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EDITORIAL

Hormone Replacement Therapy and Breast Cancer: The Situation in Korea

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The balance between the risks versus benefits associated with hormone replacement therapy (HRT) is controversial. Although there is a debate on the potential harm associated with breast cancer, it is commonly known that the relative benefits and safety of HRT changes as the duration of use increases. In other words, breast cancer is a primary concern among women on long-term or current HRT.*(1-3)* Many risks of developing breast cancer have hormonal components and a relationship to estrogen in particular. In fact, epidemiological data suggest a dose-response relationship between the serum levels of endogenous sex hormones and the risk of breast cancer.*(4-6)* Some types of breast cancer therapies, such as oophorectomy, natural menopause, and the use of estrogen, strengthen the causal links between estrogen and breast cancer.*(7-10)* In addition, it is well known that an increase in caloric uptake and energy expenditure leads to a stimulation of adrenal androgen secretion, a decrease in sex hormone binding globulin (SHBG), and an elevated aromatization of androgens in the excessive fat tissue. A significant correlation between the serum levels of total and free estradiol and the risk of breast cancer in postmenopausal women has been reported.*(11-13)*

The exact mechanism for the association between estrogen or progesterone and breast cancer has not been fully elucidated. The main theory argues that when estrogen binds estrogen receptors, it stimulates cellular proliferation, and allowing for errors in DNA replication in each cell cycle. If the errors are not repaired, these mutations lead to transformation that results in breast cancer.*(14, 15)* Another theory states that the increased risks of breast cancer are more likely to be the result of accelerated growth with attendant earlier detection than that of primary tumor initiation.*(9,16-20)* This theory suggests that the metabolites of oral estrogen react with breast tissue DNA to have an oncological effect.*(21)* It is very possible that more than one of these mechanisms are involved in breast cancer development.*(22)*

Many questions have been raised regarding the role of progesterone in breast cancer development. When combined estrogen-progesterone therapy (EPT) is used, the risk of breast cancer is consistently higher than that of therapy with estrogen alone (ET) (Figure 1).*(16, 17)* Regarding EPT, many studies have examined the type of progestin, method of administration, and whether the progestin is testosterone-derived, or not. Campagnoli et al.*(23)* suggest that the relative risks of continuous progestin are generally two to three times higher than that of cyclic progestin regimens. Continuous progestin inhibits the sloughing of mammary epithelium. This leads to amenorrhea, which in fact may increase medication adherence of patients, ultimately leading to a higher effective exposure to the drug.*(24)* Different derivatives of progesterone also seem to confer different risks. Some authors point to the non-progesterone properties of

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synthetic progestins that may potentiate breast tissue proliferation, decrease insulin sensitivity and increase insulin-like growth factor activity.*(23,25)* Testosterone-derived progestins have greater androgenic and estrogenic activities and, thereby, may confer an increased risk of breast cancer.*(26,27)* Maximum mitotic activity in breast tissue occurs in the mid to late luteal phase, when progesterone is at its highest level.*(28)*

According to the United Kingdom Public Assessment Report, the risk of breast cancer increases with increasing duration of the use (Figure 2). The HRT-associated increase in breast cancer risk drops rapidly after ceasing use of HRT.*(9,17)* The risk of death from breast cancer is elevated in women who are currently using HRT.*(17, 29)* Use of HRT by women with a previous diagnosis of breast cancer increases the risk of recurrence.*(30)* Screening mammography is less effective in women currently using HRT, with an increased number of false positives and a greater chance that breast cancers will be missed at screening.*(18,22)* The only factor found to significantly modify the effect of HRT is body size; HRT results in a larger increase in the risk of breast cancer in women who have a lower compared with a higher body mass index (BMI); specifically, thinner women on HRT have a higher

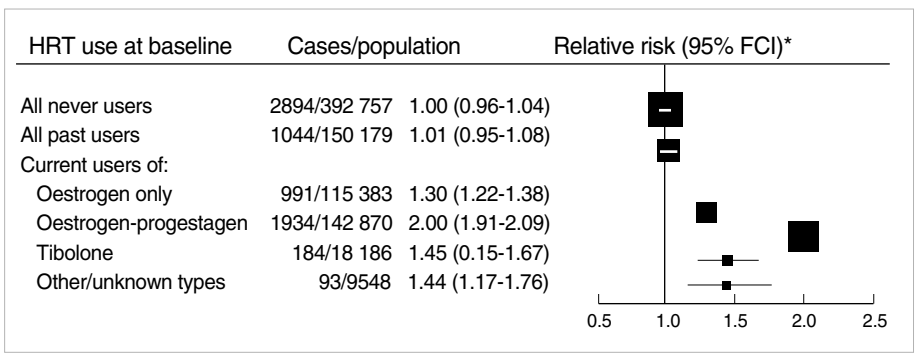

Figure 1. Relative risk of incident invasive breast cancer in relation to recency and type of HRT used. FCI=floated CI.
Relative to never users of HRT, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region, and deprivation index (From Beral V, et al. Lancet 2003;362:419-27, with permission from Elsevier).(17)*

