Menopausal Hormone Therapy and Breast Cancer Risk (Postprint)

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Date: 2018-06-14T00:00:00+00:00

Abstract

Menopausal hormone therapy (MHT) is a treatment centered on estrogen supplementation; in women with a uterus, treatment often requires combined estrogen and progestogen. Gynecological endocrinology and breast surgery experts have discussed and reached a consensus on whether perimenopausal MHT increases breast cancer risk: MHT can increase breast cancer risk, and a comprehensive assessment of risks and benefits is required during application; MHT has a therapeutic window, indications, and contraindications, and relevant risks must be communicated to patients and informed consent obtained before application. Controversy remains regarding whether natural progestogens, tibolone, and estrogen-only therapy increase breast cancer risk.

Full Text

Menopausal Hormone Therapy and the Risk of Breast Cancer

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Abstract

Menopausal hormone therapy (MHT) is a medical treatment that alleviates menopausal symptoms through the administration of supplementary sex hormones, typically involving both estrogen and progestogen. Experts from the departments of gynecological endocrinology and breast surgery have carefully

examined the risk of breast carcinoma associated with MHT and reached consensus on several key issues: MHT increases the risk of breast carcinoma; treatment decisions should be made only after careful and comprehensive assessment of both breast carcinoma risk and potential benefits. Since MHT administration has a specific window period, thorough discussion with patients is essential to fully inform them of indications and contraindications, and informed consent must be obtained. Controversies persist regarding the breast carcinoma risk associated with natural progesterone, tibolone, and estrogen-only therapy.

Keywords: menopausal hormone therapy; breast carcinoma; risk

The period from the beginning of ovarian function decline to one year after menopause is defined as perimenopause. Menopause signifies ovarian failure, after which women experience estrogen deficiency leading to symptoms such as musculoskeletal pain, sweating, and increased risk of cardiovascular disease. Menopausal hormone therapy (MHT), with estrogen supplementation at its core, has been used since the 1960s to treat menopausal symptoms in perimenopausal women and prevent age-related degenerative issues. In women with a uterus, progestogen must be added to protect the endometrium. However, this treatment has experienced significant fluctuations in acceptance throughout history, not because of efficacy issues but due to concerns about increased risks of breast cancer and cardiovascular disease.

Breast cancer ranks first in incidence among female cancers globally, accounting for 25% of new female cancer cases and representing the second leading cause of cancer-related mortality in women. As a target organ for estrogen and progestogen, prolonged estrogen exposure is a well-established risk factor for breast cancer, with early menarche and late menopause both increasing risk. Chinese women exhibit different breast cancer patterns compared to Western populations, with a peak incidence age of 45-55 years—10-20 years earlier than their Western counterparts. This peak overlaps with perimenopause, raising concerns about whether additional estrogen or progestogen exposure during this period further increases risk.

1. Does Estrogen-Only Therapy Increase Breast Cancer Risk?

1.1 The WHI Study and Its Controversies

The Women's Health Initiative (WHI) was a large-scale, multicenter randomized controlled trial (RCT) in the United States that began in 2002. The study comprised two components: one comparing estrogen plus progestin versus placebo, and another comparing estrogen-only versus placebo. The estrogen-only arm included perimenopausal women aged 50-70 who had undergone hysterectomy, thus not requiring progestogen supplementation. This component was also halted prematurely after 11.3 years of follow-up.

WHI data initially suggested that estrogen-only therapy might reduce breast cancer risk (HR = 0.79, 95% CI: 0.67-0.97). However, breast surgeons caution against concluding safety based solely on this halted study. The intervention was stopped precisely because of increased health risks, and numerous other studies indicate estrogen-only therapy elevates breast cancer risk. The Million Women Study reported a risk ratio of 1.38 (95% CI: 1.32-1.44), while the Nurses' Health Study showed a risk ratio of 1.07-1.36. Other research, including studies by Simin et al. (HR = 1.95, 95% CI: 1.15-3.32) and Saxena et al. (HR = 1.59, 95% CI: 1.42-2.22), consistently demonstrate increased risk with estrogen-only therapy. A meta-analysis by Wang et al. reported a risk ratio of 1.04 (95% CI: 1.01-1.06), while another analysis showed HR = 1.72 (95% CI: 1.55-1.92). Consequently, substantial evidence suggests estrogen-only therapy increases breast cancer incidence, and controversy persists regarding its safety profile.

