportional hazards models. All analyses were performed using SAS, version 9.3 (SAS Institute Inc).

4.4 RESULTS

Patients 50 years of age or older with a diagnosis of primary stage I or stage II BC between Jan. 1st, 2005 and Dec. 31st, 2011 were eligible for this study (n=2,172). Patients with a history of heart disease (n=103) and dyslipidemia (n=380) before BC diagnosis or diagnosis of these up to 3 months after BC diagnosis were excluded from our study population. Patients with incomplete hormone therapy information, lacking starting or stopping dates, were excluded (n=307). Patients without hormone therapies for whom estrogen and progesterone receptor status was unknown and patients with HR- BC were excluded (n=414). The final population included 968 BC patients. All included patients were followed up from the diagnosis of BC until occurrence of the event, the last contact date, or end of the study period, Dec. 31st, 2015, whichever came first (Figure 15).

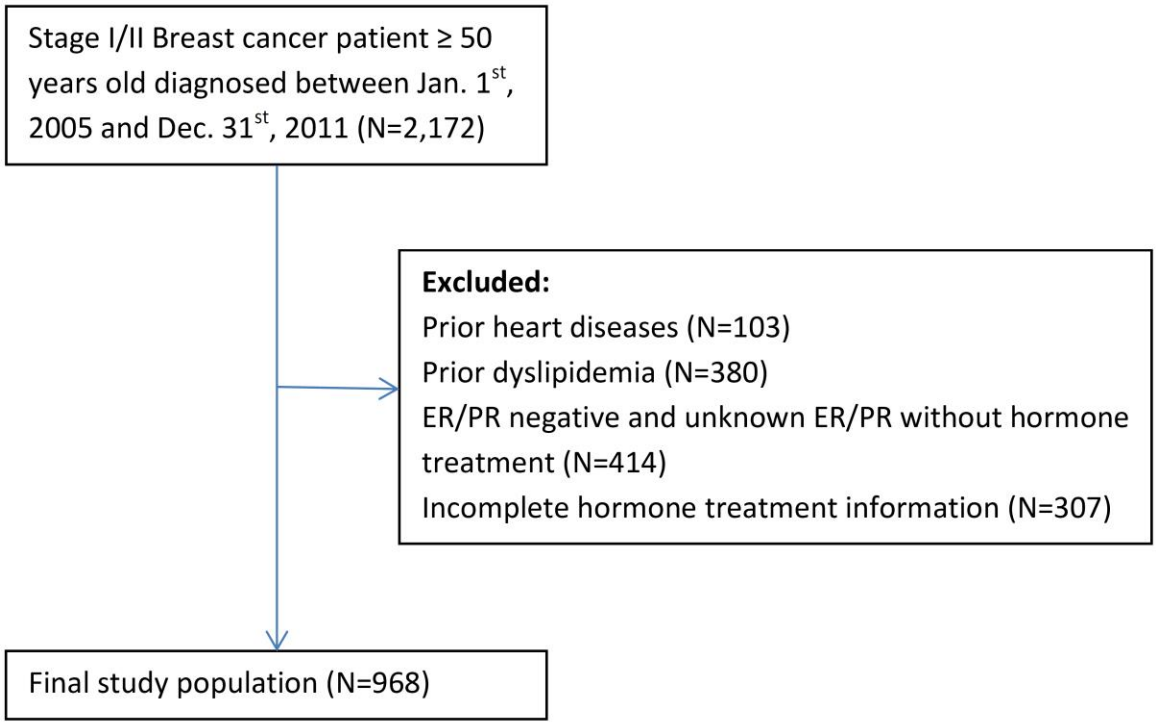


Figure 15. Flow chart describing eligibility and exclusion of the breast cancer population in the study

Table 6 summarizes the characteristics of the study participants. As our study population included only BC patients with HR+ BC, most patients received hormone treatment. Seventy-five percent of the population received AIs only, and 11% of patients received both AIs and SERMs. Therefore, the majority of our population was exposed to AIs during the course of cancer treatment. Mean follow-up duration ranged from 70.9 months (5.9 years) to 76.6 months (6.4 years). Nineteen percent of the AI-only users developed dyslipidemia while about 13% of the SERM-only, both, and never users were diagnosed with dyslipidemia. Few patients developed heart disease (n=16), and most of them also developed dyslipidemia (n=11). More than 90% of the population was white. More AI-only users were known to be post-menopausal than SERM-only users (94% vs. 56%). Prevalence of tobacco and alcohol consumption was low in our population, 11% and 5%, respectively. Almost one third of all AI-only users had pre-existing hypertension while the percentages of pre-exiting hypertension in the other treatment groups ranged from 19% to 22%. The prevalence of pre-existing diabetes was low in all treatment groups (6%). More than two thirds of the patients received radiotherapy, but only about one third of patients had chemotherapy prior to hormone treatment. More than 90% of patients taking hormone drugs survived during our study period.

Table 6. Characteristics of the HR+ BC patients

	Drug Prescription During Follow-Up Period				Total	
	SERM-only	**AI-only**	**Both**	**No**		**p-value**
All Patients	53 (6)	725 (75)	108 (11)	82 (8)	968 (100)	
Demographics						
Age at Diagnosis	57.3 (9.0)	63.1 (8.6)	56.3 (7.6)	64.6 (11.4)	62.2 (9.2)	<0.01
White	50 (94)	683 (94)	107 (99)	77 (93)	917 (94)	0.12
BMI						0.20
Normal /Underweight	20 (37)	163 (22)	27 (25)	26 (31)	236 (24)	
Overweight	16 (30)	221 (30)	33 (30)	20 (24)	290 (29)	
Obese	16 (30)	266 (36)	36 (33)	28 (34)	346 (35)	
Unknown	1 (1)	75 (10)	12 (11)	8 (9)	96 (9)	
Medical History						
Current tobacco use	6 (11)	76 (10)	12 (11)	14 (17)	108 (11)	0.36
Current alcohol use	5 (9)	45 (6)	7 (6)	1 (1)	58 (5)	0.15
History of Diabetes	2 (3)	53 (7)	2 (1)	2 (2)	59 (6)	0.05
History of Hypertension	12 (22)	234 (32)	21 (19)	16 (19)	283 (29)	< 0.01
Post-menopausal	30 (56)	682 (94)	59 (54)	73 (89)	844 (87)	<0.01
Breast Cancer Characteristics						
AJCC stages						0.04
Stage 1	33 (63)	468 (65)	59 (55)	61 (75)	621 (65)	
Stage 2	20 (37)	257 (35)	49 (45)	21 (25)	347 (35)	
Radiotherapy	35 (66)	523 (72)	77 (71)	55 (67)	690 (71)	0.64
Chemotherapy	12 (22)	263 (36)	45 (41)	29 (35)	349 (36)	0.13
Family history of breast cancer	38 (71)	537 (74)	78 (72)	59 (71)	712 (73)	0.94
Treatment Summary and Outcomes						
Follow-up (months)	71.2 (19.9)	74.5 (25.4)	76.6 (28.4)	70.9 (34.2)	74.3 (26.3)	0.39
Treatment duration (months)	45.5 (20.6)	42.9 (22.8)	50.5(25.3)	0 (0)	40.2 (25.3)	0.01
New Dyslipidemia	7 (13)	139 (19)	15 (13)	12 (14)	173 (17)	0.34
New CHD	1 (1)	12 (1)	0 (0)	3 (3)	16 (1)	0.20
Dyslipidemia/CHD	7 (13)	143 (19)	15 (13)	13 (15)	178 (18)	0.31
Alive at end of study	49 (92)	663 (91)	104 (96)	57 (69)	873 (90)	<0.01

Data are presented as Mean (SD) or N(%)

There were no significant differences for rates of dyslipidemia/CHD for AI treatment categories (current AI vs. never hormone users (HR: 0.99, 95% CI: 0.54, 1.82) and prior AI vs. never hormone users (HR: 1.00, 95% CI: 0.27, 3.70)). In contrast, current SERM had a borderline impact on risk of dyslipidemia/CHD (HR: 0.49, 95% CI: 0.19, 1.25), but prior SERM users did not have increased risk of the events (HR: 0.89, 95% CI: 0.35, 2.28) compared to never hormone users, respectively. Risk of dyslipidemia/CHD was higher for patients currently taking AIs compared to those who were currently taking SERMs (HR: 2.02, 95% CI: 0.94, 4.33), but the risk difference disappeared after discontinuing AIs/SERMs, prior AI vs. prior SERM, (HR: 1.13, 95% CI: 0.43, 2.93). The treatment effects were attenuated after adjusting the covariates (Table 7).

Table 7. Time-dependent Cox proportional hazards models for dyslipidemia/CHD

	Model 1	**Model 2**	**Model 3**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Model			
Current AI	0.99 (0.54, 1.82)	1.01 (0.55, 1.87)	1.00 (0.54, 1.86)
Current SERM	0.49 (0.19, 1.25)	0.54 (0.21, 1.39)	0.58 (0.22, 1.53)
Prior AI	1.00 (0.27, 3.70)	0.97 (0.27, 3.54)	0.98 (0.27, 3.55)
Prior SERM	0.89 (0.35, 2.28)	0.97 (0.38, 2.49)	0.95 (0.35, 2.59)
Never hormone	Reference	Reference	Reference
Contrast			
Current AI vs Current SERM	2.02 (0.94, 4.33)	1.87 (0.86, 4.03)	1.74 (0.77, 3.93)
Prior AI vs Prior SERM	1.13 (0.43, 2.93)	1.00 (0.38, 2.63)	1.03 (0.37, 2.85)
Current AI vs Prior AI	0.99 (0.28, 3.54)	1.04 (0.30, 3.67)	1.01 (0.30, 3.48)
Current SERM vs Prior SERM	0.55 (0.15, 1.98)	0.56 (0.16, 2.00)	0.60 (0.17, 2.18)
Prior AI and prior SERM vs Never	0.94 (0.33, 2.66)	0.97 (0.35, 2.70)	0.97 (0.35, 2.72)

Model 1: current AI, current SERMs, prior AI, prior SERM
Model 2: Model 1, age at diagnosis, BMI, race, smoking, alcohol
Model 3: Model 2, diabetes history, hypertension history, postmenopausal status, breast cancer stage, chemotherapy, radiotherapy

4.5 DISCUSSION

Our results suggest that, among HR+ BC patients, current SERM users may have lower risk of dyslipidemia/CHDs compared to never SERM users, while prior SERM usage and current/prior AI usage appear to not impact risk of dyslipidemia/CHD. Compared to current SERM usage, current AI usage had higher risk of dyslipidemia/CHD. The other comparisons between treatment groups showed similar risk of dyslipidemia/CHD. The benefit of current SERM usage was attenuated after adjusting for important demographic and clinical covariates. The results were not statistically significant due to few dyslipidemia/CHD events during the whole follow-up period.

Previous studies have reported similar findings that better lipid profiles can be observed in current SERM users but not in current AI users. A systematic review indicated that lipid profiles were improved after initiating tamoxifen treatment, but AIs did not have consistent beneficial effect on lipids[210]. Several clinical trials also observed similar effects on lipids for tamoxifen, but not for AIs[197–199,204]. Regarding CHDs, the number of events in our study population was very low. A breast cancer preventive trial using tamoxifen showed that tamoxifen was not associated with CVD events within mean 49 months of follow-up[211]. Normally, tamoxifen and AIs are prescribed for 5 years to prevent recurrence of BC. Five years is generally not long enough to develop CHDs, especially in the younger population. The mean age of our patients was 62.17 years old, so few CHD events within 5 years of hormone treatment in such young age population were expected.

