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Review

The oncologic impact of hormone replacement therapy in premenopausal breast cancer survivors: A systematic review

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ABSTRACT

Synopsis: This is the first systematic review to investigate the risk of recurrence in breast cancer survivors <50 years old who have used hormone replacement therapy (HRT).
Background: The risk of HRT in premenopausal breast cancer survivors is unclear. Due to the higher incidence of estrogen receptor negative tumours in women <50, the potential for HRT to promote breast cancer recurrence may differ from older age groups.
Methods: We performed a search of Medline, EMBASE and CINAHL through June 2016. For the observational studies relative risk (RR) and 95% confidence interval (CI) were calculated for the recurrence rate among HRT users and nonusers. A random effects model was used to estimate the combined RR using the Mantel-Haenszel method.
Results: Four papers satisfied our inclusion criteria. 3477 subjects were analyzed. On pooled meta-analysis of breast cancer recurrence in the observational studies, no significant association was found between HRT and risk of recurrence (RR 1.04 [95% CI 0.45, 2.41]). The randomized controlled trial (RCT) included found an increased risk of recurrence with HRT among women <50 (HR 1.56 [95% CI 1.1–2.2]). However, among women of all ages with an estrogen receptor negative tumour there was no significant difference in recurrence when compared to hormone receptor positive tumours (HR 1.15 [95% CI 0.7–1.8, $p = 0.55$]).
Discussion: This review on HRT in breast cancer survivors <50 revealed conflicting results between randomized and observational study data. Further studies are warranted to investigate the association between HRT and recurrence rates in younger breast cancer survivors.

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1. Introduction

Breast cancer (BC) most commonly affects postmenopausal women, with only 20% of cases occurring in women under 50 [1]. Tumours in younger patients however, typically confer a worse prognosis given their more aggressive nature. Women under 40 years of age have a lower 5-year cancer specific survival rate and women under 35 have higher overall recurrence rates locally and systemically [2,3]. Younger women typically present with more aggressive, higher grade and advanced disease with larger tumours and more commonly lymph node involvement when compared to women ≥65 years old [4]. Furthermore, triple negative breast cancers (TNBC), which are associated with an increased likelihood of distant recurrence and death are more commonly seen in women <40 years old [5,6]. In fact, in an analysis of 38,813 cases from the National Cancer Database, 16.7% of women under 50 years had TNBC compared to 11.9% of women over 50 [7]. Finally, among newly diagnosed breast cancer patients fewer than 10% of women harbour a BRCA1/2 mutation [8]. However, among young women <40 with a TNBC, up to 37% harbour a BRCA1/2 mutation [9].

Due to the aggressive nature and biologic composition of breast cancers originating in younger women, most of these patients receive adjuvant chemotherapy [10]. While varying chemotherapy options exists, anthracyclin based regimens are most widely used due to their superior reduction in recurrence and mortality [11]. Although adjuvant chemotherapy improves overall mortality, it is cytotoxic to the ovaries, leading 20%–80% of women to experience ovarian dysfunction with premature ovarian failure [12,13]. Women may experience symptoms related to low estrogen production by the ovaries such as vasomotor symptoms, loss of bone density, mood swings, and changes in cognition and libido [14]. Importantly, women suffering from premature menopause report a reduced quality of life [15].

Hormone replacement therapy (HRT) in breast cancer survivors to alleviate menopausal symptoms has been evaluated with conflicting results. After a median follow-up of 2.1 years, the HABITS (Hormone replacement therapy after breast cancer—is it safe?) trial found an increased risk of breast cancer recurrence among survivors on HRT (hazard ratio [HR] = 3.3, 95% confidence interval [CI] = 1.5 to 7.4) [16]. This finding is supported by the LIBERATE (Livial Intervention following Breast cancer: Efficacy, Recurrence, And Tolerability Endpoints) trial which demonstrated a higher risk of breast cancer recurrence in survivors on tibolone versus placebo ([HR] = 1.40, 95% CI = 1.14–1.70) [17]. In contrast, the Stockholm trial, with a median follow-up of 4.1 years, found no association between recurrence and HRT use in BC survivors (HR = 0.82, 95% CI = 0.35 to 1.9) [18].

Subgroup analyses in these studies, demonstrated no significant difference in breast cancer recurrence among estrogen receptor negative tumours [16,17,18]. However, these studies were underpowered to identify any significant differences in these post hoc analyses. In premenopausal breast cancer survivors the potential for HRT to promote breast cancer recurrence may differ given the higher incidence of estrogen receptor negative tumours [5]. Furthermore, HRT may impart the greatest benefit in this cohort, given the likelihood of chemotherapy induced menopause and subsequent negative impact on quality of life.

This systematic review aimed to assess the oncologic impact of HRT in premenopausal breast cancer survivors and in particular those with estrogen receptor negative tumours.

2. Materials and methods

2.1. Search strategy

We registered our protocol with the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42016041877 [19]. We performed a search of databases Medline, EMBASE and CINAHL from the beginning of these databases through June 2016 using Medical Subject Heading terms Hormone Replacement Therapy, Hot Flashes, Breast Neoplasm and Survivors. The search strategy was peer reviewed using the Peer Review of Electronic Search Strategies (PRESS) [20] checklist by a second librarian. Scanning of included studies and relevant reviews was conducted to ensure literature saturation.

2.2. Eligibility criteria

We included randomized controlled trials, controlled trials, quasi-experimental studies, and observational studies comparing the rate of recurrence in breast cancer survivors on HRT to no HRT that included premenopausal women in the study sample. Articles not fulfilling these criteria were excluded. If these outcomes were not reported in the published manuscript authors were contacted to obtain further data.

2.3. Study selection

After pilot-testing the eligibility criteria, citations were reviewed in duplicate by three independent reviewers for eligibility. Level 1 screening of titles and abstracts identified all potentially relevant citations, and level 2 screening evaluated these citations in full-text for final inclusion. Discordance between reviewers was resolved by a third party.

2.4. Data extraction

Two of the authors extracted data independently from each included study in parallel. Data was extracted on study characteristics, patient demographics, tumour characteristics, breast cancer treatments, menopausal status, number of subjects on HRT prior to BC diagnosis, treatment details, and oncologic outcomes. As papers were variably comprehensive, not all variables yielded data entry. Categories presented in Table 1 were included if at least two papers had provided information.