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REVIEW ARTICLE

Tibolone and Breast Cancer

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Tibolone, a selective tissue estrogenic activity regulator, is a synthetic steroid with distinct pharmacological and clinical characteristics in contrast to conventional menopausal hormone therapy. Tibolone induces estrogenic activity in the brain, vagina, and bone but remains inactive in the endometrium and breast. In particular, several studies have investigated whether tibolone usage increases the risk of breast cancer. This study aims to determine the effects of tibolone on the breast by focusing on the relation between tibolone use and breast cancer. Our investigation emphasizes recent studies, particularly those based on Asian populations.

Key Words: Breast density, Breast neoplasms, Postmenopausal hormone replacement therapy, Tibolone

INTRODUCTION

After the results of the Women's Health Initiative (WHI) study were published, many women discontinued menopausal hormone therapy (MHT) due to fear of breast cancer [1]. Although WHI study showed that estrogen-progesterone therapy (EPT) increased risk of breast cancer [1-6], the absolute risk of breast cancer associated with EPT is very low (< 10/10,000/y) [7]. In addition, the relative risk of breast cancer may be different depending on the formulation and dose of MHT [8].

Tibolone, a selective tissue estrogenic activity regulator, is one of the treatment options for menopause symptoms, but it has distinct pharmacological and clinical characteristics compared to EPT [9-14]. Tibolone is thought to reduce estrogen activity in breast tissue [15-18], which in fact causes less breast tenderness and does not increase mammographic density [19-24], a well-defined risk factor for breast cancer in clinical practice [25,26]. However, tibolone's effects on breasts are still unclear. This review describes the effects of tibolone on breast. We focused on the relationship between tibolone use and the risk of breast cancer with results from recent studies and Asian population-based studies.

TIBOLONE AND BREAST TISSUE

Tibolone is mainly converted to 3 alpha-hydroxy (3α-OH) tibolone and 3 beta-hydroxy (3β-OH) tibolone by 3α- and 3β-hydroxy dehydrogenase (HSD) in the liver and intestines, and directly converted to Δ4-isomer by 3β-HSD-isomerase [9,10,27,28]. Among these metabolites, 3α-OH and 3β-OH metabolites have estrogenic properties, and Δ4-isomer has progestogenic and androgenic properties [27,28]. The two hydroxylated metabolites exhibit different estrogenic activities depending on the tissue, which is the result of tissue-specific metabolism. Therefore, tibolone is classified as a selective tissue estrogenic activity regulator, showing estrogenic activity in the brain, vagina, and bone, but not in the endometrium and breast [29].

Figure 1 summarizes the effect of tibolone in the estrogen metabolism in the breast tissue. In breast tissue, tibolone and its metabolites suppress sulfatase and

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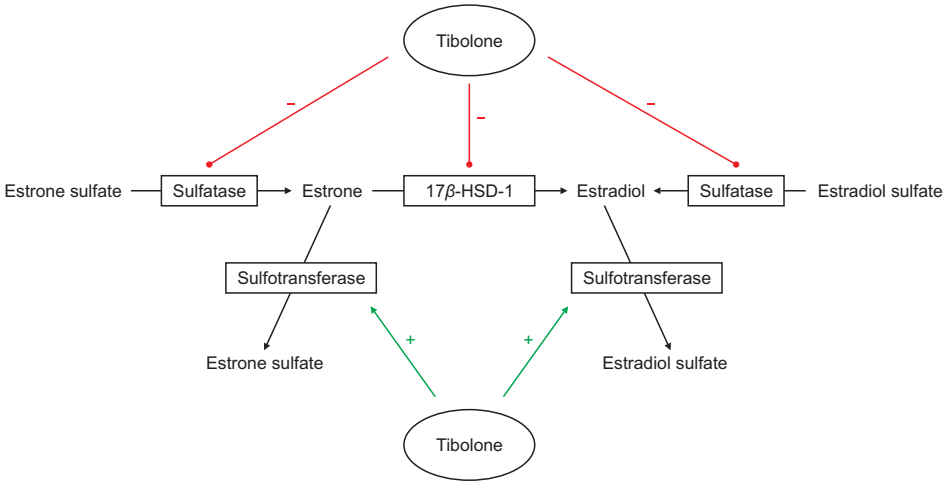

Fig. 1. Effect of tibolone in the estrogen metabolism in the breast tissue. HSD: hydroxysteroid dehydrogenase.