The unique feature of our study is that we examined the risk of dyslipidemia/CHDs after discontinuing hormone treatment. Our results showed that the potential benefits of current SERM (mainly tamoxifen) usage on dyslipidemia/CHDs disappeared after discontinuing

treatment compared to non-hormone usage. Current AI users tended to have a higher risk of dyslipidemia/CHDs compared to current SERM users. The risk difference disappeared after discontinuing treatment. The function of tamoxifen to compete with estrogen for estrogen receptors is reversible. Estrogen regains its normal binding capacity to estrogen receptors (ERs) after tamoxifen is discontinued and metabolized[212]. AIs inhibit production of estrogen either reversibly (non-steroidal type) or irreversibly (steroidal type). Most AI users in our study took the non-steroidal type of AIs, so production of estrogen returned to its normal status after discontinuing AI treatment for most patients. Since our outcome was driven by dyslipidemia, which is reversible, it is possible that the protective effect of tamoxifen compared to no hormone treatment and the adverse effects of AIs compared to SERM on dyslipidemia were temporary.

Our study has several strengths. First, we collected hormone treatment information throughout the whole follow-up period. Therefore, we were able to examine changes of the risk of dyslipidemia/CHDs with respect to transition of hormone treatment during the period. Second, our hormone treatment data were obtained by reviewing medical records, so we were able assess adherence of hormone treatment in our population.

There are several limitations to our study. First, few cases of CHD developed in our population. We combined events of dyslipidemia and CHD as there were few CHD events. However, our data revealed that most patients with CHD also had dyslipidemia. Using dyslipidemia as a proxy may capture most CHD events. Second, we combined all AIs for intervention and all lipid profiles for the outcome in this study. Regarding dyslipidemia, our prior meta-analysis (Chapter 3) showed that individual AIs had different effect on different lipids during treatment, so the mixed effects of AIs may offset individual significant impacts on dyslipidemia. Third, quality of medical records is critical for accuracy of medication

information. Though we can better understand compliance of medication from the medical records, reviewing the records is very time-consuming, and health care provider notes may not be well organized potentially leading to misclassification. To minimize misclassification of hormone treatment, we verified consistency of EMR data with data from the Cancer Registry.

In addition to the current cohort focusing on patients in Pittsburgh, our future efforts to expand our study cohort include using the whole UPMC service areas and acquiring the pharmacy claims to better ascertain information on hormone treatment. Our current population is relatively young, so few CHDs can be observed within a short follow-up period. Next, we would follow up the cohort longer to have enough statistical power in examining the effects of hormone treatment on CHDs. If enough events are available, we will specifically investigate effects of individual hormone drugs on CHD, and whether these effects may be mediated by poor lipid profiles.

5.0 CONCLUSIONS

With the goal of performing a systematic review and NMA, we realized methods available were not adequate. The first paper proposed two adaptations to an existing BEST-ITP method: 1) adapt heterogeneous reporting to homogeneous reporting, and 2) expand arm based consistency models for use with longitudinal outcomes. The second paper utilized these methods for the systematic review/NMA where we characterized the longitudinal effect of two SERMs, 3 AIs, and placebo on TC, LDL-C, HDL-C, and TG. The third paper used medical record data to investigate with long-term follow-up effects of SERMs and AIs on dyslipidemia and CHD of patients in a community setting.

To apply NMA to longitudinal data, two objectives are including as many as studies as possible and testing the consistency assumption of NMA. We have to convert heterogeneous reporting formats to a homogeneous reporting format. We proposed methods converting values to changes from baseline at follow-up time points by using AR(1) covariance structure across time points and testing consistency of estimates from direct and indirect evidences by expanding the Arm Based consistency model proposed by Hong et al. To accommodate longitudinal repeated data a simulation successfully demonstrated efficiency of our proposed statistical methods. The small biases and MSEs implied that the estimated parameter values are close to the true values. The AB model can detect inconsistency of estimates when inconsistent parameter values were introduced to the simulation data. The power to detect inconsistency improved as the

magnitude of inconsistency increased. However, assuming an AR(1) model for the correlated follow-up data is a simplistic assumption that may not completely reflect the relationship of the baseline and all the follow-up data. This assumption is needed for NMA with a smaller number of included studies. Future studies exploring the data structure by assuming unstructured relationship could be conducted to examine robustness of AR(1) and unstructured model. Our proposed methods allow researchers to include more studies with longitudinal data in the meta-analyses and verify application of NMA to longitudinal data by being able to examine the consistency assumption.

The second project aimed to apply what we proposed in the first project and the Bayesian NMA proposed by Ding to examine the impact of BC hormone drugs on changes of lipid profiles. We identified eligible published articles from PubMed and EMBASE using pre-determined selection criteria. The randomized clinical trials reporting lipid data in all intervention arms were included in this project. The results revealed different effects of 2 SERMs and 3 AIs and placebo on changes of lipids during hormone treatment. SERMs, especially toremifene, improved most lipids while most AIs did not significantly impact lipids. SERMs performed better than AIs. Our results were compatible with the prior meta-analysis that showed the higher odds of CVDs for patients taking AIs compared to those taking tamoxifen. Furthermore, we were able to compare individual hormone drugs to each other and identify the specific drugs that deteriorated lipids. However, our meta-analysis included only 17 studies and some of them had very few participants. Therefore, the estimates derived from the NMA model had large variances which are more prominent when testing consistency of the estimates from direct and indirect evidence. The sample sizes from either direct or indirect evidence became smaller than those from combined evidences, so the variances of the estimates from separated

evidences were even larger than the combined evidence. Therefore, we were less likely to reject the null hypothesis that the estimates from direct and indirect evidences are the same. Our future effort will include more studies to increase the statistical power of the analysis. This project successfully compared all BC hormone drugs in one study and showed that SERMs are beneficial to most lipids and AIs do not significantly deteriorate lipid profiles.

To expand the results from the NMA which focused on clinical trials, the third project investigated effects of BC hormone drugs throughout the whole course of BC treatment, including on and off hormone treatment, in a hospital cohort using electronic medical records. Two honest brokers extract data from Cancer Registry and e-MARs within the coverage of UPMC. We used time-dependent Cox proportional hazards model to handle transition of hormone treatment during follow-up periods. Our cohort study showed that current SERM usage tended to reduce the risk of the outcomes, dyslipidemia and CHD when compared to never SERM usage. Compared to current SERM usage, current AI usage increased the risk of the outcome events. However, the trends disappeared after discontinuing hormone treatment. We do not have enough statistical power because of few events; however, our results suggest an effect of current hormone treatment on the outcome events, which was not observed for prior hormone usage. Our cohort also showed that the major outcome event was dyslipidemia and most CHDs were accompanied by dyslipidemia. We will expand our study population by including more hospitals within UPMC service areas and expect to observe more events and gain statistical power of the estimates. Using the longitudinal EMRs and the time-dependent Cox proportional model, we can investigate changes of the BC hormone drug effects during on and off treatment in this project. The results showed that the protective effect of SERMs on dyslipidemia/CHD events may be temporary, which disappear when discontinuing SERMs.

This dissertation project successfully showed efficiency of the proposed statistical methods for the Bayesian NMA using longitudinal data, and the potential protective effects of SERMs on lipid profiles and events of dyslipidemia/CHD compared to AIs during hormone treatment. Individual AI may deteriorate lipids, especially HDL-C. Though we do not have enough power to ascertain our findings, we revealed the trend that current AI usage is related to dyslipidemia compared to current SERM usage, which was not observed in prior usage. Therefore, we should mainly focus on adverse effects of hormone drugs during treatment. We revealed deterioration of lipids for some AIs in NMA but did not find significant adverse effects of AIs on dyslipidemia and CHDs in the cohort study. The contrasting results may be related to the different methods of categorizing treatment between the two studies. We tested individual AIs in the NMA, but combined them together in the cohort study. Therefore, the adverse effects of the specific AIs, accounting for a small proportion of AI usage, may be offset by the beneficial effects of the other AIs. After including more participants and potential events in future studies, we can specifically test individual hormone treatment and their usage across time on individual lipids and subsequent CHDs.

The work in this project adds value and innovation to the literature. First, we developed methods to unify reporting formats of longitudinal data, so more studies can be included in the Bayesian NMA. Second, expanding arm-based models to examine consistency of estimates from direct and indirect evidence for longitudinal data validates the consistent assumption of Bayesian NMA. We confirmed that BEST-ITP, a Bayesian NMA focusing on longitudinal drug effects, is applicable for clinical applications. Third, we revealed effects of individual BC hormone drugs on changes of lipid profiles, which have not been investigated before, so the clinicians can provide a better care for the BC patients who already have higher risk of dyslipidemia/CVD

when prescribing BC hormone drugs. Fourth, the study in community practice setting is the first one to investigate the effects of the "prior use" of BC hormone drugs on risk of dyslipidemia/CHD.

5.1 PUBLIC HEALTH SIGNIFICANCE

This dissertation demonstrated methods to convert heterogeneous reporting formats into a homogeneous format and to examine the consistency assumption of NMA for longitudinal data. After this dissertation, studies that use different reporting formats can be used in NMA to compare effects of more than two therapeutic options. The consistency test validates the results from NMAs using longitudinal data. The work on breast cancer hormone treatment showed protective effects of SERMs and diverse effects of AIs on lipid profiles and subsequent CHDs during the therapeutic period. The results encourage carefully monitoring lipids, which are associated with subsequent CHD events, during hormone treatment, especially for patients with risk of dyslipidemia on some types of AIs.

APPENDIX: SUPPLEMENTARY MATERIAL FOR CHAPTER 3

Table S 1. Literatures search criteria for PubMed

Breast Neoplasms [MeSH][Text Word]	Randomized Controlled Trials [MeSH][Publication Type]
Breast Cancer [Text Word]	Clinical Trials [MeSH][Publication Type][Text Word]
Breast Malignancy [Text Word]	Controlled Clinical Trial [Publication Type]
Breast Tumor [Text Word]	Evaluation Studies [Publication Type]
Lipids [MeSH] [Text Word]	Double-Blind Method [MeSH][Text Word]
Cholesterol [MeSH] [Text Word]	Single-Blind Method [MeSH][Text Word]
Lipoprotein [MeSH] [Text Word]	Comparative Study [Publication Type][Text Word]
Cholesterol, HDL [MeSH] [Text Word]	Placebos [MeSH][Text Word]
Cholesterol, LDL [MeSH] [Text Word]	Tamoxifen [MeSH][Text Word]
Lipoproteins, HDL [MeSH] [Text Word]	Soltamox [MeSH][Text Word]
Lipoproteins, LDL [MeSH] [Text Word]	Nolvadex [MeSH][Text Word]
Triglycerides [MeSH] [Text Word]	Toremifene [MeSH][Text Word]
Hypercholesterolemia [MeSH] [Text Word]	Fareston [MeSH][Text Word]
Hyperlipidemia [MeSH] [Text Word]	Aromatase Inhibitors [MeSH][Text Word]
Dyslipidemia [MeSH] [Text Word]	Anastrozole [MeSH][Text Word]
Cardiovascular Diseases [MeSH]	Arimidex [MeSH][Text Word]
Myocardial Ischemia [MeSH]	Letrozole [MeSH][Text Word]
Coronary Artery Disease [MeSH]	Femara [MeSH][Text Word]
Coronary Disease [MeSH]	Exemestane [MeSH][Text Word]
Coronary Vessels [MeSH]	Aromasin [MeSH][Text Word]
Angina Pectoris [MeSH]	
Postmenopause [MeSH][Text Word]	

