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Postmenopausal hormone therapy and ductal carcinoma in situ: A population-based case control study

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Abstract

Background and aim—The relationship between hormone therapy (HT) and invasive breast cancer has been extensively investigated, but the relationship between HT and in situ breast cancer has received relatively little attention. We examined the relationship between HT and ductal carcinoma in situ (DCIS) among postmenopausal women who participated in a population-based case control study in Connecticut, USA.

Methods—This analysis included 1,179 post-menopausal women (603 controls and 576 cases), who comprised a subset of a population-based case-control study that included all incident cases of breast carcinoma in situ (BCIS) in Connecticut and frequency-matched controls by 5-year age intervals.

Results—We found no association between DCIS and ever use of any HT (adjusted odds ratio (OR) = 0.85, 95 % confidence interval (CI): 0.65-1.11); of estrogen alone (adjusted OR = 0.93; 95 % CI: 0.68-1.29) or of estrogen and progesterone (adjusted OR = 0.75; 95 % CI: 0.52-1.08). There was also no association between DCIS and current use of these hormones. In addition, estimated risk of DCIS did not increase with duration of use of these preparations.

Conclusions—These results add to a small literature that remains inconclusive. To determine whether HT poses risk of in situ breast cancer, larger studies with greater power and precise control of important covariates (e.g., mammography screening) are needed, as are meta-analyses of available data.

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Keywords

Carcinoma; intraductal; noninfiltrating; hormone therapy; postmenopause; case control studies

1. Introduction

Largely attributed to an increase in mammography screening [1], the incidence of breast carcinoma in situ (BCIS) in the United States has increased from 5.83 cases per 100,000 women in 1975 to 34.59 per 100,000 in 2007 [2]. In situ tumors now account for nearly 22% of all breast cancers [2]. Though we know that women with these lesions are far more likely to develop invasive breast cancer than women without in situ disease [3], our understanding of the natural history of BCIS remains limited, making it difficult to provide optimum treatment [1]. Epidemiological studies that examine whether established risks of invasive breast cancer are also implicated in non-invasive disease bear on whether these lesions share a common etiology. These studies may also help to elucidate when, in the sequence of events that may culminate in invasive cancer, particular risks factors exert their greatest influence [4, 5].

Evidence is emerging that several risks may contribute to both BCIS and invasive breast lesions including older age [6], family history of breast cancer [4, 7], and higher breast density [6]. Some endogenous hormonal factors associated with invasive breast cancer have also been associated with in situ disease (e.g., fewer full-term pregnancies, older age at first birth, older age at menopause) [7], while others have not (e.g., age at menarche, breastfeeding) [8]. For *invasive* breast cancer, postmenopausal hormone therapy (HT) is a well-established risk. In an analysis of 51 studies of breast cancer and HT conducted in 1997 by the Collaborative Group on Hormonal Factors in Breast Cancer, risk increased with greater duration of use, and current users were at greater risk than past users [9]. More recent studies have refined the relationship between invasive breast cancer and HT and demonstrated greater risk with combined estrogen and progesterone formulations than with estrogen alone [10]. There is also some evidence that among women using combination HT, continuous use of progesterone may put women at higher risk than sequential use [11]. However, with regard to *in situ* disease, information is much more limited. Two reviews [12, 13] found inconsistent results among studies that examined the relationship between HT and DCIS. The more recent review, commissioned by the National Institutes of Health (NIH) for a state-of-the-science conference on diagnosis and management of ductal carcinoma in situ (DCIS), included only 5 observational studies and one clinical trial [13]. Previous studies included women with both invasive and in situ lesions, with in situ cases comprising a subset of the women in those studies. Given the increase in non-invasive breast cancers and our limited understanding of the risks associated with development and progression of this disease, additional studies that focus on potential risks specifically for in situ breast lesions are needed.

Unlike prior work, our analysis is based on a study of exclusively in situ cases. Our objective was to examine the association between HT and DCIS in a population-based case-control study that included a relatively large number of DCIS cases. In addition to examining ever use of HT, we examined whether: 1) risk increased with duration of use; 2) current users were at greater risk than those who had ever used HT; and 3) continuous users of combined estrogen and progesterone were at higher risk than sequential users.

2. Materials and Methods

These analyses are based on data from a population-based case control study that examined a broad range of potential risks of BCIS [7]. The study was approved by the Human Investigations Committees of Yale University School of Medicine and the State of Connecticut Department of Public Health.

The methods have been previously described [7]. Briefly, the study invited to participate all English-speaking incident cases of BCIS among female residents of Connecticut, at least 20 years of age, diagnosed between September 15, 1994 and March 14, 1998. The Rapid Case Ascertainment Shared Resource of the Cancer Center at Yale University identified the cases whose diagnosis was confirmed by review of the pathology report. Additionally, some data used in this study were directly obtained from the CT Tumor Registry in the Connecticut Department of Public Health. The authors assume full responsibility for analyses of these data.

Controls were English-speaking female residents of Connecticut, frequency matched to the cases by 5-year age group. The consulting firm Northeast Research of Orono, Maine selected the controls by random digit dialing. Cases and controls with a history of breast cancer or of breast biopsy with unknown outcome were excluded from the study, as were cases that could not be identified as either DCIS or LCIS by pathology report review. Only cases with physician permission to participate were included. Potential subjects received an introductory letter, followed by a telephone call from a trained interviewer, requesting participation. Subjects verbally consented to be interviewed by telephone and they gave written consent to release medical records. The structured telephone interview obtained information on demographics, family medical history, menstrual and pregnancy histories, exogenous hormone use, personal medical and screening histories, and alcohol and smoking behaviors. Risks were assessed to date of diagnosis for cases and to date of interview for controls. The original study population included 999 controls and 998 cases (n = 875 with DCIS and n = 123 with lobular carcinoma in situ (LCIS)).