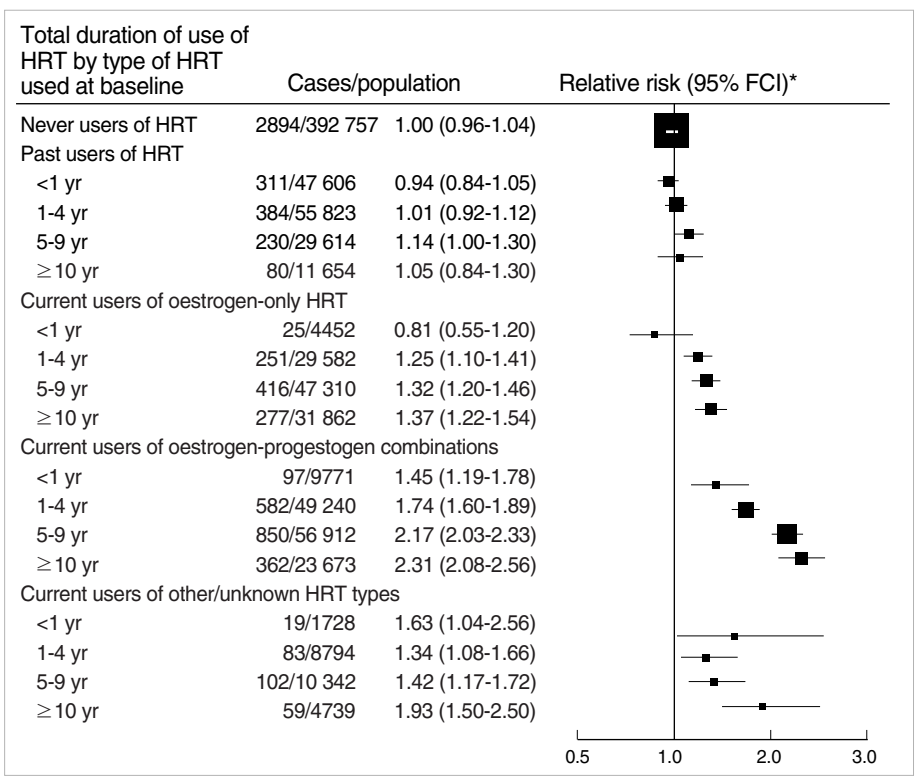

Figure 2. Relative risk of invasive breast cancer in relation to recency, total duration of use, and type of HRT used at baseline.
FCI=floated CI.
Relative to never users of HRT, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region, and deprivation index (From Beral V, et al. Lancet 2003;362: 419-27, with permission from Elsevier).(17)*

risk of breast cancer compared to women with a higher BMI who also take HRT. Consistent with this is the finding that the effect of HRT on breast cancer is greater in Europe than in North America, where average BMI levels are higher.*(31)*

HRT is highly effective in the treatment of menopausal symptoms such as hot flushes, night sweats,*(32)* and vaginal dryness. Though it may seem difficult, women must balance the severity of these symptoms against the risk of serious disease attributable to the use of HRT. The effect of HRT on other non-life-threatening conditions, such as an increased risk of incontinence, gallbladder disease and reduced peripheral fractures, should also be considered.*(33-35)*

The Korean Society of Menopause 2007 referred to Women's Health Initiative (WHI) 2002. Women reporting prior postmenopausal hormone use had higher hazard ratio (HR) for breast cancer associated with EPT than those who never used postmenopausal hormones (among never users, 114 vs. 102; HR, 1.06; 95% CI, 0.81-1.38; for women with 5 yr of prior use, 32 vs. 15; HR, 2.13; 95% CI, 1.15-3.94; for women with 5-10 yr of prior use, 11 vs. 2; HR, 4.61; 95% CI, 1.01-21.02; and for women with 10 yr of prior use, 9 vs. 5; HR, 1.81; 95% CI, 0.60-5.43; test for trend, z=2.17).*(16)* And the 26% excess of breast cancer is consistent with estimates from pooled epidemiological data, which reported a 15% increase in the risk of breast cancer for women using EPT for less than 5 yr and a 53% increase in the breast cancer risk for those using EPT more than 5 yr.*(9)* However, the incidence and developing aspect of breast cancer in Korea were different from the United States. According to the Korean Breast Cancer Society Breast Cancer Facts and Figures 2006-2008, the risk of breast cancer increased 24% per year for women using oral contraceptives and 2.3% per year for women using HRT, especially those on EPT. In comparing 1996 to 2006, it was reported that the rate of early menarche (menarche before 13 yr of age) increased from 8.0% to 15.1%; in other words, the number of patients with breast cancer risk factors increased. In addition, most breast cancer patients in Korea are in their 40s and premenopausal, but the number of breast cancer patients in the West are postmenopausal, and their ages range from 60-70. Also, the breast cancer incidence among premenopausal women has reached approximately 60% in Korea.*(36)* Consequently, The Korean Society of Menopause and Korean Breast Cancer Society have different views on HRT and breast cancer than their Western counterparts. When considering the use of HRT for postmenopausal symptoms, we would have more thorough breast examinations, including imaging studies, before starting HRT, because it is more common to find premenopausal women with breast cancer in Korea than in the Western countries.

The degree of association between breast cancer and postmenopausal HRT remains controversial. Women should be reassured that the possible risk of breast cancer associated with HRT is small, less than 0.1% per year.

The U.S. Food and Drug Administration (FDA), the U.K. Medicines and Healthcare Products Regulatory Agency, and the Australian Therapeutic Goods Administration are in agreement that HRT should only be prescribed for the short-term treatment of menopausal symptoms. Women considering the use of HRT must be informed of its risks and benefits, and HRT should not be used for the prevention of disease or as first-line treatment for osteoporosis. HRT should be used for as short a period of time as possible and, if continuous use is necessary, a breast examination should be performed every 6 months or annually.*(37)* We suggest that HRT be used for less than 5 yr. In addition, it is necessary to monitor patients having HRT every 6 months for breast cancer; these patients should have complete breast examinations with imaging before starting HRT. Patients should also be given full information, including debates, on the topic.

HRT can improve the quality of women's life, but the risk of breast cancer should be carefully considered before its initiation. We need a nationwide randomized controlled trial or well-designed observational study of HRT and breast cancer in Korea.

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