Table 1. Tibolone use and risk of breast cancer

Study	Description	Population of tibolone users in the study[a]	RR of breast cancer (95% CI)
Beral (2003) (Million Woman Study) [35]	Observational study	18,186 women aged 50 to 64	1.45 (1.25–1.67)
Cummings et al. (2008) (LIFT trial) [39]	Randomized controlled trial	4,538 women with osteoporosis aged 60 to 85	0.32 (0.13–0.80)
Opatrny et al. (2008) [38]	Case-control study (UK General Practice Research Database)	61 cases and 385 controls aged 50–75 years	0.86 (0.65–1.13)
Kenemans et al. (2009) (LIBERATE trial) [41]	Randomized controlled trial	3,098 women treated with surgery for breast cancer (1,556 in the tibolone group and 1,542 in the placebo group)	1.40 (1.14–1.70)
Cordina-Duverger et al. (2013) [42]	Case-control study	17 cases and 8 controls aged 35–74 years old	2.42 (0.96–6.10)
Román et al. (2016) [43]	Observational study (Norwegian Prescription Database, the Cancer Registry of Norway)	9,420 women aged 45 to 79 years with no previous history of cancer	1.91 (1.61–2.28)
Baek et al. (2022) [44]	Case-control study (Korean National Health Insurance Service database)	14,250 women who used tibolone for more than 1 year aged > 50 years	0.77 (0.66–0.90)

RR: relative risk, CI: confidence interval, UK: United Kingdom.
[a]Total study population are mentioned in the manuscript.

17β-HSD. These enzymes convert estrone sulfate, a form of inactive estrogen, into estradiol in the breast [30-32]. Additionally, 3-OH metabolite increase the activity of sulfotransferase, which converts estrone back to estrone sulfate [33]. Tibolone and Δ4 -isomer suppress proliferation and induce cell death in breast cells [34]. Through this action, it is known to reduce the concentration of active estrogen in breast tissue and suppress the development of breast cancer.

TIBOLONE AND MAMMOGRAPHIC DENSITY

In a prospective study comparing the effects of different MHT regimens on mammographic density in 210 postmenopausal women, mammographic density was not increased in women who used tibolone or estriol after 1 year [21]. Increases in mammographic density have been reported in women who received estradiol- or conjugated equine estrogens (CEE)-containing regimens, with or without medroxyprogesterone acetate, sequentially or continuously, with estradiol-containing regimens showing a greater tendency to increase than comparable CEE-containing regimens. Another prospective study compared pre- and post-treatment mammographic density in 121 postmenopausal women who received various types of MHT, including tibolone or transdermal estradiol, for 1 year [22]. No statistically significant difference was found in the increase in mammographic density between women who used tibolone and those who did not. Mammographic density increased in women using transdermal estradiol alone

or in combination with nomegestrol acetate, which was statistically significant when compared to untreated women.

One randomized controlled trial (RCT) compared the difference in mammographic density between women who used tibolone and women who used continuous EPT [23]. After one year of treatment, the mean breast density score decreased from 2.22 to 1.67 in the tibolone group and increased from 1.84 to 2.63 in the EPT group, with a statistically significant difference between the two groups. In addition, Ki-67 expression, a cellular marker for proliferation, decreased in 80% of women in the tibolone group, while Ki-67 expression increased in 78.9% of women in the EPT group, and the difference in expression between the two groups was statistically significant.

TIBOLONE AND BREAST CANCER

Table 1 summarizes studies that investigated the association between tibolone and the risk of breast cancer.

The Million Women Study (MWS) is an observational study that compared the incidence of breast cancer (BC) according to the type of MHT: estrogen therapy, EPT, and tibolone among 1,084,110 women aged 50 to 64 in the United Kingdom (UK) [35]. In this study, tibolone use was found in 18,186 women and increased the risk of breast cancer (relative risk [RR], 1.45; 95% confidence interval [CI], 1.25–1.67), but less than EPT (RR, 2.00; 95% CI, 1.88–2.12). However, the MWS has some important limitations [36,37]. Among the women who participated in the study, the incidence of breast cancer, as well as the proportion of women who received MHT, was higher than that of the general population. The average time from recruitment to diagnosis of breast cancer was 1.2 years, and the average time from diagnosis of breast cancer to death was only 1.7 years, meaning that a significant number of breast cancers had already existed for a considerable period of time before recruitment.

