Postmenopausal Hormone Therapy and Risk of Breast Cancer

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Risks from hormone use among postmenopausal women will be particularly important in the future, given the worldwide increase in the number of older women in the population. Recent randomized clinical trials and epidemiological studies have reported various opinions on the association between the risk of breast cancer and postmenopausal hormone therapy (HT), especially the differences between therapy with unopposed estrogen and combined estrogen-progestin. The currently available data do not provide sufficient evidence to prove a causal association between postmenopausal HT and breast cancer. However, a possible risk of breast cancer associated with long-term HT usage should not be ignored, given that the degree of association between breast cancer and postmenopausal HT remains controversial. Unanswered questions include whether HT has a positive impact on breast cancer, and whether different types and routes of estrogen and progestogens, as well as the duration and cessation of HT use have different impacts on this disorder. Despite this, HT is still the most effective method of relieving climacteric symptoms for many postmenopausal women. Since the effect of HT on breast cancer risk may be related to individual susceptibility, we recommend close follow-up through mammography and/or breast sonography and an even more detailed evaluation of the potential of exogenous hormones inducing epithelial hyperplasia in those with increased breast density or any other high risk factors. *(Chang Gung Med J 2009;32:140-7)*

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Breast cancer is one of the most common cancers among women. The incidence of breast cancer is related to the interaction of several risk factors such as genetic susceptibility, environment, nutrition and other lifestyle risk factors. Since the results of the Women's Health Initiative (WHI)[1,2] and the Million Women Study (MWS)[3] were reported, discussions on whether there is an association between postmenopausal hormone therapy (HT) and breast cancer have produced marked fluctuations in opinion and concerns among women, physicians, and the media.

An association between breast cancer and hormone use is plausible, since the incidence of breast cancer is increased by hormone factors stimulating breast epithelial growth, such as early menarche and delayed menopause. In the WHI trial of combined estrogen-progestin,[1] an increased risk of breast cancer was not significant until after 5 years of HT use.

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Breast cancers usually take more than 5 years to develop from early carcinogenesis to the clinical stage. However, since many other studies have reported an association of HT with breast cancer risk, concerns about a causal association between HT and breast cancer remain. The WHI trial of unopposed estrogen use[2] supported the conclusion that estrogen use does not raise the risk of breast cancer. In contrast, the unadjusted hazard ratio (HR) of 1.26 for combined estrogen-progestin in breast cancer in the WHI trial was significant.[1] However, when adjusted for risk factors of breast cancer, the 95% confidence interval (CI) showed it was insignificant (0.83-1.92). Recent published studies indicate that estrogen can be safely given to women with a history of breast cancer.[4] Therefore, whether exposure to estrogen-progestin truly confers a greater risk of breast cancer remains unsettled.

The WHI trial[1] reported a significant z score for the trend over the duration of estrogen-progestin use. However, analysis of the HRs for each follow-up year showed the risk of use duration is due mainly to HRs of less than 1 in years 1 and 2. If it is concluded that risk increases with time, then it must also be concluded that risk is reduced during the first two years of use. A collaborative re-analysis of 51 observational studies[5] demonstrated that there was no significant elevation in risk with an increasing duration of HT up to 14 years. Thus, there is still little consistency in assessing the risk of the duration of HT.

The collaborative analysis[5] indicated that breast tumors diagnosed in past and present users of HT were significantly less likely to have spread beyond the breast or to the axillary lymph nodes than tumors diagnosed among women who had never used HT. In contrast, the WHI results in the estrogen-progestin arm[1] indicated an earlier appearance of more advanced breast cancer in the HT group than in the placebo group. These results are inconsistent with those previously reported in case-control and cohort studies. It is still obscure whether combined HT confers a greater risk of breast cancer or causes greater differentiation and earlier detection of breast cancer, resulting in better outcomes. Climacteric syndrome affects more than 50% of women, and HT is still the most effective therapy.[6] The duration of treatment is crucial for attaining benefits from long-term HT use, such as prevention of osteoporosis, a decreased risk of fracture, and a reduced incidence of colon cancer. Therefore, this review will further discuss the association of postmenopausal HT and the risk of breast cancer from the aforementioned discrepancy, a casual association, the impact of different HT, the duration of HT, and prognosis of breast cancer. It is vital to reveal what is ideally required for HT use in postmenopausal women.

Is there a causal association between postmenopausal hormone therapy and breast cancer?

The exact cause of breast cancer is not known. Early menarche and late menopause are associated with an increased risk, and early menopause with a reduced risk of breast cancer. Furthermore, a number of studies have also reported a risk of postmenopausal breast cancer in relation to hormone levels, as indexed by high blood concentrations of endogenous estrogens.[7-9] A reduced risk of breast cancer has been reported in postmenopausal women with a history of osteoporotic fracture,[10,11] while one study found that, as bone mineral density increased, the risk of breast cancer also increased.[12] These observations are obviously consistent with the notion of prolonged exposure to endogenous estrogen as an adverse risk factor.

