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Progestogen in menopausal hormone therapy and breast cancer risk

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Menopausal hormone therapy (MHT) is widely used to treat menopausal symptoms, but concerns about breast cancer risk remain a major barrier, particularly following the Women's Health Initiative (WHI) study involving conjugated equine estrogen (CEE)/medroxyprogesterone acetate (MPA) [1]. Consequently, in South Korea, there has been a notable decline in the prescription frequency of CEE+MPA, owing to its association with breast cancer [2]. However, compared to CEE+MPA, estradiol hemihydrate (EH)/drospirenone (DRSP), EH/norethisterone acetate (NETA), EH/dydrogesterone (DYD), and estradiol valerate (EV)/cyproterone acetate (CPA) have been prescribed more frequently in South Korea [2]. This might be due to the lack of large-scale studies pertaining to the risk of breast cancer associated with these agents.

However, numerous studies have demonstrated that the risk of breast cancer associated with MHT is primarily influenced by progestogens rather than by estrogen. The findings from the WHI study revealed that women with a hysterectomy who used only CEE did not exhibit an increased risk of breast cancer, as opposed to those who were prescribed CEE in combination with MPA [1]. Furthermore, the E3N study showed that the type of progestin used in MHT can affect the breast cancer risk [3]. Micronized progesterone (MP) and DYD were not associated with increased breast cancer risk, whereas other progestogens were [3]. The Health Insurance Database in South Korea-1 (HISK-1) study found that estrogen-progestogen therapy (EPT) provided as a single-pill (e.g., EH/DRSP, EH/NETA, and EH/DYD) delivery system by pharmaceutical companies, was associated with increased breast cancer risk [4]. However, no increased risk was observed for estrogen only, transdermal estrogen, tibolone, or EPT provided as a double-pill (e.g., EH+MP) by a physician.

Therefore, it is necessary to study the risk of breast cancer associated with the various EPTs prescribed in South Korea. In a recent study (HISK-2) conducted in Korea which used Health Insurance Review and Assessment Service data, EH/DRSP (hazard ratio [HR], 1.511; 95% confidence interval [CI], 1.38-1.655), EH/NETA (HR, 1.664; 95% CI, 1.343-2.063), EH/DYD (HR, 1.367; 95% CI, 1.115-1.676), and EV/CPA (HR, 1. 741; 95% CI, 1.544-1.964] were associated with a higher risk of breast cancer [2]. EV/MPA and EV/NETA also had increased HRs, although these were not statistically significant owing to the small number of prescriptions. However, MP was not associated with breast cancer risk.

The overall dose or potency of progesterone may be more important than its components in terms of influencing the risk factors of breast cancer, for several reasons: first, when physicians can adjust the progesterone dosage, such as with MP (100 or 200 mg) the risk of breast cancer did not increase significantly [4]. Second, EH/DYD, although associated with an increased risk of breast cancer, tended to be at a lower risk than other progestogens. EH/DYD was associated with a mix of doses (DYD 5 mg or 10 mg) and methods of use (continuous or sequential method), resulting in a lower total amount of progestogen prescribed per month. Therefore, further research is warranted regarding the relation between

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breast cancer risk and EPT formulations containing low doses of progestogens.

In conclusion, when prescribing single-pill EPT, clinicians should thoroughly inform patients about the potentially increased risk of breast cancer by employing an approach similar to that used for CEE+MPA in the past. However, the absolute increase in risk is relatively low (approximately 1 breast cancer case per 1,000 woman-year) [2,4]. This emphasizes the importance of individualized discussions and treatment plans that consider the medical history, risk factors, and preferences of each patient. For patients seeking MHT with a lower breast cancer risk than single-pill EPT, options such as tibolone, tissue-selective estrogen complex, transdermal estrogen, or estrogen alone (for women who have undergone hysterectomy) can be considered as first-line options.

Conflict of interest

Author declares no competing interests.

Ethical approval

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Patient consent

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