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A Concise Viewpoint on Menopause, Hormone-Replacement Therapy and Breast Cancer Risk

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Menopause is accompanied by numerous physiological and psychological symptoms degrading the quality of life.[1] Hormone Replacement Therapy (HRT), introduced in the 1960s, effectively manages many menopausal symptoms. During the 1970s, a link between estrogen therapy and increased incidence of endometrial cancer was found and resolved by combination-HRT containing estrogen and progestin.[2] Nevertheless, its usage declined dramatically when the Women's Health Initiative (WHI) published its findings in 2002 reporting excess risk of breast cancer (BC) with HRT usage, particularly with the combination regime.[3] Eventually, studies contradicting this finding were published.[4-6] Recently, significantly higher BC risk in combined HRT users has been re-established.[7,8]

Menopause, generally commencing in the forties, consists of three stages; perimenopause or transition phase, menopause, and post-menopause marking the cessation of menstrual cycle.[9] Menopausal symptoms can be somatic (vasomotor and psychic disorders), organic (skin, urogenital and weight changes) and metabolic (changes in lipid spectrum, atherosclerosis and osteoporosis).[10]

HRT is effective in alleviating menopausal symptoms and preventing diseases associated with long-term E2 deprivation and categorized as E2-only therapy (ERT) or a combination of E2+P4 (EPT) (Table 1). The American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) clinical practice guidelines provide recommendations for patients based on medical history and specific needs.[11]

Table 1. Different estrogen and progesterone prescriptions for HRT

HRT preparations and doses		Doses (mg/d)
Estrogen based preparation and doses Oral		
	17 β- ESTRADIOL	0.5
	ETHINYL ESTRADIOL	2.5 mcg/d
	CONJUGATED ESTROGEN	0.3-0.45
Transdermal		
	17 β- ESTRADIOL PATCH	0.014-0.0375
	17 β- ESTRADIOL GEL	0.25 or 0.75
	17 β- ESTRADIOL SPRAY	1.53
	17 β- ESTRADIOL EMULSION	8.7
Vaginal		
	17 β- ESTRADIOL VAGINAL CREAM	0.2
	CONJUGATED ESTROGEN VAGINAL CREAM	0.3125
	17 β- ESTRADIOL VAGINAL TABLET	10 mcg/d
	17 β- ESTRADIOL VAGINAL RING	2mg/ring or 12.4mg/ring
Progestogen based preparation and doses Oral		
	MEDROXYPROGOSESTERONE ACETATE	1.5-2.5
	NORETHINDRONE ACETATE	0.1
	DROSPIRENONE	0.25
	MICRONIZED PROGESTERONE	100-200
Transdermal		
	NORETHINDRONE ACETATE	0.14
	LEVONORGESTRIL	0.015

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In 2002, the WHI reported a 26% increase in BC in women receiving EPT with a relative risk (RR) of 1.26.[3] This caused widespread panic.[6,12] However, in the WHI study, the RR was calculated from 30/10,000 non-users versus 38/10,000 HRT users, representing a very minute absolute risk of 8/10,000

or 0.08% per year. Later, re-analysis of the WHI data demonstrated that the benefits of HRT exceed the risks in a majority of women entering menopause.[13] Studies analyzing the effects of EPT for 5 years or less on BC risk identified only 6% of the tumors diagnosed over a 5-7-year period occurring de novo, leaving 94% pre-existing tumors growing in size reaching the diagnostic limit. It was also found that natural P4 rather than synthetic progestogens is a safer choice in this regard.[4,5] In 2019, a meta-analysis with worldwide epidemiological evidence collected between Jan 1, 1992 and Jan 1, 2018 analyzed the BC risk with different HRT types. According to this study, in women starting HRT at 50 years of age and continuing it for 5 years, the BC incidence at 50-69 years would increase by 1 in 50 in the E_2 plus daily P_4 group, 1 in 70 in the E_2 plus intermittent P_4 group and 1 in 200 in the E_2 only group. With 10 years of HRT use, these risks would double. This study found no significant differences among progestagenic constituents contributing to the risk, including the commonly preferred micronized progesterone preparation. Also, very little risk was associated with local (vaginal) E_2 application.[7]

Finally, in 2020, a UK-based study confirmed a definitive BC risk with different HRT preparations. While the extent of risk varies with the type of HRT used, higher risk is almost always associated with combined HRT and longer duration of use.[8]

A strong association between HRT use and increased BC risk exists. This is more prominent with EPT than the ERT and persists even a decade after discontinuation. Therefore, doctors and health care professionals should take the medical history and existing BC risk of the patients into account prior to making treatment decisions.

Conflict of Interest

The authors declare no conflict of interest.

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