Table S 2. Literature search criteria for Embase

Breast Cancer /exp	Randomized Controlled Trial /exp
Breast Neoplasms /exp	Randomized Controlled Trial (Topic) /exp
Breast Malignancy /exp	Clinical Trial /exp
Breast Carcinoma /exp	Controlled Clinical Trial /exp
Cholesterol /exp	Controlled Clinical Trial (Topic) /exp
Lipid /exp	Double Blind Procedure /exp
HDL Cholesterol /exp	Single Blind Procedure /exp
LDL Cholesterol /exp	Comparative Studies /exp
Triglycerides /exp	Evaluation Study /exp
Hypercholesterolemia /exp	Placebo /exp
Hyperlipidemia /exp	Tamoxifen /exp
Dyslipidemia /exp	Soltamox /exp
Cardiovascular Disease /exp	Nolvadex /exp
Ischemic Heart Disease /exp	Toremifene /exp
Coronary Heart Disease /exp	Fareston /exp
Coronary Artery /exp	Aromatase Inhibitors /exp
Myocardial Infarction /exp	Anastrozole /exp
Angina /exp	Arimidex /exp
Postmenopause /exp	Letrozole /exp
	Femara /exp
	Exemestane /exp
	Aromasin /exp

Table S 3. Summary of the reported outcomes of the selected articles				
Author (Year)	Level of Evidence/ Study Design/Participants/ Inclusion Criteria	Intervention and Control for analysis	Outcome Measures	Results
Love RR, et al. (1990)[187]	Level 2 Subcohort of RCT N=140 (Tamoxifen (n=70) vs. Placebo (n=70)) Inclusion: postmenopausal operable breast cancer patients without evidence of disease, tumor size <5cm.	Tamoxifen (n=70) vs. Placebo (n=70)	Total Cholesterol HDL-C LDL-C Triglyceride	**Total Cholesterol (mmol/L):** change from baseline (Mean±SE) Tamoxifen: Baseline 5.619±0.794 3 months -0.683±0.077*# 6 months -0.652±0.076*# 12 months -6.676±0.081*# Placebo: Baseline 5.950±0.918 3 months 0.052±0.074# 6 months -0.016±0.091# 12 months -0.0596±0.068# **HDL-C (mmol/L):** Tamoxifen Baseline 1.481±0.382 3 months -0.069±0.29* 6 months -0.028±0.027 12 months -0.099±0.022*# Placebo: Baseline 1.528±0.348 3 months -0.014±0.023 6 months 0.015±0.025 12 months 0.010±0.028# **LDL-C (mmol/L):** Tamoxifen Baseline 3.904±0.820 3 months -0.666±0.065*# 6 months -0.664±0.064*# 12 months -0.626±0.074*#

Table S 3. (cont.)				
				Placebo Baseline 4.195±0.932 3 months 0.056±0.070# 6 months -0.050±0.082# 12 months -0.052±0.062# **Triglyceride (mmol/L):** Tamoxifen Baseline 1.174±0.491 3 months 0.258±0.082*# 6 months 0.206±0.064* 12 months 0.246±0.066*# Placebo Baseline 1.134±0.481 3 months 0.046±0.050# 6 months 0.089±0.056 12 months 0.018±0.055#
Love RR, et al. (1991)[188]	Level 2 Subcohort of RCT N=140 (Tamoxifen (n=70) vs. Placebo (n=70)) Inclusion: postmenopausal operable breast cancer patients without evidence of disease, tumor size <5cm.	Tamoxifen (n=64) vs. Placebo (n=62)	Total Cholesterol HDL-C LDL-C Triglyceride	**Total Cholesterol (mmol/L):** change from baseline (Mean±SE) Tamoxifen: Baseline 5.619±0.794 18 months -0.747±0.164*# 24 months -0.672±0.167*# Placebo: Baseline 5.950±0.918 18 months -0.092±0.175# 24 months -0.140±0.154# **HDL-C (mmol/L):** Tamoxifen Baseline 1.481±0.382 18 months -0.106±0.056* 24 months -0.093±0.055* Placebo: Baseline 1.528±0.348 18 months -0.077±0.059* 24 months -0.117±0.057*

Table S 3. (cont.)

				LDL-C (mmol/L): Tamoxifen Baseline 3.904±0.820 18 months -0.737±0.135*# 24 months -0.725±0.143*# Placebo Baseline 4.195±0.932 18 months -0.058±0.148 24 months -0.017±0.141 **Triglyceride (mmol/L):** Tamoxifen Baseline 1.174±0.491 18 months 0.207±0.121* 24 months 0.319±0.139*# Placebo Baseline 1.134±0.481 18 months 0.093±0.144 24 months -0.012±0.116#
Love RR, et al. (1994)[189]	Level 2 Subcohort of a RCT N=140 (Tamoxifen (n=70) vs. Placebo (n=70)) Inclusion: postmenopausal operable breast cancer patients without evidence of disease, tumor size <5cm. No lipid-lowering medication was taken in this cohort.	Tamoxifen (n=30) vs. Placebo (n=32)	Total Cholesterol HDL-C LDL-C Triglyceride	**Total Cholesterol (mmol/L):** change from baseline Tamoxifen: Baseline 5.62±0.10 60 months -0.73±0.13*# Placebo: Baseline 5.95±0.11 60 months -0.12±0.10# **HDL-C (mmol/L):** Tamoxifen Baseline 1.48±0.05 60 months -0.17±0.04* Placebo: Baseline 1.48±0.05 60 months -0.19±0.06*

Table S 3. (cont.)

				LDL-C (mmol/L): Tamoxifen Baseline 3.90±0.09 60 months -0.80±0.12*# Placebo Baseline 4.20±0.11 60 months -0.06±0.10# **Triglyceride (mmol/L):** Tamoxifen Baseline 1.17±0.06 60 months 0.52±0.11* Placebo Baseline 1.13±0.06 60 months 0.27±0.11*
Gylling H, et al. (1995)[190]	Level 2 Subcohort of a randomized trial (subjects with lipid data were included) N=48 (Tamoxifen (n=24) vs. Toremifene (n=24)) Inclusion: postmenopausal breast cancer patients without residual cancer, systemic disease, hypercholesterolemic drugs.	Tamoxifen (n=10) vs. Toremifene (n=14)	Total Cholesterol HDL-C LDL-C Triglyceride	**Total Cholesterol (mmol/L)** Tamoxifen: Baseline 5.2±0.4 2 months 4.8±0.2 6 months 4.8±0.3 12 months 4.7±0.3* Toremifene: Baseline 5.8±0.3 2 months 5.4±0.3 6 months 5.4±0.3 12 months 5.1±0.3* **HDL-C (mmol/L)** Tamoxifen: Baseline 1.1±0.1 2 months 1.2±0.1 6 months 1.2±0.1 12 months 1.2±0.1 Toremifene: Baseline 1.3±0.1 2 months 1.3±0.1 6 months 1.3±0.1 12 months 1.2±0.1

Table S 3. (cont.)				
				LDL-C (mmol/L) Tamoxifen: Baseline 3.3±0.3 2 months 2.7±0.2 6 months 2.7±0.2* 12 months 2.7±0.3* Toremifene: Baseline 3.5±0.3 2 months 3.3±0.3 6 months 3.3±0.3 12 months 3.0±0.3* **Triglyceride (mmol/L)** Tamoxifen: Baseline 1.8±0.3 2 months 1.9±0.3 6 months 1.8±0.2 12 months 1.9±0.3 Toremifene: Baseline 1.9±0.3 2 months 2.1±0.4 6 months 1.9±0.3 12 months 1.8±0.2
Saarto T, Blomqvist C, Ehnholm C, et al. (1996)[191]	Level 1 RCT N= 49 (Tamoxifen (n=26) vs. Toremifene (n=23)) Inclusion: less than 75 y/o postmenopausal node-positive breast cancer patients with appropriate performance status and without recurrence within 6 months	Tamoxifen (n=26) vs. Toremifene (n=23)	Total Cholesterol HDL-C LDL-C Triglyceride	**Total Cholesterol (mmol/L)** Tamoxifen: Baseline 6.16±1.03 12 months 5.46±0.91* Toremifene: Baseline 5.88±1.16 12 months 5.26±1.06* **HDL-C (mmol/L)** Tamoxifen: Baseline 1.63±0.40 12 months 1.55±0.34# Toremifene: Baseline 1.36±0.33 12 months 1.55±0.45*#

Table S 3. (cont.)				
				LDL-C (mmol/L) Tamoxifen: Baseline 4.01±0.91 12 months 3.17±0.95* Toremifene: Baseline 3.74±1.03 12 months 3.01±1.06* **Triglyceride (mmol/L)** Tamoxifen: Baseline 1.02±0.47 12 months 1.31±0.86* Toremifene: Baseline 1.08±0.90 12 months 1.04±1.02
Kusama M, Miyauchi K, Aoyama H, et al. (2004)[192]	Level 1 RCT N= 73 (Toremifene (n=37) vs. Tamoxifen (n=36)) Inclusion: postmenopausal breast cancer patients with appropriate performance status without evidence of metastasis.	Toremifene (n=34) vs. Tamoxifen (n=31)	Total Cholesterol HDL-C LDL-C Triglyceride	**Total Cholesterol (mg/dL)** Tamoxifen: Baseline 211.4 3 months 189.3* 6 months 182.6* 12 months 184.4* Toremifene: Baseline 214.7 3 months 200.5* 6 months 198.9* 12 months 201.8* **HDL-C (mg/dL)** Tamoxifen: Baseline 57.8 3 months 59.5 6 months 56.9 12 months 58.6#

Table S 3. (cont.)

				Toremifene: Baseline 54.7 3 months 64.2* 6 months 63.9* 12 months 68.1*# **LDL-C (mg/dL)** Tamoxifen: Baseline 125.7 3 months 106.4* 6 months 102.9* 12 months 106.4* Toremifene: Baseline 126.2 3 months 113.1* 6 months 113.3* 12 months 115.8* **Triglyceride (mg/dL)** Tamoxifen: Baseline 127.4 3 months 134.1 6 months 146.6 12 months 150.8*# Toremifene: Baseline 152.4 3 months 128.0 6 months 132.2 12 months 115.9*#

Table S 3. (cont.)				
Markopoulos C, Polychronis A, Zobolas V, et al. (2005)[193]	Level 2 Subcohort of a randomized trial (subjects with lipid data were included) N=176 (Exemestane (n=90) vs. Tamoxifen (n=86)) Inclusion: postmenopausal early breast cancer patients without residual cancer.	Exemestane (n=90) vs. Tamoxifen (n=86)	Total Cholesterol HDL-C LDL-C Triglyceride	**Total Cholesterol (mg/dL)** Exemestane: Baseline 222 3 months 230 6 months 232.5§ 9 months 227 12 months 223§ ¶ Tamoxifen: Baseline 219.5 3 months 228.5 6 months 214.5§ 9 months 209 12 months 199§ ¶ **HDL-C (mg/dL)** Exemestane: Baseline 52 3 months 50 6 months 50§ 9 months 49 12 months 53 Tamoxifen: Baseline 59.7 3 months 57 6 months 57§ 9 months 54 12 months 59 **LDL-C (mg/dL)** Exemestane: Baseline 137 3 months 152§ ¶ 6 months 148.5§ ¶ 9 months 146 12 months 147

Table S 3. (cont.)

				Tamoxifen: Baseline 140 3 months 137.5§ ¶ 6 months 139§ ¶ 9 months 131 12 months 124 **Triglyceride (mg/dL)** Exemestane: Baseline 128.5 3 months 114¶ 6 months 115¶ 9 months 111.5¶ 12 months 132.5 Tamoxifen: Baseline 109 3 months 142¶ 6 months 123¶ 9 months 140¶ 12 months 99

Table S 3. (cont.)