Whether exogenous estrogen administration is associated with an increased breast cancer risk needs to be considered. The WHI demonstrated that an average 6.8 years of treatment with conjugated equine estrogen did not increase the risk of invasive breast cancer in 5310 hysterectomized women, compared with 5429 women assigned a placebo.[2] A review of 45 studies of unopposed estrogen use showed this therapy did not raise the risk of breast cancer. It was also noted that the low circulating levels of estrogens in postmenopausal women have little bearing on the concentrations of estrogen in a breast tumor, which can reach levels at least one order of magnitude greater than those present in the circulation. Thus, the estrogen which is responsible for breast cancer development is not circulating estrogen but rather that produced locally at specific sites within the breast.[14] Therefore, there is a lack of sufficient evidence to prove that exogenous estrogen initiates the development of breast cancer. It has been speculated that this discrepancy between endogenous and exogenous estrogen may be related to the difference in their effects.

As in the WHI trial,[1] recent studies suggest that the relative risk of breast cancer is higher in post-

menopausal women using combined estrogen-progestin HT, and an increased risk has been detected within a few years. The mean of 5.2 years of follow-up in the WHI trial[1] was too short. Since a tumor generally doubles in size every 100 days, it takes 7 to 8 years for a single malignant cell to grow large enough to be detectable by mammography or become a clinically detectable mass.[15] The discovery of an increased risk within a few years of beginning treatment suggests that these studies are detecting preexisting tumors.

The collaborative analysis[5] indicated that stopping HT for 5 or more years resulted in no significant excess breast cancer overall (relative risk 1.07 [95% CI 0.97-1.81]), even among women who had used HT for 5 years or longer (relative risk 0.92 {0.72-1.12}). After the publication of the WHI trial,[1,2] US national data revealed a 7% decrease in the breast cancer incidence in 2003, with the greatest decrease in women 50-69 years old and mostly in estrogen receptor positive (ER+) tumors.[16] There was also a 10% decrease in the Northern California Kaiser program in the years 2003 and 2004.[17] It is possible that the decrease in breast cancer may be related to a decline in the prevalence of screening mammography for many women discontinuing HT. However, it may reflect existing cancers just below the detection limit in 2002 that slowed or stopped growing after cessation of HT.

The aforementioned data do not reflect a causal association between postmenopausal HT and breast cancer, but do raise concerns about hormonal effects on preexisting tumors. However, the impact of combined estrogen-progestin HT on preexisting breast tumors remains controversial. An increase in breast density was detected by mammography in about 15 to 20% of women who took HT in our study[18] and in other reports.[19-22] Also, only a small proportion of the population exposed to HT develops breast cancer. This seems to support the idea that exogenous hormones preserve the existing parenchyma in a majority of postmenopausal women. The effect of HT on breast cancer risk should be related to individual susceptibility. Nevertheless, the degree of association between breast cancer and HT remains controversial.

Unopposed estrogen therapy and risk of breast cancer

Recent randomized clinical trials, as well as most epidemiological studies, suggest that unopposed estrogen use does not increase the risk of breast cancer[2,5,23-32] (Fig. 1). In the WHI trial,[2] the hazard ratio for breast cancer among women randomized to unopposed estrogen was 0.77 (95% confidence interval 0.59-1.01) compared with a placebo after an average follow-up of 6.8 years. Other randomized clinical trials[24,25] also demonstrated a reduction of the risk of breast cancer with unopposed estrogen use.

As shown in Figure 1, epidemiological studies of the association between estrogen and breast cancer have had inconsistent results. Most of the estimates of risk converge around 1.0, and the range of the estimates is limited. In 45 studies of unopposed estrogen use, 20% reported risk estimates less than 0.9, 33% reported risk estimates greater than 1.1, and 47% reported risk estimates between 0.9 and 1.1.[13] The data did not support the conclusion that estrogen use raises the risk of breast cancer.

Although both randomized clinical trials and epidemiologic studies do not seem to show an increased breast cancer risk, the effect related to the duration of using estrogen remains a consideration in some studies. The Nurses' Health Study reported that the multivariated risks (RRs) for breast cancer with current use of unopposed estrogen for less than 5 years, 5 to 9.9 years, 10 to 14.9 years, 15 to 19.9 years, and 20 years or longer were, respectively, 0.96 (95% CI, 0.75-1.22), 0.90 (95% CI, 0.73-1.12), 1.06 (95% CI, 0.87-1.30), 1.18 (95% CI, 0.95-1.48), and 1.42 (95% CI, 1.13-1.77) (p for trend < .001).[33] The collaborative study[5] reported a modest increase in the risk of breast cancer associated with any use of unopposed estrogen (relative risk [RR] 1.14; p <

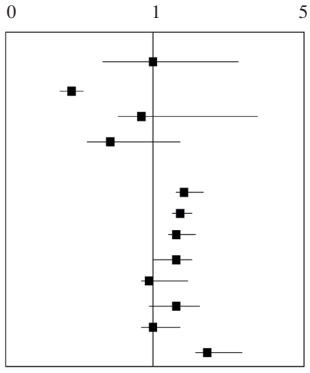

Fig. 1 Risk estimates for breast cancer incidence with unopposed estrogen hormone therapy from randomized clinical trials (RCT) and epidemiological studies.

