An Insight into the Great Debate on Hormone Therapy: are its Effects on Breast Density the Link to Breast Cancer Development?

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CLINICAL POINTS

Breast density, measured radiologically, is a strong independent risk factor for the development of breast cancer.

Many regimens of hormone therapy exist; they differ in their hormone composition, cyclic versus continuous administration, dose and duration of use. The most common regimens include: estrogen alone, estrogen given with cyclic progestin and estrogen given with continuous progestin.

The majority of hormone therapy regimens cause an increase in breast cancer risk however the underlying mechanism remains to be fully elucidated.

Certain hormone therapy regimens have an effect on breast density, with some estrogen plus progestin regimens causing a larger increase in breast density compared to estrogen alone therapy.

Future research needs to focus on the elucidation of the link between hormone therapy, breast density and breast cancer risk. Specifically, is breast density the common denominator between hormone therapy and breast cancer risk?

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Abstract

Breast density is one of the strongest independent risk factors for breast cancer development. Although many factors affect breast density, hormone therapy is one of the known controllable variables and will be discussed in this article. Hormone therapy, prescribed to at least 20 million women worldwide, is used in the management of menopausal symptoms. Not only has it been shown to increase breast cancer risk, certain regimens have also demonstrated an increase in breast density. Investigating the differences between regimens on breast density may provide insight into the link between hormone therapy, breast density and breast cancer. Studies have shown that certain hormone therapy regimens have an effect on breast density. It has been found that progestin given continuously with estrogen leads to a larger increase in breast density compared to progestin given cyclically with estrogen. In addition, a retrospective observational study has shown that women taking estrogen plus progestin for greater than 4 years had a significantly larger increase in breast density than estrogen alone therapy. With the variety of hormone therapy regimens available today, more research is needed to further evaluate the effects of different regimens on breast density. This will be an important step in the future management of menopausal women in regards to breast cancer risk.

Introduction

Breast cancer is the second most common cancer in the world and by far the most frequent in women[1]. In addition, breast cancer remains one of the most feared diseases among American women[2]. Due to these staggering figures, immense research has been done to try and decipher ways that the medical community can better identify and treat breast cancer in its early stages. Breast density has been shown to be one of the strongest independent risk factors for breast cancer development and it may account for a large fraction of the aetiology of the disease[3]. Having an increased breast density puts women at a 4-6 times greater risk of developing breast cancer[4-6]. Despite this strong association, breast density has historically been excluded from the clinical risk assessment for breast cancer, which is measured using the Gail model. This model incorporates age, age at menarche, age at first live birth, number of first-degree relatives with breast cancer, number of breast biopsies and presence of atypical hyperplasia on a biopsy. Recently, research which incorporates breast density into the Gail model has been performed however no definitive model which includes this variable has yet been developed[7].

Due to the clinical significance of breast density, a substantial amount of research is being done to try and uncover the important factors that contribute to breast density and how these can be altered to lower a woman's risk of developing breast cancer. Hormone therapy (HT), prescribed to at least 20 million women worldwide[8], is used in the treatment of menopausal symptoms and has been shown to have a profound effect on breast density[9-16]. HT not only increases breast density but has also been shown to increase breast cancer rate amongst women taking certain regimens[17,18]. Although the precise link between HT, breast density and breast cancer remains unknown, research is being conducted to uncover any potential links that may exist. Discovering these links may be a pivotal step towards better identification of women who are at a high risk of developing breast cancer. Thus, the aim of this article is to discuss the possibility that breast density may be involved in the underlying mechanism by which HT contributes to breast cancer risk.

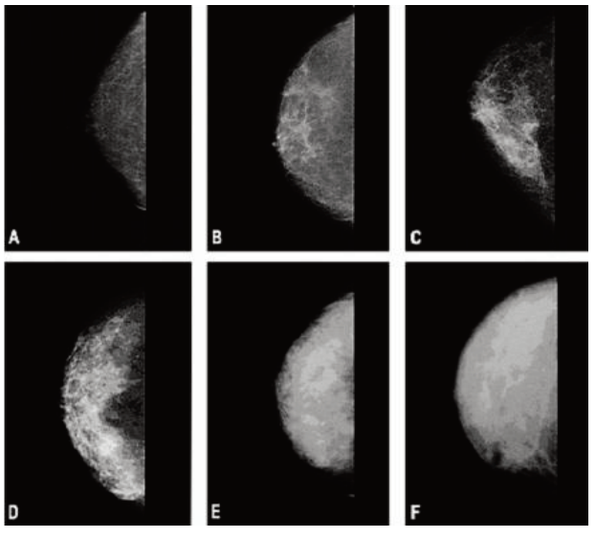
What is breast (mammographic) density?