Sawada S, Sato, K, Kusuhara M, et al. (2005)[194]	Level 1 RCT N= 49 (Tamoxifen (n=25) vs. Anastrozole (n=24)) Inclusion: postmenopausal breast cancer patients with appropriate performance status without evidence of metastasis, chemotherapy, radiotherapy, lipid medication.	(Tamoxifen (n=22) vs. Anastrozole (n=22)	Total Cholesterol HDL-C LDL-C Triglyceride	**Total Changes of lipid profiles (baseline to 3 months)** **Median (IQ range)** **Cholesterol (mg/dL)** Tamoxifen -34.5 (-50.0~-15.0)* Anastrozole 4.0 (-9.0~17.0) **HDL-C (mg/dL)** Tamoxifen 0.5 (-2.5~6.8) Anastrozole 6.0 (3.3~11.9)* **LDL-C (mg/dL)** Tamoxifen -35.5 (-44.0~-25.0)* Anastrozole -3.5 (-23.0~8.0) **Triglyceride (mg/dL)** Tamoxifen 26.0 (0.0~44.0)* Anastrozole -27.0 (-44.0~-9.0)*

Table S 3. (cont.)

Wasan KM, Goss PE, Pritchard PH, et al. (2005)[195]	Level 2 Subcohort of a randomized trial (subjects with lipid data were included) N=347 (Letrozole (n=183) vs. Placebo (n=164)) Inclusion: postmenopausal early breast cancer patients without residual cancer, hyperlipidemia, and lipid drugs.	Letrozole (n=183) vs. Placebo (n=164)	Total Cholesterol HDL-C LDL-C Triglyceride	**Percentage changes of lipid profiles (vs. baseline)** **Total Cholesterol (mmol/l)** Letrozole 6 months 13.58±12.51 12 months 14.55±14.95 24 months 13.35±14.70 36 months 40.53±16.39 Placebo 6 months 12.49±14.06 12 months 11.15±15.57 24 months 10.19±18.37 36 months 8.36±24.50 **HDL-C (mmol/l)** Letrozole 6 months 1.46±15.47# 12 months 3.07±16.41 24 months 1.22±18.70 36 months 2.08±23.43 Placebo 6 months 4.31±13.41# 12 months 3.21±17.01 24 months 6.53±29.54 36 months 12.90±43.02 **LDL-C (mmol/l)** Letrozole 6 months 25.40±23.65 12 months 27.65±27.35# 24 months 23.07±27.39 36 months 20.72±25.98 Placebo 6 months 23.40±25.13 12 months 21.49±29.82#

Table S 3. (cont.)				
				24 months 22.03±32.94 36 months 18.19±43.56 **Triglyceride (mmol/l)** Letrozole 6 months 5.13±43.49 12 months 3.52±41.00 24 months 11.87±44.25# 36 months 8.44±46.95 Placebo 6 months 1.87±45.58 12 months 6.40±71.25 24 months -1.33±42.19# 36 months 3.11±35.84
Lønning PE, Geisler J, Krag LE, et al. (2005)[196]	Level 1 RCT N=147 (Exemestane (n=73) vs. Placebo (n=74)) Inclusion: postmenopausal early breast cancer patients without residual cancer, hyperlipidemia, and lipid drugs.	Exemestane (n=64) vs. Placebo (n=62)	Total Cholesterol HDL-C LDL-C Triglyceride	**Percentage changes of lipid profiles (vs. baseline)** **Mean (95% CI)** **Total Cholesterol (mg/dL)** Placebo 6 months 0 (-3~-2) 12 months -4 (-6~-1) 24 months -5 (-7~-2) Exemestane 6 months -3 (-6~-1) 12 months -4 (-6~-2) 24 months -6 (-9~-4) **HDL-C (mmol/l)** Placebo 6 months 1 (-2~5)# 12 months 1 (-2~5)# 24 months 2 (-2~6)# Exemestane 6 months -7 (-10~-3)# 12 months -6 (-10~-2)#

Table S 3. (cont.)

				24 months -9 (-13~-5)# **LDL-C (mmol/l)** Placebo 6 months -2 (-6~1) 12 months -5 (-8~-1) 24 months -6 (-10~-3) Exemestane 6 months -3 (-6~0) 12 months -3 (-6~1) 24 months -6 (-10~-3) E vs. P $p<0.05$ **Triglyceride (mg/dL)** Placebo 6 months 7 (-2~15) 12 months 1 (-7~8) 24 months -3 (-13~6) Exemestane 6 months 2 (-6~10) 12 months -4 (-12~4) 24 months 1 (-9~10)

Table S 3. (cont.)

Markopoulos C, Chrissochou M, Michailidou A, et al. (2005)[197]	Level 2 Subcohort of a randomized trial (subjects with lipid data were included) N=340 (Exemestane (n=172) vs. Placebo (n=168)) Inclusion: postmenopausal early breast cancer patients without residual cancer, hyperlipidemia, and lipid drugs.	Letrozole (n=172) vs. Placebo (n=168)	Total Cholesterol HDL-C LDL-C Triglyceride	**Percentage changes of lipid profiles (vs. baseline)** **Total Cholesterol (mg/dL)** Exemestane 6 months 6.2* 12 months 8.9* Placebo 6 months 8.0* 12 months 9.2* **HDL-C (mmol/l)** Exemestane 6 months -0.9 12 months 2.6 Placebo 6 months 6.4 12 months 9.7 **LDL-C (mmol/l)** Exemestane 6 months 11.1* 12 months 10.3* Placebo 6 months 11.2* 12 months 9.7* **Triglyceride (mmol/l)** Exemestane 6 months -20.6 12 months -20.1* Placebo 6 months -8.9* 12 months -14.7*

Table S 3. (cont.)				
Francini G, Petrioli R, Montagnani A, et al. (2006)[198]	Level 1 RCT N= 55 (Tamoxifen→ Exemestane (n=28) vs. Tamoxifen (n=27)) Inclusion: Prior TAM for 2 years of postmenopausal breast cancer patients with appropriate performance status without evidence of metastasis.	Tamoxifen→ Exemestane (n=28) vs. Tamoxifen (n=27)	Total Cholesterol HDL-C LDL-C Triglyceride	**Total Cholesterol (mg/dl mean±SD)** TAM→ Exemestane: Baseline 215.12±10.01 6 months 216.23±10.44 12 months 215.32±11.21 Tamoxifen: Baseline 215.68±9.31 6 months 224.27±13.33 12 months 224.17±12.83 **HDL-C (mg/dl mean±SD)** TAM→ Exemestane: Baseline 58.62±6.17 6 months 58.22±8.77 12 months 57.98±8.01 Tamoxifen: Baseline 58.07±6.40 6 months 53.41±8.10 12 months 51.20±8.08* **LDL-C (mg/dl mean±SD)** TAM→ Exemestane: Baseline 131.15±14.51 6 months 133.56±19.10 12 months 132.31±19.24 Tamoxifen: Baseline 130.91±15.10 6 months 149.8±17.18* 12 months 152.81±18.12*# **Triglyceride (mg/dl mean±SD)** TAM→ Exemestane: Baseline 124.87±46.1

Table S 3. (cont.)

				6 months 119.30±47.81 12 months 127.63±40.60 Tamoxifen: Baseline 124.11±58.27 6 months 107.21±64.30* 12 months 101.04±43.65*
Montagnani A, Gonnelli S, Cadirni A, et al. (2008)[199]	Level 1 RCT N=68 (TAM→ Exemestane (N=33) vs. TAM (N=35)) Inclusion:	TAM→ Exemestane (N=33) vs. TAM (N=35)	Total Cholesterol LDL-C HDL-C Triglyceride	**Change of lipid profiles (%)** **LDL-C** TAM→ E 12 months 16.5*# 24 months 10.1*# TAM 12 months -1.1# 24 months -0.5# **HDL-C** TAM→ E 12 months -12.7*# 24 months -15.2*# TAM 12 months -2.1# 24 months 2.4# **Triglyceride** TAM→ E 12 months -16.9*# 24 months -18.1*# TAM 12 months 2.5# 24 months 4.1#

Table S 3. (cont.)

Markopoulos C, Dafni U, Misitzis J, et al. (2009)[200]	Level 2 Subcohort of a randomized trial (subjects with lipid data were included) N=411 (Exemestane (N=211) vs. Observation (N=200)) Inclusion: 5-year TAM treated postmenopausal BC patients without metastasis and recurrence	Exemestane (N=211) vs. Observation (N=200)	Total Cholesterol HDL-C LDL-C Triglyceride	**Change values of lipid profiles** **Total Cholesterol (mg/dl)** Exemestane 6 months 11.5±5.6* 12 months 14.4±5* 18 months 15.3±7* 24 months 8.9±7.4 Observation 6 months 16.8±4.7* 12 months 21.6±4.1* 18 months 24±5.3* 24 months 17±6* **HDL-C** Exemestane 6 months -4.3±1.8* 12 months -3±2.3 18 months -6.5±2.6* 24 months -8.3±2.1* Observation 6 months 2.2±1.5 12 months 1.7±1.4 18 months 1.5±1.2 24 months 1.1±1.9 **LDL-C** Exemestane 6 months 24.3±6.3* 12 months 20.1±6.3* 18 months 22.7±9.5* 24 months 32.1±8.1* Observation 6 months 19.8±5.7* 12 months 22.3±4.9* 18 months 30.4±6.2* 24 months 23±8.4*

Table S3. (cont.)

				Triglyceride Exemestane 6 months -24.1±7.8* 12 months -32.2±7.6* 18 months -26.8±9.3* 24 months -20.7±9.6* Observation 6 months -13.7±6.1* 12 months -17.6±7.6* 18 months -9.4±7.2 24 months -19.8±9*
Markopoulos C, Polychronis A, Dafni U, et al. (2009)[201]	Level 2 Subcohort of a randomized trial (subjects with lipid data were included) N=211 (Exemestane (N=110) vs. Tamoxifen (N=101)) Inclusion: 5-year TAM treated postmenopausal BC patients without metastasis and recurrence	Exemestane (N=110) vs. Tamoxifen (N=101)	Total Cholesterol HDL-C LDL-C Triglyceride	**Change values of lipid profiles** **Total Cholesterol (mg/dl)** Exemestane 12 months -13.1±5.6* 18 months -10.2±7.1 24 months -8.3±7.2 Tamoxifen 12 months -28.9±4.8* 18 months -19.0±7.3* 24 months -29.3±6.3* **HDL-C** Exemestane 12 months -2.7±2.2 18 months -5.3±2.5* 24 months -3.0±2.7 Tamoxifen 12 months 0.9±2.0 18 months 0.7±1.7 24 months 0.8±2.6 **LDL-C** Exemestane 12 months -7.7±5.4 18 months -7.5±6.8 24 months -2.3±5.1

Table S 3. (cont.)

				Tamoxifen 12 months -21.1±6.5* 18 months -24.6±7.1* 24 months -28.4±8.0* **Triglyceride** Exemestane 12 months -9.0±11.2 18 months 2.9±10.2 24 months -21.6±13.3 Tamoxifen 12 months 13.4±9.2 18 months -9.9±16.3 24 months 22.0±10.4*
Anan K, Mitsuyama S, Yanagita Y, et al. (2011)[202]	Level 1 RCT N=69 (Toremifene (N=36) vs. Anastrozole (N=33)) Inclusion: Postmenopausal BC patients having appropriate organ function without residual tumor	Toremifene (N=32) vs. Anastrozole (N=29)	Total Cholesterol HDL-C LDL-C Triglyceride	**Change percentage of lipid Total Cholesterol mean(95% CI)** Toremifene 6 months -6.2 (-10.4~-2.1)* 12 months -8.3 (-11.7~-4.8)* 24 months -7.2 (-11.2~-3.1)* Anastrozole 6 months 0.1 (-5.3~5.6) 12 months 1.7 (-2.7~6.6) 24 months -1.2 (-8.5~6.0) **HDL-C** Toremifene 6 months 17.1 (8.5~25.6)* 12 months 17.0 (6.8~27.3)* 24 months 22.0 (9.5~34.5)* Anastrozole 6 months 0..8 (-4.1~5.8) 12 months 3.2 (-1.1~7.5) 24 months 2.7 (-3.4~8.9)

Table S 3. (cont.)