2. Does Estrogen Plus Progestogen Therapy Increase Breast Cancer Risk?

2.1 Estrogen Plus Progestogen Therapy Increases Breast Cancer Risk

Both gynecological endocrinologists and breast surgeons agree that combined estrogen-progestogen therapy increases breast cancer risk. In the WHI study, after 11.3 years of follow-up, the estrogen-plus-progestin group showed increased breast cancer incidence (HR = 1.28, 95% CI: 1.11-1.45) and all-cause mortality (HR = 1.96, 95% CI: 1.00-4.04). The risk continued to increase with extended follow-up, persisting even after intervention cessation. Notably, the estrogen-plus-progestin group had significantly more lymph node-positive breast cancers than the placebo group, with all-cause mortality also significantly higher (95% CI: 1.00-4.04, p = 0.049).

The Million Women Study reported a risk ratio of 1.96 (95% CI: 1.90-2.02) for combined therapy. Stahlberg et al. found a risk ratio of 1.47 (95% CI: 1.20-1.75), while Simin et al. reported HR = 1.31 (95% CI: 1.15-1.48). These consistent findings across large-scale studies confirm that estrogen plus progestogen therapy substantially increases breast cancer risk.

2.2 Does Choice of Progestogen Matter?

While acknowledging the increased risk, gynecological endocrinologists note that the WHI study used conjugated equine estrogen combined with medroxyprogesterone acetate—an old, inexpensive synthetic progestogen. Studies from France and Finland using the same estrogen with different progestogens found that natural progesterone did not increase breast cancer risk, whereas other synthetic progestogens (except dydrogesterone) did increase risk. The International Menopause Society' s 2016 guidelines suggest natural progesterone may confer lower breast cancer risk than synthetic alternatives.

However, breast surgeons argue that current evidence is insufficient to confirm

the safety of natural progesterone, as existing studies have small sample sizes and limited follow-up duration. They emphasize that more robust research is needed before concluding that natural progesterone is safer.

3. Does Tibolone Increase Breast Cancer Risk?

Tibolone, a synthetic steroid with estrogenic, progestogenic, and androgenic properties, is metabolized into active compounds that exert different tissue-specific effects. In breast tissue, its primary metabolite exhibits clear anti-estrogenic effects, while in the endometrium it has mild progestogenic activity. Preclinical studies show tibolone inhibits mammary duct and alveolar development.

The LIFT (Long-term Intervention on Fractures with Tibolone) study initially suggested tibolone reduced breast cancer incidence in postmenopausal women (HR = 0.32, 95% CI: 0.13-0.18). However, the study was halted due to increased stroke risk. Breast surgeons point to other evidence showing tibolone significantly increases breast cancer risk: the Million Women Study reported HR = 1.38 (95% CI: 1.25-1.52), the Nurses' Health Study showed HR = 4.27 (95% CI: 1.74-10.51), and Simin et al. found HR = 1.36 (95% CI: 1.25-1.49). These conflicting results indicate that tibolone' s safety profile remains controversial.

4. Summary

4.1 Consensus

Based on comprehensive literature review and discussion, gynecological endocrinologists and breast surgeons from Peking Union Medical College Hospital reached the following consensus:

1. MHT increases breast cancer risk and should not be dismissed solely for this reason, as it remains one of the most effective treatments for menopausal symptoms.
2. Individual risk-benefit assessment is mandatory before initiation.
3. A treatment window period exists; MHT should be used only with clear indications.
4. Patients must be fully informed of risks and provide informed consent.
5. Controversies remain regarding natural progesterone, tibolone, and estrogen-only therapy.

Indications for MHT include: severe menopausal symptoms (hot flashes, night sweats, musculoskeletal pain, mood disturbances), recurrent urinary tract infections, urinary urgency/frequency, and risk factors for osteoporosis.

Contraindications include: known or suspected breast cancer, hyperprolactinemia, and benign breast disease. Women with family history of breast cancer require cautious use. Patients should undergo annual physical examination, with continuation decisions based on ongoing indications, absence of

contraindications, and patient preference.

4.2 Ongoing Controversies

Gynecological endocrinologists believe natural progesterone does not increase breast cancer risk, while breast surgeons consider current evidence insufficient to establish its safety. Controversies also persist regarding tibolone and estrogen-only therapy, requiring further clinical research.

4.3 Conclusion

MHT should be reserved for patients with clear indications, not for those seeking to "retain youth" or maintain energy. Treatment requires enhanced breast monitoring, close follow-up with breast surgeons, and documented informed consent.

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(Received: 2018-03-28)

Note: Figure translations are in progress. See original paper for figures.