Mammographic imaging is used to characterize the tissue composition of the breast. Breast tissues are assessed radiologically by their densities, with epithelial and connective tissues being characterized as dense tissue and fat cells as lucent tissue. Visually, mammographic images have white areas which correspond to dense tissue and dark areas which correspond to lucent tissue[19] (see Fig. 1). Breast density is a measure of the radiodense area on a mammogram[5], which can be measured quantitatively and qualitatively[4], with quantitative measurements frequently being expressed as a percentage of the total breast area. Densities more than 60-75% have been shown to increase breast cancer risk 4-6 times more compared to women with little to no densities[4]. Of significance, having increased breast density is common in the population, with approximately 26-32% of women in the general population having densities of 50% or greater[7].

Many variables affect breast density including age, parity, menopausal status and HT[20]. HT in particular has been widely investigated for its potential effects on breast density, given its frequent use in menopausal women. Despite the research that has been done with HT and breast density, there still remain many gaps in demonstrating the effects of certain HT regimens on breast density.

Hormone therapy

HT has been used for at least 60 years as an effective treatment for menopausal vasomotor symptoms that include hot flushes and night sweats, as well as to combat potentially serious effects of menopause such as reduced bone density. Initially, management included an estrogen only regimen. However, reports in 1975 showed increased cases of endometrial cancer with this regimen, thus creating concern about its safety[21]. Subsequently, it was found that the addition of progestin to estrogen therapy prevented these increases[21] due to ➔



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▲ ***Fig. 1. Examples of percentage categories of breast density estimated by radiologists.***
A: *0%*
B: *<10%*
C: *<25%*
D: *<50%*
E: *<75%*
F: *≥75%.*

progestin's known antiproliferative role on the endometrium. Estrogen only regimens, however, are still prescribed today for women that have undergone hysterectomies as endometrial cancer is no longer a risk[22].

Today, various regimens exist, differing in their hormone composition, cyclic versus continuous administration, dose and duration of use. HT is most commonly used in North America and Europe; however the regimens differ from country to country. The three most common regimens of HT used throughout the world are: estrogen alone, estrogen in cyclic combination with progestin and estrogen in continuous combination with progestin[9]. These regimens involve a 28 day cycle that include continuous estrogen with no progestin, progestin given for 10-14 days or progestin given for 28 days, respectively. Furthermore, within these regimens, different progestins are used. In the United States, a synthetic progestin, medroxyprogesterone acetate (MPA), is by far the most predominant progestin used whereas in France, there is widespread use of the micronized natural progesterone[23].

Alternatives to these traditional regimens of HT are also available. For example, progesterone alone therapy has also been shown to decrease menopausal symptoms[24,25]. Although uncommonly used by physicians, the progesterone alone HT regimen has been shown to be equally as effective at relieving vasomotor symptoms as conjugated equine estrogen (CEE), the hormone used in many estrogen alone HT regimens[26].

Although HT has been used for years in the treatment of menopause, its safety has again been recently challenged. This debate was initiated in 2002 when a large randomized controlled trial, the Women's Health Initiative (WHI), found that women on an estrogen plus progestin regimen were found to have an increased risk of breast cancer and coronary heart disease. The estrogen plus progestin arm of the study was terminated early due to these findings[17]. In addition, results from a large scale observational study in the UK, the Million Women Study (MWS), further called into question the use of HT in the treatment of menopause when it showed that users of estrogen combined with either MPA, norethisterone or levonorgestrel (all three synthetic progestins) had an increased risk of developing breast cancer[18]. As a result, the benefits versus risks of HT were re-evaluated. More recently, however, a French prospective cohort study (E3N study) showed that estrogen in combination with certain progestins, natural progesterone and dydrogesterone (the closest progestin to natural progesterone), had a decreased risk of breast cancer in comparison to estrogen alone[27]. Importantly, this study is contrary to previous findings that used synthetic progestins and it is suggestive that the type of progestin in HT regimens may be an important factor to consider.

It is still not known how each of these hormones affects the breast or how some cause an increased risk of developing breast cancer; however, it is thought that breast density may play a role. To this end, research is being done to try and uncover the relationship between HT, breast density and breast cancer.

How do different HT regimens affect breast density?