				LDL-C Toremifene 6 months -12.9 (-19.7~-6.2)* 12 months -10.2 (-14.7~-5.7)* 24 months -11.3 (-17.8~-4.8)* Anastrozole 6 months 1.4 (-6.7~9.6) 12 months 2.8 (-5.0~10.7) 24 months -1.8 (-13.2~9.4) **Triglyceride** Toremifene 6 months 10.2 (-11.9~32.4) 12 months -8.6 (-21.5~4.3) 24 months -12.3 (-28.7~4.0) Anastrozole 6 months 11.1 (-11.4~33.7) 12 months 6.3 (-16.4~29.0) 24 months 24.9 (-9.8~59.6)

Table S 3. (cont.)

Bell LN, Nguyen ATP, Li L, et al. (2012)[203]	Level 1 RCT N=246 (Exemestane (N=117) vs. Letrozole (N=129)) Inclusion: Postmenopausal BC patients without residual tumor	Exemestane (N=117) vs. Letrozole (N=129)	Total Cholesterol HDL-C LDL-C Triglyceride	**Change values of lipid** **Total Cholesterol mean±SD** Exemestane 3 months -8±28* Letrozole 3 months 8±24* **HDL-C** Exemestane 3 months -8±9* Letrozole 3 months -1±9 **LDL-C** Exemestane 3 months 2±27 Letrozole 3 months 7±25* **Triglyceride** Exemestane 3 months -12±42* Letrozole 3 months 0.4±43

Note.
RCT = randomized clinical ; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol
* $p<0.05$ (vs. baseline); # $p<0.05$ between groups;
¶ $p<0.05$ (E vs. T for percentage changes from baseline);
§ $p<0.05$ (E vs. T for absolute values)

Table S 4.Quality and bias assessment[175]

Authors	Sequence generation	Allocation concealment	Blinding of participants personnel and outcome assessors	Incomplete outcome data	Selective outcome report	Other potential bias
Love R, et al.[175-177]	?	?	+	+	+	+
Gylling H, et al.[178]	?	?	+	+	+	-
Saarto T, et al.[179]	?	?	?	+	+	+
Kusama M, et al.[180]	+	?	+	-	+	?
Markopoulos C, et al.[181,189]	+	+	+	+	+	+
Sawada S, et al.[182]	?	?	+	+	+	+
Wasan KM, et al.[183]	+	?	+	+	+	+
Lønning PE, et al.[184]	+	?	+	+	+	+
Markopoulos C, et al.[185,188]	?	?	+	?	+	+
Francini G et al.[186]	+	?	+	+	+	?
Montagnani A, et al.[187]	?	?	+	+	+	+
Anan K, et al.[190]	+	?	+	?	+	+
Bell LN, et al.[191]	?	?	+	+	+	+

+: the criteria are fulfilled; -: the criteria are not fulfilled; ?: cannot be determined

Table S 5. Characteristics of population in selected trials

Article	Medication	Prior TAM	TAM duration	Number of Subject	Mean Age	Mean weight (kg)	Mean Height (cm)	Mean BMI	Overall follow/up year	Number of C/T	Number of R/T	Baseline			
												TC	HDL-C	LDL-C	TG
Love RR, et al.[187–189]	TAM	N	0	70	57.6	-	-	26.2	5	-	12	217.3	57.3	151.0	104.0
	Placebo	N	0	70	57.8	-	-	27.6	5	-	17	230.1	59.1	162.2	100.4
Gylling H, et al.[190]	TAM	N	0	24	60.0	66.2	161	25.6	1	-	-	201.1	42.5	127.6	159.4
	Toremifene	N	0	24	60.0	66.2	161	25.6	1	-	-	224.3	50.3	135.3	168.3
Saarto T, et al.[191]	TAM	N	0	26	60.0	68.0	163	25.6	1	-	-	238.2	63.0	155.1	90.3
	Toremifene	N	0	23	63.0	75.0	163	28.2	1	-	-	227.4	52.6	144.6	95.7
Kusama M, et al.[192]	TAM	N	0	36	63.0	55.0	154	22.7	1	0	0	211.4	57.8	125.7	127.4
	Toremifene	N	0	37	64.0	54.7	151	23.3	1	0	0	214.7	54.7	126.2	152.4
Markopoulos C, et al. [181,189]	Exemestane	N	0	90	65.0	74.4	-	-	1	41	46	222.0	52.0	137.0	128.5
	TAM	N	0	86	63.0	73.5	-	-	1	41	42	219.5	59.7	140.0	109.0
Sawada S, et al.[182]	TAM	N	0	25	59.3	54.7	153	23.4	0.25	-	-	217.0	61.0	132.0	129.0
	Anastrozole	N	0	24	58.7	55.6	155	23.1	0.25	-	-	213.0	59.0	130.0	134.0
Wasan KM, et al.[183]	Letrozole	Y	5	183	62.9	-	-	-	3	-	-	206.9	61.5	116.8	192.2
	Placebo	Y	5	164	63.1	-	-	-	3	-	-	213.1	58.0	124.5	266.6
Lønning PE, et al.[184]	Exemestane	N	0	73	60.0	-	-	-	2	-	-	253.4	65.7	166.3	110.8
	Placebo	N	0	74	59.0	-	-	-	2	-	-	257.1	65.7	170.1	110.4
Francini G, et al.[186]	Exemestane	Y	2	28	61.9	69.9	156	29.2	1	8	14	215.1	58.6	131.2	124.9
	TAM	Y	2	27	61.2	69.8	156	29.0	1	6	11	215.7	58.1	130.9	124.1
Montagnani A, et al.[187]	Exemestane	Y	2.5	33	61.6	67.2	156	28.1	2	-	-	215.8	59.1	130.9	122.4
	TAM	Y	2.5	35	62.2	67.4	156	28.0	2	-	-	218.2	57.3	136.4	125.4
Markopoulos C, et al.[185,188]	Exemestane	Y	5	211	62.6	71.8	-	-	2	80	117	215.0	57.0	139.4	118.0
	Placebo	Y	5	200	61.8	69.6	-	-	2	79	99	213.5	56.0	133.0	123.0
Anan K, et al.[190]	Toremifene	N	0	36	62.5	55.0	154	23.2	2	0	-	220.8	57.5	139.4	133.1
	Anastrozole	N	0	33	60.0	43.3	151	24.0	2	0	-	220.8	57.5	139.4	133.1

Table S 5. (cont.)															
Bell LN, et al.[191]	Exemestane	Y	2.5	117	59.0	-	-	-	0.25	51	-	212.0	63.0	127.0	112.0
	Letrozole	Y	2.5	129	57.0	-	-	-	0.25	69	-	203.0	60.0	121.0	110.0

TAM: Tamoxifen; BMI: body mass index; C/T: chemotherapy; R/T: radiotherapy; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: tryglyceride

Table S 6. Rank probabilities of effects of hormone therapy on TC

Probability of rank and SUCRA(cumulated probability)						
		SERMs		AIs		
Rank	Placebo	Tamoxifen	Toremifene	Letrozole	Anastrozole	Exemestane
1	0 (0)	0.07 (0.07)	0.93 (0.93)	0 (0)	0 (0)	0 (0)
2	0 (0)	0.93 (1)	0.07 (1)	0 (0)	0 (0)	0 (0)
3	0 (0)	0 (1)	0 (1)	0 (0)	0.01 (0.01)	0.99 (0.99)
4	0.71 (0.71)	0 (1)	0 (1)	0 (0)	0.28 (0.29)	0.01 (1)
5	0.29 (1)	0 (1)	0 (1)	0.37 (0.37)	0.34 (0.63)	0 (1)
6	0 (1)	0 (1)	0 (1)	0.63 (1)	0.37 (1)	0 (1)
SUCRA	34%	81%	99%	8%	18%	60%

TC: Total Cholesterol; SERMs: Selective Estrogen Receptor Modulators; AIs: Aromatase Inhibitors

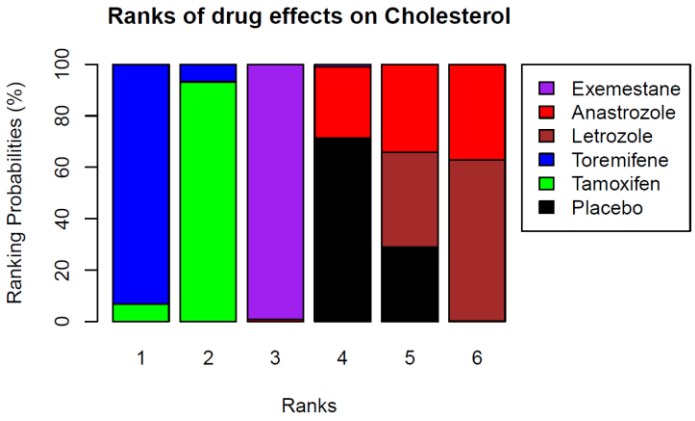


Figure S 1. Rankgram of effects of hormone therapy on total cholesterol

Table S 7. Rank probabilities of effects of hormone therapy on HDL-C

HDL-C Probability of rank and SUCRA(cumulated probability)						
		SERMs		AIs		
Rank	Placebo	Tamoxifen	Toremifene	Letrozole	Anastrozole	Exemestane
1	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
2	0.96 (0.96)	0 (0)	0 (1)	0 (0)	0.04 (0.04)	0 (0)
3	0.04 (1)	0 (0)	0 (1)	0.66 (0.66)	0.31 (0.34)	0 (0)
4	0 (1)	0.14 (0.14)	0 (1)	0.34 (1)	0.52 (0.86)	0 (0)
5	0 (1)	0.86 (1)	0 (1)	0 (1)	0.14 (1)	0 (0)
6	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	1 (1)
SUCRA	79%	23%	100%	53%	45%	0%

HDL-C: High Density Lipoprotein Cholesterol; SERMs: Selective Estrogen Receptor Modulators; AIs: Aromatase Inhibitors

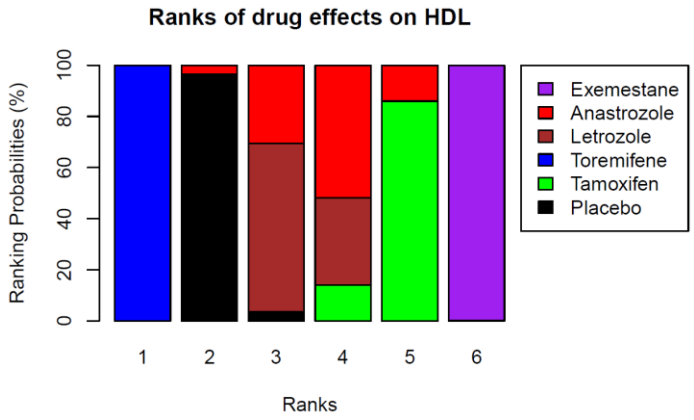


Figure S 2. Rankgram of effects of hormone thearpy on HDL-C

Table S 8. Rank probabilities of effects of hormone therapy on LDL-C

LDL-C Probability of rank and SUCRA (cumulated probability)						
		SERMs		AIs		
Rank	Placebo	Tamoxifen	Toremifene	Letrozole	Anastrozole	Exemestane
1	0 (0)	0.16 (0.16)	0.84 (0.84)	0 (0)	0 (0)	0 (0)
2	0 (0)	0.84 (1)	0.16 (1)	0 (0)	0 (0)	0 (0)
3	0.05 (0.05)	0 (1)	0 (1)	0.05 (0.05)	0.06 (0.06)	0.83 (0.83)
4	0.61 (0.67)	0 (1)	0 (1)	0.18 (0.23)	0.06 (0.12)	0.15 (0.98)
5	0.30 (0.97)	0 (1)	0 (1)	0.58 (0.81)	0.09 (0.22)	0.02 (1)
6	0.03 (1)	0 (1)	0 (1)	0.19 (1)	0.78 (1)	0 (1)
SUCRA	34%	83%	97%	22%	8%	56%