Another large case-control study based on the UK General Practice Research Database analyzed the RR of breast cancer according to various MHT formulations. In this study, 6,347 cases of breast cancer were matched with 31,516 controls in women aged 50–75 years [38]. In this study, there was an increase in breast cancer in women who used EPT (RR, 1.33; 95% CI, 1.21–1.46), but there was no significant increase in breast cancer in women who used tibolone (RR, 0.86; 95% CI, 0.65–1.13). However, the rate of breast cancer was increased in women who switched from EPT to tibolone (RR, 1.29; 95% CI, 1.09–1.52).

The the Long-Term Intervention on Fractures with Tibolone (LIFT) trial is a RCT that analyzed the effects of 1.25 mg of tibolone on the risk of vertebral fracture, cardiovascular disease, and breast cancer in 4,538 women with osteoporosis aged 60 to 85 [39]. Women who received tibolone had a 68% reduced risk of invasive breast cancer compared with women who received placebo (relative hazard, 0.32; 95% CI, 0.13–0.80). A Cochrane review that analyzed 4 RCTs related to the association between tibolone and breast cancer, including the LIFT trial, also found that tibolone did not increase the incidence of breast cancer in women without a history of breast cancer (odds ratio [OR], 0.52; 95% CI, 0.21–1.25) [40].

The The livial intervention following breast cancer: Efficacy, Recurrence, and Tolerability Endpoints (LIBERATE) trial was conducted to evaluate the risk of breast cancer recurrence when taking tibolone in breast cancer patients treated for vasomotor symptoms [41]. This trial was stopped early because breast cancer patients receiving tibolone 2.5 mg were found to have an increased risk of recurrence. Of the 1,556 women who took tibolone, 237 (15.2%) relapsed, and among the 1,542 women who did not receive treatment, 165 (10.7%) relapsed, showing a statistically significantly higher recurrence rate in women who took tibolone (HR, 1.40; 95% CI, 1.14–1.70). However, tibolone did not differ from placebo in terms of mortality (72 vs. 63, respectively).

Population-based case-control study in France analyzed the risk of breast cancer by type of MHT. 1,555 menopausal women (739 breast cancer cases and 816 controls) aged 35–74 years old were recruited for analysis. Current tibolone users were 8 women in the control group and 17 women in the breast cancer group. The study reported an elevated but non-significant increased risk of breast cancer (OR, 2.42; 95% CI, 0.96–6.10) and association with increased ER-positive (OR, 2.57; 95% CI, 0.97–0.83) and PR-positive tumors (OR, 2.80; 95% CI, 0.99–7.89), and with lobular carcinomas (OR, 5.87; 95% CI, 1.66–20.7). However, this study included only a limited number of patients who used tibolone, thus the results should be translated carefully [42].

Data from the Norwegian Prescription Database and the Cancer Registry of Norway also investigated postmenopausal hormone therapy and the risk of breast

cancer [43]. A total of 686,614 Norwegian women aged 45 to 79 years with no previous history of cancer were followed from 2004 to 2008 with 9,420 women prescribed with tibolone. The average duration of follow-up was 4.8 years and tibolone use was associated with a nearly twofold higher breast cancer risk than in nonusers (OR, 1.91; 95% CI, 1.61–2.28). However, the authors mentioned possible influence from previous EPT use on before 2004 in these patients for the cause of increased risk of breast cancer.

Recently, a nested case-control study in Korea among 36,446 women who used MHT for more than 1 year and 36,446 women who did not use MHT for more than 1 year was perform. Of these women, 14,250 women were prescribed with tibolone and this study reported that tibolone use was associated with a reduced risk of BC (HR, 0.77; 95% CI, 0.66–0.90) [44]. In particular, the risk of BC was lower with tibolone in women treated early stage in menopause.

CONCLUSION

The relationship between tibolone and BC risk is not yet conclusive. However, considering the results obtained from various studies, the risk of BC with tibolone does not seem to be as high as with EPT. The safety of tibolone with respect to BC risk requires further investigation, particularly through well-designed RCTs targeting breast cancer risk as a primary end point. Meanwhile, tibolone is not recommended for BC patients because it increases the recurrence rate of BC.

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CONFLICT OF INTEREST

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

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