.001), with evidence of an increasing RR with increasing duration of use. The risk of breast cancer was increased among current users (RR, 1.21; 2 p = .00002), but not among past users (RR, 1.07; p = .10).

All these studies show that whether the risk is increased or decreased, the magnitude of the effect of unopposed estrogen on breast cancer is small. However, the effects of long-term use of unopposed estrogen (15 years or more) should not be discounted.

Combined estrogen-progestin therapy (EPT) and risk of breast cancer

Two combined EPT clinical trials[1,36] and most recent epidemiologic studies[5,26-32,37,38] indicate that EPT appears to be associated with an increased risk of breast cancer (Fig. 2). The WHI clinical trial of conjugated equine estrogen combined with medroxyprogesterone acetate in postmenopausal women with a uterus showed that during 5.6 years of follow-up, there were 199 and 150 new invasive breast cancer cases in the EPT and placebo groups, respectively (relative hazard (RH) 1.24, 95% CI, 1.01-1.54, p = 0.003).[1] The Heart and Estrogen/ Progestin Replacement Study (HERS) involving 2763 women with proven coronary artery disease demonstrated a non-significant increase in the likelihood of breast cancer for EPT users (RH 1.27, 95% CI, 0.84-1.94) during 6.8 years of follow-up.[36] In contrast, Nachtigall et al.'s continuous 22-year study of EPT did not show an increase in the incidence of breast cancer in 86 pairs of postmenopausal women (0% in EPT vs 11.5% in placebo groups).[34] In the aforementioned four randomized clinical trials (RCTs), 248 EPT patients developed breast cancer, but the number was too insignificant to provide a precise estimate of the risk.

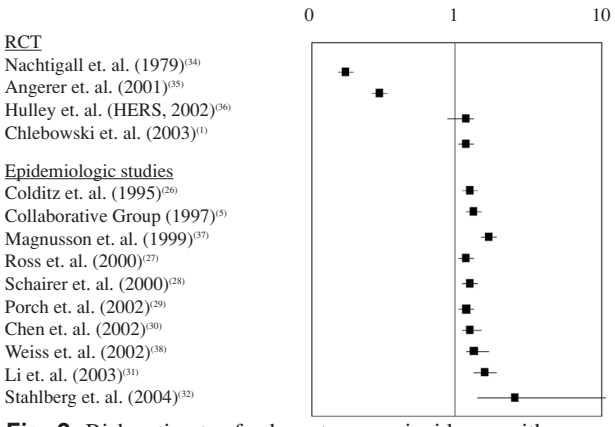

Fig. 2 Risk estimates for breast cancer incidence with combined estrogen- progestin hormone therapy from randomized clinical trials (RCT) and epidemiological studies.

As shown in Figure 2, most epidemiological studies demonstrated a higher risk of breast cancer associated with EPT. In contrast, in an assessment of studies from 1975 to 2000 by Bush et al., only 4 of 20 observational studies reported statistically significant findings: 2 showed a significantly higher risk of breast cancer with EPT use, and the other 2 found a significant protective effect of EPT on breast cancer risk.[13] In the collaborative study, the RRs with current or recent EPT use were 1.15 (95% CI, 0.78-1.52) and 1.53 (95% CI, 0.88-2.18) for less than 5 years and 5 or more years of therapy, respectively.[5] Inconsistent results are apparent in studies of the effect of EPT on breast cancer risk.

The differences between unopposed estrogen and EPT lead to questions about whether various hormone regimens induce different effects on breast tumors. A French cohort study reported that micronized progesterone or didrogesterone used with oral or percutaneous estradiol showed no increase or decrease in the risk of breast cancer when compared to synthetic progestins after at least 4 years of treatment.[39] A recent re-evaluation of that study demonstrated no apparent increase in breast cancer risk even after 8 years using the same regimen.[40] The French cohort study[39,40] found no evidence of an association with risk according to the route of estrogen administration (oral or transdermal), but the choice of the progestogen component in EPT resulted in different effects. However, further evaluation is needed in this study to determine whether progesterone and synthetic progestin have different effects on the breast, or whether the more potent synthetic progestin has a greater impact on the breast leading to earlier detection.