LDL-C: Low Density Lipoprotein Cholesterol; SERMs: Selective Estrogen Receptor Modulators; AIs: Aromatase Inhibitors

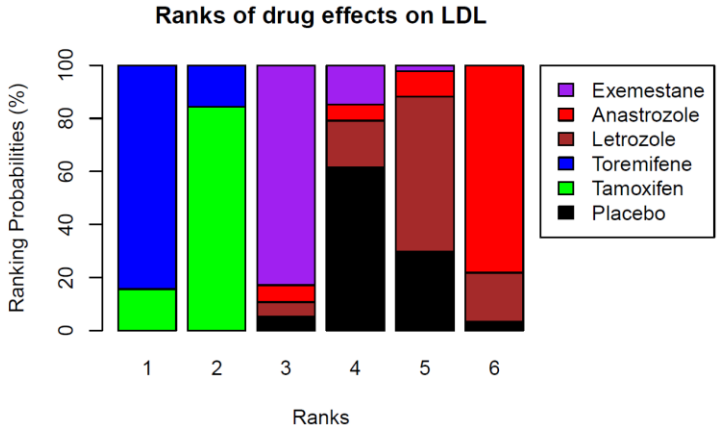


Figure S 3. Rankgram of effects of hormone therapy on LDL-C

Table S 9. Rank probabilities of hormone therapy on Triglyceride

Triglyceride Probability of rank and SUCRA(cumulated probability)						
		SERMs		AIs		
Rank	Placebo	Tamoxifen	Toremifene	Letrozole	Anastrozole	Exemestane
1	0 (0)	0 (0)	0.73 (0.73)	0 (0)	0.26 (0.26)	0.01 (0.01)
2	0 (0)	0 (0)	0.26 (1)	0 (0)	0.60 (0.86)	0.13 (0.14)
3	0.02 (0.02)	0 (0)	0 (1)	0 (0)	0.12 (0.98)	0.86 (1)
4	0.97 (0.99)	0 (0)	0 (1)	0.01 (0.01)	0.02 (1)	0 (1)
5	0.01 (1)	0 (0)	0 (1)	0.99 (1)	0 (1)	0 (1)
6	0 (1)	1 (1)	0 (1)	0 (1)	0 (1)	0 (1)
SUCRA	40%	0%	95%	20%	82%	63%

SERMs: Selective Estrogen Receptor Modulators; AIs: Aromatase Inhibitors

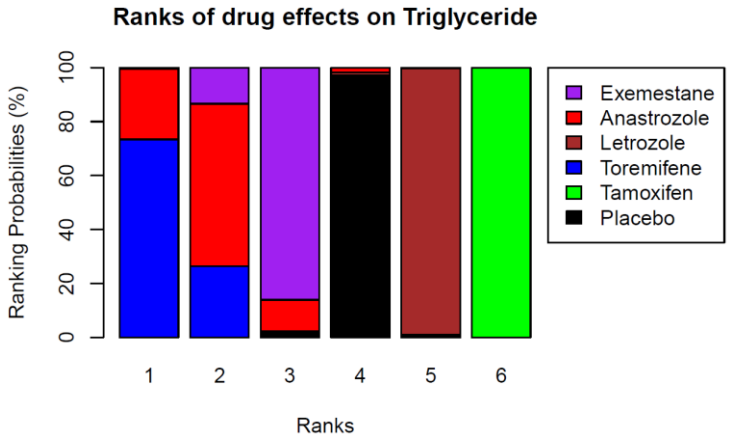


Figure S 4. Rankgram of effects of hormone therapy on Triglyceride

Table S 10. Estimates of changes of TC levels with the presence of metaregressors

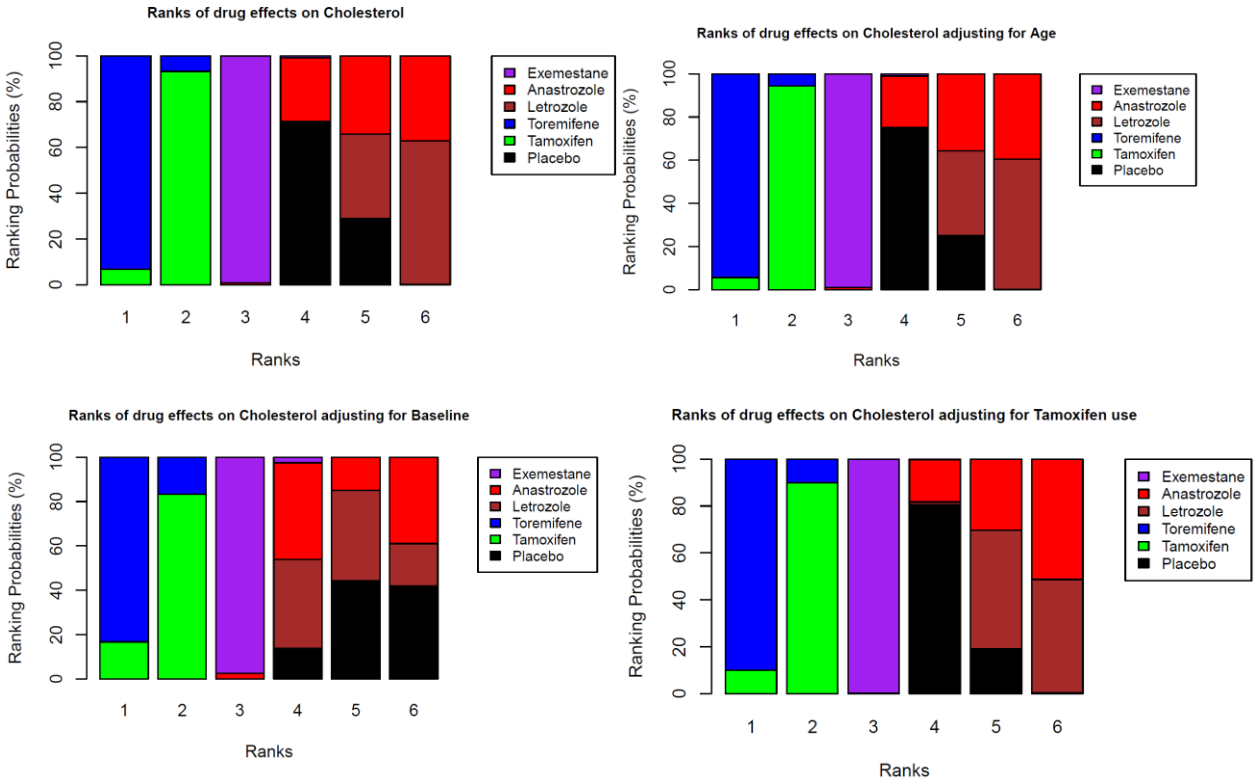
Drug	No Adjustment	Adjust for Age ($\bar{x} = 60.91$)	Adjust for Baseline ($\bar{x} = 220.75$)	Adjust for Tamoxifen use
	Mean (95% Credible Interval)			
Metaregressor		**1.51 (0.56 , 2.52)**	**-0.24 (-0.37 , -0.11)**	**5.86 (1.79 , 9.97)**
Tamoxifen	**-21.62 (-24.17 , -19.12)**	**-19.37 (-22.29 , -16.48)**	**-21.91 (-24.45 , -19.35)**	**-24.19 (-27.18 , -21.02)**
Toremifene	**-26.37 (-33.04 , -19.70)**	**-25.96 (-32.53 , -19.37)**	**-25.87 (-32.37 , -19.43)**	**-28.72 (-35.32 , -22.10)**
Letrozole	**3.89 (0.83 , 6.97)**	2.11 (-1.27 , 5.40)	0.95 (-2.53 , 4.36)	-1.35 (-6.12 , 3.43)
Anastrozole	2.40 (-5.90 , 10.81)	6.50 (-2.30 , 15.18)	2.55 (-5.66 , 10.90)	0.07 (-8.13 , 8.51)
Exemestane	**-7.55 (-9.53 , -5.58)**	**-9.15 (-11.40 , -6.94)**	**-7.43 (-9.41 , -5.53)**	**-11.50 (-14.82 , -8.12)**

TC: Total Cholesterol
Baseline and age are centered to their mean in the model.
Placebo: $Y_{i1} = \mu_i$
Hormone drugs: $Y_{ik} = \mu_i + \theta_k + b(x_i - \bar{x})$
k: treatments, k=1 (placebo), k=2, …, 6 (hormone drugs)
Y_{ik}: trial-specific treatment-specific outcome
μ_i: trial-specific mean effect without treatment (placebo)
θ_k: drug effect relative to placebo
b: covariate coefficient
x_i: trial-specific covariate value
$\bar{x}$: grand mean of age/baseline
Bold: p<0.05

Table S 11. SUCRA reports of hormone therapeutic options for TC based on presence of metaregressors

SUCRA of hormone therapeutic options with metaregressors						
Drug	Placebo	Tamoxifen	Toremifene	Letrozole	Anastrozole	Exemestane
No Adjustment	34%	81%	99%	8%	18%	60%
Adjust for Age	36%	80%	100%	18%	5%	60%
Adjust for Baseline	29%	82%	98%	19%	13%	60%
Adjust for Tamoxifen use	16%	81%	99%	27%	18%	60%

TC: Total Cholesterol



TC: Total Cholesterol

Figure S 5. Rank plots of hormone therapeutic options for TC based on presence of metaregressors

Table S 12. Estimates of changes of HDL-C levels with the presence of metaregressors

Drug	No Adjustment	Adjust for Age ($\bar{x} = 60.91$)	Adjust for Baseline ($\bar{x} = 57.53$)	Adjust for Tamoxifen use
	Mean (95% Credible Interval)			
Metaregressor		-0.24 (-0.57 , 0.08)	**-0.48 (-0.60 , -0.36)**	**-3.94 (-5.26 , -2.62)**
Tamoxifen	**-3.90 (-4.73 , -3.08)**	**-4.27 (-5.27 , -3.32)**	**-2.49 (-3.39 , -1.60)**	**-2.32 (-3.31 , -1.32)**
Toremifene	**7.30 (5.23 , 9.35)**	**7.23 (5.21 , 9.30)**	**7.74 (5.64 , 9.82)**	**8.61 (6.53 , 10.70)**
Letrozole	**-1.89 (-2.91 , -0.87)**	**-1.60 (-2.68 , -0.51)**	-0.69 (-1.74 , 0.37)	**1.74 (0.20 , 3.34)**
Anastrozole	-2.50 (-5.18 , 0.17)	-3.19 (-6.14 , -0.34)	-2.31 (-5.02 , 0.39)	-1.20 (-3.88 , 1.46)
Exemestane	**-6.57 (-7.24 , -5.90)**	**-6.33 (-7.05 , -5.58)**	**-6.33 (-7.00 , -5.64)**	**-4.01 (-5.09 , -2.94)**

Placebo: $Y_{i1} = \mu_i$

Baseline and age are centered to their mean in the model.