Each of the different HT regimens has varying effects on breast density upon examining the composition, cyclic versus continuous administration, dose and duration of use of each regimen. It is well established that estrogen alone therapy has less of an effect on breast density than estrogen-progestin therapy[9-11]. This is confirmed in the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, one of the only large randomized, placebo-controlled trials, which investigated the effects of estrogen alone and that of three different estrogen/progestin regimens (all with differing progestins) on breast density. They concluded that women in the three different estrogen/progestin treatment arms had mean increases in breast density ranging from 3-5% over the 12 months as opposed to the placebo and the estrogen alone groups that both demonstrated no increase from baseline. However, there were no differences seen in the increases in breast density from each of the different estrogen/progestin treatment arms[12]. Additionally, Sendag et al.[13] have also shown that estrogen in combination with different progestins (MPA or norethisterone acetate) revealed no difference in their increasing effect on breast density.

Furthermore, Sendag et al. looked at different frequencies of progestin administration for HT regimens used in clinical practice such as estrogen given with continuous progestin and estrogen given with cyclic progestin. They showed that 31% of the women in the estrogen with continuous progestin group had an increase in breast density as opposed to 2% of the women in the estrogen with cyclical progestin group. The differences seen with the varying progestin administration was also demonstrated in a study that collected data from a population-based screening program which showed that 52% of women taking estrogen in combination with continuous progestin had an increase in breast density compared to 13% of women taking the estrogen in cyclic combination with progestin[14]. A mechanism to explain the differences seen in the outcomes between the cyclic and continuous combination therapies has not been found. One hypothesis is that the withdrawal of progestin in the cyclic combination therapy induces spontaneous apoptosis of epithelial cells in the breast[28] leading to a less dense breast.

Varying doses in different HT regimens may also play a role in the effect of HT on breast density; however limited studies are available demonstrating this relationship. One such study has shown that low dose HT (estrogen plus progestin) did not differ in its increase in breast density compared to women using estrogen alone therapy. Furthermore, the incidence of increased breast density progressed over time with 7.5% of women in the combined group having an increased breast density after 1-2 years and 22.4% of these women showing an increase after more than 5 years. In contrast, the incidence of women having increased breast density in the estrogen alone group did not significantly differ between the 1-2 year and the greater than 5 year periods[15].

Another large observational study revealed similar results and demonstrated that upon continuous use of HT, an increase in breast density was sustained[30]. Interestingly, this study also looked at the effect of discontinuation of HT and found that upon stopping therapy, breast density decreased. ➔

Therefore, a strong relationship exists between HT and breast density, however, a clear picture of how they interact and their potential contribution to the development of breast cancer has yet to be determined.

Future research

Due to the known link between increased breast density and the risk of breast cancer development, research has been geared towards investigating the variables that determine and affect breast density. HT is one of those controllable variables; however, due to its success in the treatment of menopausal symptoms, it is still widely used. Despite the significant amount of research performed exploring the effect of HT on breast density, there are still gaps that exist. This is due to the abundant number of HT regimens that are currently in use in clinical practice. Differences exist with respect to hormones being used, cyclic versus continuous administration, doses, and duration of use. As a result, further research is needed to fully elucidate the effects that each individual HT regimen has on breast density in order to provide safe HT options for women.

In addition, studies such as the French prospective E3N study that showed a decrease in breast cancer risk among women that used certain progestins combined with estrogen[27], suggest that the effects of synthetic versus natural progestins on breast density should also be explored. Those studies will be important because although all progestins share the antiproliferative effects on the endometrium, they differ in many aspects such as in structure and metabolism[31], which could lead to varying effects on the breast. Moreover, no studies are available that look at the effects of progesterone alone therapy, a potential alternative to the conventional HT regimens[24,25], on breast density and its relation to breast cancer risk.

Uncovering the underlying mechanisms that contribute to the potential physiological effects of the hormones used in HT on the breast will help clinicians understand any possible risk of breast cancer development and additionally, will enable them to alter future management regimens for menopausal symptoms.

Conclusion

Breast density is a strong independent risk factor for the development of breast cancer. Although it is not yet included in the clinical risk assessment for breast cancer, it remains an important factor in determining the likelihood that one will develop the disease. Many variables affect breast density and each of these are being investigated to decipher how they interact with the breast. An important variable that affects breast density is HT. More research is needed to fully understand the link between HT and breast density in order to increase the safety of different HT regimens. Establishing a clear link between HT, breast density and breast cancer will be important in the future management of postmenopausal women, and in the early detection and prevention of breast cancer.

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