Whether exposure to EPT confers a greater risk of breast cancer is still obscure. Although reports have shown inconsistent results, the possibility of a small increase in breast cancer risk with EPT use or an increased risk with a long duration of use cannot be ignored.

Prognosis of breast cancer in postmenopausal women using hormone therapy

Most studies that have evaluated mortality rates

in breast cancer associated with HT,[41-51] as well as the collaborative re-analysis,[5] have generally documented improved survival rates for women using HT compared with those who have never used it. It is possible that women using HT are more likely to be screened for breast cancer than non-users; therefore, they are more likely to have their breast tumors diagnosed at an earlier and more curable stage. In addition, HT users have breast cancers of a lower grade and lower stage disease, resulting in better outcomes. Some studies report that breast cancer in HT users is more likely to be ER+, grade 1, well differentiated, low S-phase, and node-negative than that in non-users.[52-54] Therefore, HT may have a selective growth-promoting effect on breast tumors that is connected to some unknown biological cell characteristics that they possess.

In contrast, the WHI[1] estrogen-progestin report on breast cancer found an earlier appearance of worse tumors than previously reported in case-control and cohort studies. The WHI investigators suggested that estrogen plus progestin stimulates breast cancer growth and hinders mammographic identification of breast cancer. They further considered that this discrepancy could be related to differential mammography use in women receiving HT in observational studies. However, in addition to the small impact of hormone use on mammography specificity noted in a prospective cohort study,[55] some studies examining breast cancer characteristics and outcome in HT users and non-users who have used mammography equally still identified a lower grade and lower stage disease with a better outcome in HT users.[48,50,56,57] The major difference between the WHI[1] and observational studies[5,41-51] is that the participants in the former represent an older postmenopausal population (average age of 63 y/o and an average of 14-15 years since menopause). Therefore, it is possible that this older population might have occult tumors that are larger and more prone to respond to hormonal stimulation than tumors in younger women.

The Nurse's Health Study followed 91523 women for 17 years and found a 37% decrease in the risk of death for current HT users compared with those who had never used HT.[33] However, the risk of breast cancer mortality was elevated after 10 years of taking hormones (relative risk, 1.43; 95% confidence interval, 0.82 to 2.48), even though the overall mortality was still 20% lower than in those who did not use HT. Thus, a time-dependent mechanism for the influence of HT on breast cancer should be considered.

Conclusions

There is sufficient evidence that postmenopausal HT may act as a promoter of pre-existing breast cancer cells rather than initiating the growth of premalignant tumor cells or transforming them to cancer cells. If HT is affecting preexisting tumors, further evaluation is needed to determine whether the effect confers a greater risk or a beneficial result. In addition, there are serious questions regarding the duration and choice of HT preparations, different estrogen and progestogen combinations and doses, and, more importantly, the age, physical conditions, and especially existing risk factors in women exposed to these agents. We need to further evaluate the specific action and how these different factors interact. More studies should be conducted to address issues related to HT and breast cancer risk. HT should be individualized after evaluating the condition of postmenopausal patients. It is still the most effective management for relief of climacteric symptoms in many postmenopausal women. Ideally, we recommend close follow-up of patients through mammography and/or breast sonography, and detailed studies of the potential of exogenous hormones to induce epithelial hyperplasia in those with increased breast density.

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停經後荷爾蒙治療與乳癌之危險性

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由於全世界年老婦女人口之增加，在未來停經後婦女使用荷爾蒙之危險性將特別地重要。近年來隨機對照試驗和流行病學研究對乳癌之危險性與停經後荷爾蒙治療間之關聯性有不同之意見，尤其是在對單獨雌激素治療和合併雌激素與黃體素治療兩者間之差異上。從現有可用之資訊，並沒有足夠的證據去証實停經後荷爾蒙治療與乳癌有因果關係。然而，縱然乳癌之危險性與停經後荷爾蒙治療間之關聯性程度仍然存在爭議，但長期使用荷爾蒙治療與乳癌之可能危險性仍不應該被漠視。對乳癌仍然存在許多未解之問題，例如：荷爾蒙治療對乳癌是否有正面之衝擊、使用不同種類和途徑之雌激素與黃體素以及使用荷爾蒙治療之時間和停止使用是否可能產生不同之情況。除此之外，荷爾蒙治療對許多停經後婦女仍是最有效的緩解更年期症候群之方法。既然荷爾蒙治療對乳癌之危險性可能與個體易感性有關，建議藉由乳房 X 光造影檢查和／或乳房超音波做密切追蹤，以及對那些乳房密度增加或具高危險因子有上皮增生者，甚至更仔細評估外來荷爾蒙之潛在影響。(長庚醫誌 2009;32:140-7)

關鍵詞：乳癌，停經後荷爾蒙治療，單獨雌激素治療，合併雌激素與黃體素治療

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