Hormone drugs: $Y_{ik} = \mu_i + \theta_k + b(x_i - \bar{x})$

k: treatments, k=1 (placebo), k=2, …, 6 (hormone drugs)

Y_{ik}: trial-specific treatment-specific outcome

μ_i: trial-specific mean effect without treatment (placebo)

θ_k: drug effect relative to placebo

b: covariate coefficient

x_i: trial-specific covariate value

Bold: p<0.05

Table S 13. SUCRA reports of hormone therapeutic options for HDL-C based on presence of metaregressors

SUCRA of hormone therapeutic options with metaregressors						
Drug	Placebo	Tamoxifen	Toremifene	Letrozole	Anastrozole	Exemestane
No Adjustment	79%	23%	100%	53%	45%	0%
Adjust for Age	80%	24%	100%	57%	39%	0%
Adjust for Baseline	77%	29%	100%	60%	34%	0%
Adjust for Tamoxifen use	57%	24%	100%	79%	40%	0%

HDL-C: High Density Lipoprotein Cholesterol

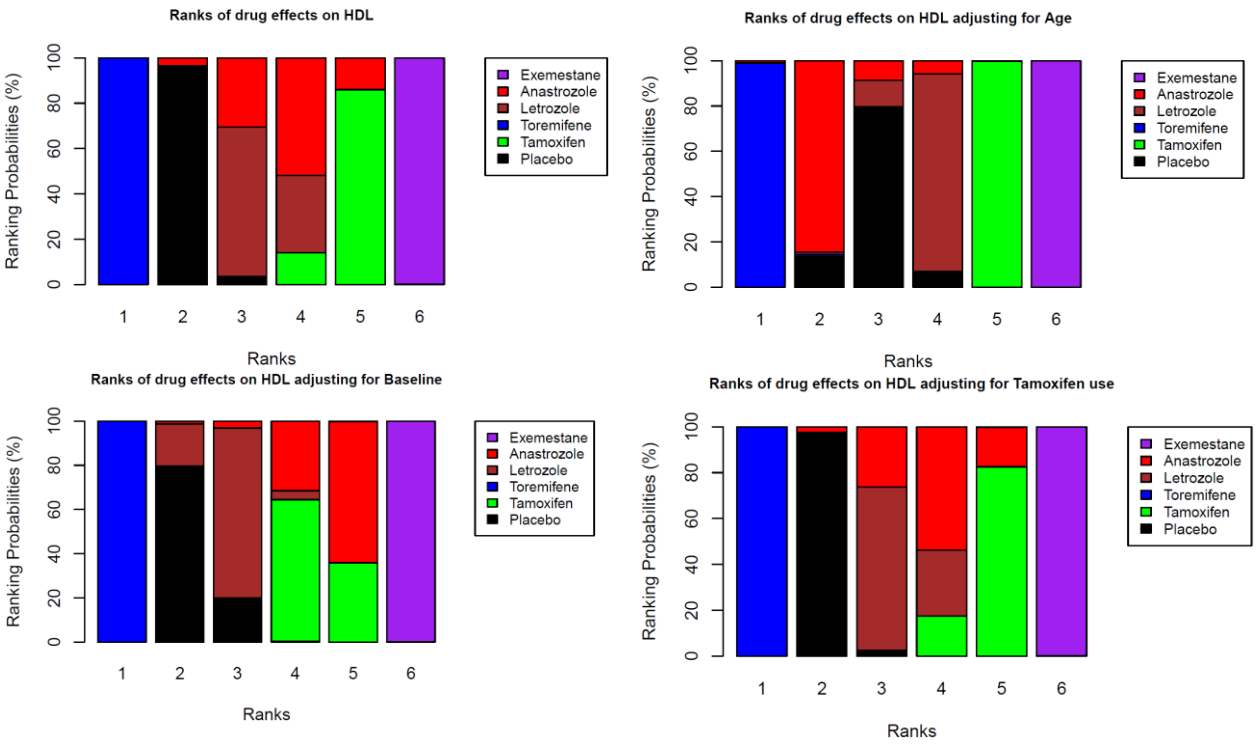


Figure S 6. Rankgrams of hormone therapeutic options for HDL-C based on presence of metaregressor

Table S 14. Estimates of changes of LDL-C levels with the presence of metaregressor

Drug	No Adjustment	Adjust for Age ($\bar{x} = 60.91$)	Adjust for Baseline ($\bar{x} = 139.35$)	Adjust for Tamoxifen use
	Mean (95% Credible Interval)			
Metaregressor		**1.98 (1.00 , 2.93)**	**-0.31 (-0.47 , -0.15)**	**10.21 (6.09 , 14.29)**
Tamoxifen	**-21.11 (-23.62 , -18.65)**	**-18.02 (-20.96 , -15.09)**	**-18.46 (-21.31 , -15.63)**	**-25.39 (-28.41 , -22.31)**
Toremifene	**-24.17 (-30.56 , -17.89)**	**-23.23 (-29.68 , -16.76)**	**-21.46 (-27.90 , -14.97)**	**-28.17 (-34.54 , -21.72)**
Letrozole	1.07 (-1.96 , 4.12)	-1.28 (-4.55 , 2.00)	**-4.30 (-8.35 , -0.20)**	**-8.07 (-12.81 , -3.38)**
Anastrozole	4.62 (-3.54 , 12.72)	**10.28 (1.83 , 19.06)**	7.05 (-1.33 , 15.40)	0.52 (-7.75 , 8.69)
Exemestane	-1.52 (-3.50 , 0.49)	**-3.47 (-5.68 , -1.37)**	-0.37 (-2.46 , 1.66)	**-8.11 (-11.37 , -4.83)**

Placebo: $Y_{i1} = \mu_i$
Baseline and age are centered to their mean in the model.
Hormone drugs: $Y_{ik} = \mu_i + \theta_k + b(x_i - \bar{x})$
k: treatments, k=1 (placebo), k=2, …, 6 (hormone drugs)
Y_{ik}: trial-specific treatment-specific outcome
μ_i: trial-specific mean effect without treatment (placebo)
θ_k: drug effect relative to placebo
b: covariate coefficient
x_i: trial-specific covariate value
Bold: p<0.05

Table S 15. SUCRA reports of hormone therapeutic options for LDL-C based on presence of metaregressors

SUCRA of hormone therapeutic options with metaregressors						
Drug	Placebo	Tamoxifen	Toremifene	Letrozole	Anastrozole	Exemestane
No Adjustment	34%	83%	97%	22%	8%	56%
Adjust for Age	24%	81%	99%	38%	0%	58%
Adjust for Baseline	27%	83%	97%	58%	2%	33%
Adjust for Tamoxifen use	11%	84%	96%	49%	10%	50%

LDL-C: Low Density Lipoprotein Cholesterol

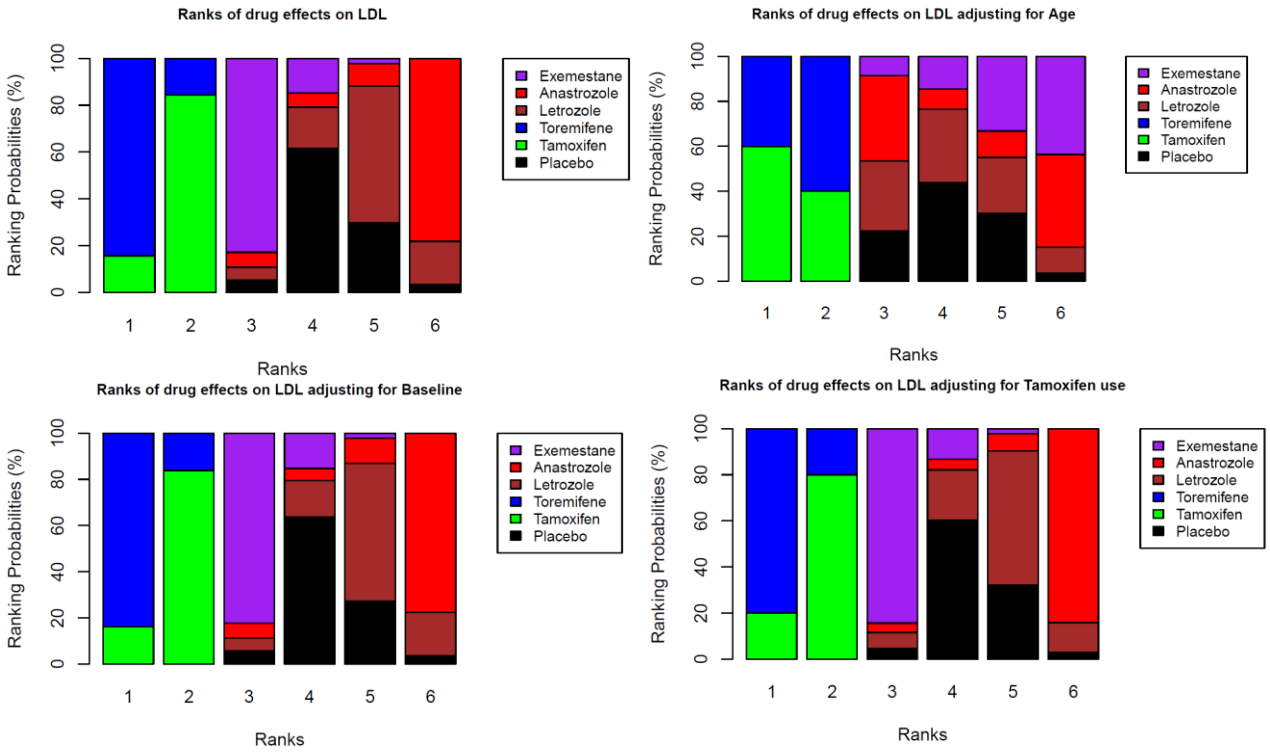


Figure S 7. Rankgrams of hormone therapeutic options for LDL-C based on presence of metaregressor

Table S 16. Estimates of changes of Triglyceride levels with the presence of metaregressor

Drug	No Adjustment	Adjust for Age ($\bar{x} = 60.91$)	Adjust for Baseline ($\bar{x} = 133.07$)	Adjust for Tamoxifen use
	Mean (95% Credible Interval)			
Metaregressor		-1.38 (-3.72 , 0.93)	**-0.58 (-0.78 , -0.38)**	-10.27 (-20.27 , 0.24)
Tamoxifen	**28.02 (21.51 , 34.51)**	**26.01 (18.64 , 33.36)**	**16.18 (8.03 , 24.16)**	**32.40 (24.56 , 40.02)**
Toremifene	**-28.12 (-43.08 , -13.46)**	**-28.52 (-43.40 , -13.42)**	**-32.55 (-48.22 , -17.12)**	**-23.50 (-38.85 , -8.97)**
Letrozole	**9.30 (1.50 , 17.11)**	**10.95 (2.81 , 19.36)**	**34.12 (22.36 , 45.84)**	**18.88 (6.52 , 31.32)**
Anastrozole	**-22.41 (-44.30 , -1.06)**	**-26.07 (-48.99 , -4.11)**	**-29.77 (-52.33 , -7.67)**	-17.25 (-39.57 , 4.32)
Exemestane	**-10.31 (-15.45 , -5.19)**	**-8.81 (-14.44 , -3.26)**	**-13.09 (-18.40 , -7.90)**	-3.51 (-11.82 , 4.73)

Placebo: $Y_{i1} = \mu_i$

Baseline and age are centered to their mean in the model.

Hormone drugs: $Y_{ik} = \mu_i + \theta_k + b(x_i - \bar{x})$

k: treatments, k=1 (placebo), k=2, …, 6 (hormone drugs)

Y_{ik}: trial-specific treatment-specific outcome

μ_i: trial-specific mean effect without treatment (placebo)

θ_k: drug effect relative to placebo

b: covariate coefficient

x_i: trial-specific covariate value

Bold: p<0.05

Table S 17. SUCRA reports of hormone therapeutic options for Triglyceride based on presence of metaregressors

SUCRA of hormone therapeutic options with metaregressors						
Drug	Placebo	Tamoxifen	Toremifene	Letrozole	Anastrozole	Exemestane
No Adjustment	40%	0%	95%	20%	82%	63%
Adjust for Age	40%	0%	92%	20%	86%	61%
Adjust for Baseline	40%	20%	92%	0%	86%	61%
Adjust for Tamoxifen use	45%	0%	95%	20%	81%	58%

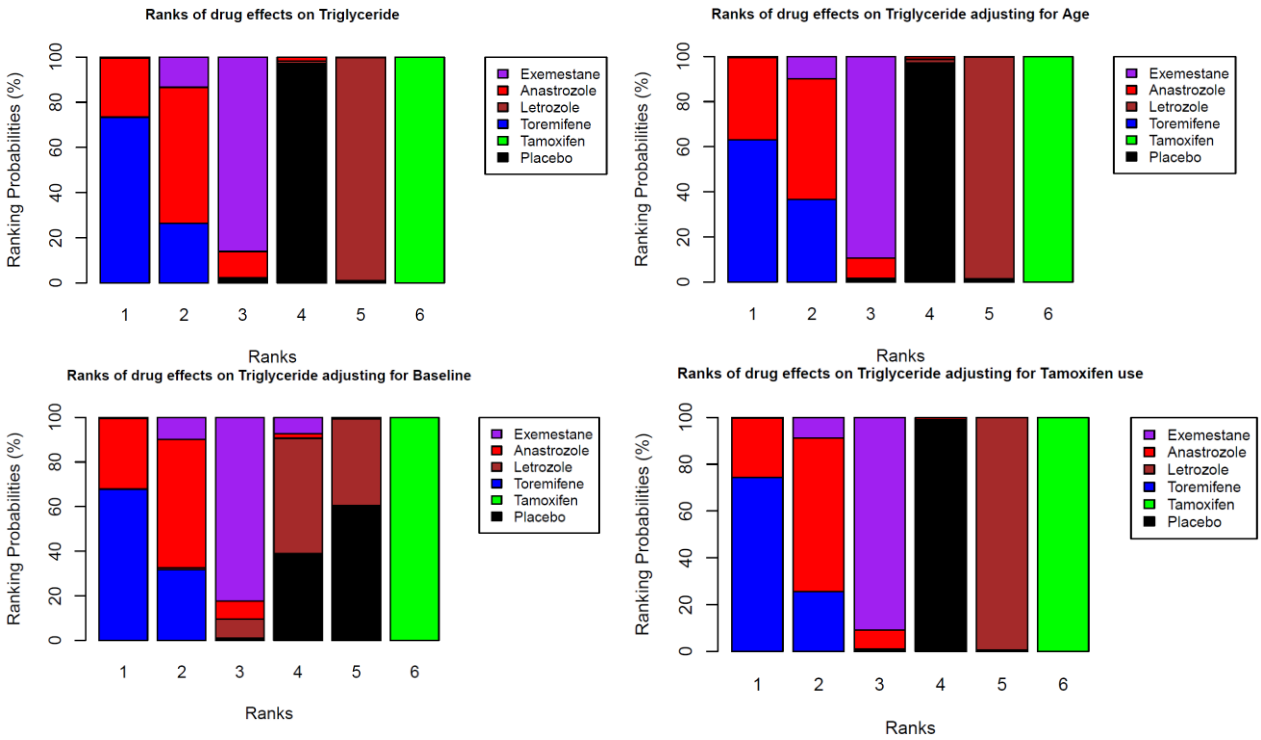


Figure S 8. Rankgrams of hormone therapeutic options for Triglyceride based on presence of metaregressor

Table S 18. Differences between direct and indirect estimates

	Mean (95% Credible Interval)
Placebo and Tamoxifen	
Total cholesterol	-7.13 (-52.77, 16.84)
HDL-C	7.22 (-51.54, 150.04)
LDL-C	-4.42 (-60.58, 45.45)
Triglyceride	2.99 (-91.31, 72.69)
Placebo and Letrozole	
Total cholesterol	3.76 (-138.54, 192.78)
HDL-C	-4.72 (-256.04, 152.88)
LDL-C	6.72 (-76.75, 178.10)
Triglyceride	-3.18 (-167.00, 184.36)
Placebo and Exemestane	
Total cholesterol	-10.61 (-92.37, 90.07)
HDL-C	-0.32 (-12.00, 11.00)
LDL-C	-16.54 (-144.18, 63.75)
Triglyceride	-21.77 (-101.60, 60.84)
Tamoxifen and Toremifene	
Total cholesterol	-36.18 (-70.28, -1.58)*
Total cholesterol (removing trials with large variation)	-24.80 (-58.84, 10.76)[¶]
HDL-C	13.82 (-3.41, 31.04)
LDL-C	-29.72 (-71.24, 11.27)
Triglyceride	14.93 (-57.82, 88.36)
Tamoxifen and Anastrozole	
Total cholesterol	-5.78 (-124.88, 173.56)
HDL-C	-6.83 (-156.38, 61.89)
LDL-C	-7.22 (-214.98, 162.04)
Triglyceride	83.65 (-121.94, 240.54)
Tamoxifen and Exemestane	
Total cholesterol	28.47 (3.61, 54.18)*
Total cholesterol (removing trials with large variation)	18.02 (-7.25, 45.18)[§]
HDL-C	-3.05 (-16.41, 10.94)
LDL-C	40.98 (6.44, 76.72)*
LDL-C (removing trials with large variation)	27.88 (-9.79, 63.96) [§]
Triglyceride	-62.14 (-122.84, -2.62)*
Triglyceride (removing trials with large variation)	-59.76 (-118.44, 0.69) [§]
Letrozole and Anastrozole	
Total cholesterol	11.60 (-175.60, 145.64)

Table S 18. (cont.)	
HDL-C	6.01 (-23.06, 33.04)
LDL-C	3.08 (-80.46, 60.97)
Triglyceride	-35.09 (-141.36, 170.22)
Letrozole and Exemestane	
Total cholesterol	-16.34 (-247.36, 127.30)
HDL-C	-1.59 (-78.51, 52.70)
LDL-C	-19.98 (-296.32, 255.70)
Triglyceride	-13.40 (-160.42, 162.92)

* The estimate difference between direct and indirect evidence is significantly away from zero
¶ Removing articles published by Francini et al. (2006)[198] and Montagnani et al. (2008)[199]
§ Removing articles published by Sawada et al (2005)[204] and Markopoulos et al. (2005 and 2009)[197,200]

Table S 19. Sensitivity analyses for total cholesterol

	Mean (95% Credible Interval)	**SUCRA**	**Rank**
Fixed-Effect model – the original model			
Placebo	3.81 (-3.27, 11.82)	34%	4
Tamoxifen	**-17.81 (-24.95, -10.06)**	81%	2
Toremifene	**-22.56 (-31.47, -13.92)**	99%	1
Letrozole	7.71 (-0.44, 15.51)	8%	6
Anastrozole	6.22 (-3.55, 16.42)	18%	5
Exemestane	-3.74 (-10.90, 3.89)	60%	3
Remove studies with median report			
Placebo	4.05 (-4.00, 11.94)	37%	4
Tamoxifen	**-20.43 (-28.43, -12.73)**	98%	1
Toremifene	**-17.44 (-25.94, -8.70)**	82%	2
Letrozole	6.70 (-1.43, 14.93)	13%	5
Anastrozole	7.91 (-1.76, 17.60)	10%	6
Exemestane	-6.24 (-13.90, 1.82)	60%	3
Random-effect model			
Placebo	5.86 (-3.67, 15.14)	26%	4
Tamoxifen	**-17.88 (-27.80, -8.28)**	81%	2
Toremifene	**-27.41 (-41.70, -14.02)**	98%	1
Letrozole	9.28 (-5.98, 25.28)	16%	6
Anastrozole	7.59 (-10.44, 25.33)	22%	5
Exemestane	-3.48 (-15.22, 6.71)	56%	3

Table S 20. Sensitivity analyses for HDL-C

	Mean (95% Credible Interval)	**SUCRA**	**Rank**
Fixed-effect model – the original model			
Placebo	**2.20 (0.46, 4.23)**	79%	2
Tamoxifen	-1.70 (-3.49, 0.17)	23%	5
Toremifene	**9.50 (7.19, 11.88)**	100%	1
Letrozole	0.31 (-1.77, 2.38)	53%	3
Anastrozole	-0.30 (-3.10, 2.64)	45%	4
Exemestane	**-4.37 (-6.12, -2.45)**	0%	6
Remove studies with median report			
Placebo	1.42 (-0.33, 3.22)	76%	2
Tamoxifen	-0.55 (-2.24, 1.25)	36%	4
Toremifene	**9.91 (1.57, 11.99)**	100%	1
Letrozole	-0.74 (-2.72, 1.19)	31%	5
Anastrozole	0.44 (-2.18, 3.05)	57%	3
Exemestane	**-5.81 (-7.53, -3.93)**	0%	6
Random-effect model			
Placebo	1.68 (-0.92, 4.04)	59%	3
Tamoxifen	-0.56 (-4.56, 3.64)	36%	5
Toremifene	**10.10 (4.35, 15.77)**	98%	1
Letrozole	-0.74 (-8.17, 7.03)	37%	4
Anastrozole	3.26 (-4.73, 11.78)	65%	2
Exemestane	**-5.41 (-10.09, -0.81)**	4%	6

HDL-C: high density lipoprotein cholesterol

Table S 21. Sensitivity analyses for LDL-C

	Mean (95% Credible Interval)	**SUCRA**	**Rank**
Fixed-effect model – the original model			
Placebo	3.81 (-5.62, 12.58)	34%	4
Tamoxifen	**-17.31 (-26.25, -8.13)**	83%	2
Toremifene	**-20.37 (-31.02, -10.69)**	97%	1
Letrozole	4.88 (-4.63, 14.25)	22%	5
Anastrozole	8.43 (-3.06, 19.08)	8%	6
Exemestane	2.29 (-7.13, 10.93)	56%	3
Remove studies with median report			
Placebo	4.37 (-5.08, 15.04)	26%	5
Tamoxifen	**-19.21 (-29.03, -8.99)**	98%	1
Toremifene	**-15.44 (-26.52, -4.99)**	82%	2
Letrozole	3.81 (-6.09, 14.34)	33%	4
Anastrozole	10.90 (-0.68, 22.16)	1%	6
Exemestane	-0.65 (-10.93, 9.24)	60%	3
Random-effect model			
Placebo	6.43 (-5.25, 18.05)	25%	5
Tamoxifen	**-17.57 (-29.84, -5.20)**	84%	2
Toremifene	**-23.51 (-39.88, -5.80)**	95%	1
Letrozole	7.05 (-13.37, 26.28)	25%	4
Anastrozole	5.10 (-17.61, 28.39)	30%	6
Exemestane	2.23 (-11.69, 15.94)	42%	3

LDL-C: low density lipoprotein cholesterol

Table S 22. Sensitivity analyses for Triglyceride

	Mean (95% Credible Interval)	**SUCRA**	**Rank**
Fixed-effect model – the original model			
Placebo	0.06 (-11.30, 11.86)	40%	4
Tamoxifen	**28.08 (16.81, 39.23)**	0%	6
Toremifene	**-28.06 (-42.95, -13.51)**	95%	1
Letrozole	9.36 (-4.00, 22.90)	20%	5
Anastrozole	**-22.34 (-43.98, -1.45)**	82%	2
Exemestane	-10.25 (-21.49, 1.32)	63%	3
Remove studies with median report			
Placebo	6.84 (-10.29, 23.13)	40%	4
Tamoxifen	**29.56 (13.22, 44.93)**	0%	6
Toremifene	**-39.05 (-58.58, -19.39)**	90%	1
Letrozole	17.06 (-0.44, 35.61)	20%	5
Anastrozole	**-38.71 (-64.51, -13.83)**	90%	2
Exemestane	-5.47 (-22.06, 11.47)	60%	3
Random-effect model			
Placebo	-0.34 (-11.88, 10.52)	42%	4
Tamoxifen	**23.42 (3.20, 45.43)**	6%	6
Toremifene	-12.28 (-41.28, 19.41)	66%	3
Letrozole	4.83 (-35.74, 45.70)	36%	5
Anastrozole	-22.87 (-68.29, 20.73)	79%	1
Exemestane	-13.74 (-38.92, 9.34)	71%	2

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