2.1 Participants, Procedures, Variables, and Measures

As the effect of HT on ductal and lobular breast cancer may differ [14], we included only DCIS cases in these analyses and excluded the 123 LCIS cases. We also restricted our sample to postmenopausal women, defined as those who: 1) reported natural menopause; 2) had bilateral oophorectomy; 3) had a hysterectomy without bilateral oophorectomy or had periods stopped by chemotherapy, radiation, or hormones and were at least age 55 years; and 4) started HT before their periods stopped. We excluded 396 controls and 299 cases from the original study population who were: 1) self-identified as pre- or perimenopausal; 2) had a hysterectomy without bilateral oophorectomy or had periods stopped by chemotherapy, radiation, or hormones and were less than age 55 years, as these women might be premenopausal; and [L1] 3) were missing information on menopausal status. The subjects for these analyses, a subset of the original study participants, thus included 1,179 postmenopausal women (603 controls and 576 cases with DCIS).

In keeping with most other studies, summarized by the Collaborative Group on Hormonal Factors in Breast Cancer [9], we defined age at menopause as age at last menstrual period (LMP) for women with natural menopause and age at bilateral oophorectomy for women who had undergone that procedure. Where age at menopause was not known, we used common conventions to impute age. First, among women who began HT before their periods stopped, we estimated age at menopause as the age they began HT, in keeping with the method employed by Ross [15]. Second, for the few women who reported natural menopause but did not recall their age at menopause, we use age 55 years. Third, there [L2]

were several groups of women who reported that their periods stopped as a result of medical treatments, including: 1) hysterectomy without bilateral oophorectomy; 2) radiation or chemotherapy; and 3) hormonal treatments (whether HT or another hormone treatment could not be determined). Because it is not known when ovarian functioning ceases among women with simple hysterectomy, and because menstruation may resume once women discontinue chemotherapy [16, 17] and other treatments, we only included women in these categories if they were ages 55 years and older and we used age 55 years as their age at menopause. We selected age 55 years because 90% of our sample had reached menopause by that age. We did not assign different ages at menopause to smokers and non smokers as have some others [18]; in our sample, age at menopause did not differ between these groups ($p=0.250$).

To examine HT use, we asked participants if they had used estrogen, progesterone, or other female hormones for purposes other than family planning or birth control. We then asked women who had used these hormones to provide the name(s)/brand(s) and dose of the medication(s) if known, the dates of use, the form in which they took the medications (e.g., oral, topical), and the pattern of use (continuous or sequential). In these analyses, we focused on oral preparations used during the postmenopausal period. We grouped hormone use as: 1) any HT (estrogen only or estrogen and progesterone); 2) estrogen only; and 3) estrogen and progesterone (continuous or sequential). If a woman used estrogen only and estrogen plus progesterone at different points in time, she was included in the estrogen plus progesterone group. We examined: 1) ever versus never use of these hormones; 2) current versus never use, where current use was defined as HT use within 12 months of diagnosis (cases) or interview (controls); and 3) duration of use.

We examined a number of covariates. These included sociodemographic factors (age, race, marital status, and education); potential risks of invasive and/or in situ breast cancer (first degree relative with the disease, younger age at first menstrual period, older age at first birth of a child, and fewer pregnancies)[6]; potential confounders of the relationship between HT and risk of breast cancer (time since menopause [9, 18], body mass index [6], frequency of mammography screening [6], and history of breast biopsy [7]); and oral contraceptive use.

2.2 Data Analysis

We began with descriptive analyses to characterize the study population, by case control status, using frequency distributions. Next, using chi square tests, we examined bivariate associations between case control status and: 1) ever use of HT; and 2) each covariate. Then, we conducted multivariate analyses that examined the relationship of HT use to DCIS, adjusted by covariates that were associated with the outcome ($p<.05$, 2-sided) at the bivariate level. In separate models, we examined: 1) ever use of HT; 2) current use; and 3) duration of use. We conducted the multivariate analyses with unconditional logistic regression to generate odds ratios (ORs) and 95% confidence intervals (CIs) as estimates of risk. To test for linear trend (i.e., whether the risk of DCIS increased with more years of HT use), we constructed a model with duration of use in its ordinal form, adjusted for the same group of significant covariates included in the above multivariate models. In addition, because BMI has been shown to modify the association between HT and breast cancer, and HT has been shown to modify the association between BMI and breast cancer [19], we examined interaction terms for use of HT (ever/never) and each category of BMI to ensure that we were not overlooking potential modifying effects of these variables on DCIS.

We conducted these analyses on all menopausal women; i.e., those with known and unknown (imputed) age at menopause (Analysis 1, $n=1,179$). Then, we repeated the analyses on the subset of menopausal women with known age at menopause; i.e., 1) women with known age at natural menopause; and 2) women with bilateral oophorectomy (Analysis

2, n=926). We conducted these analyses with SAS software, version 9.1 (The SAS System for Windows. Cary, NC: SAS Institute, Inc., Copyright 2003).

3. Results

Among subjects invited to participate in the original study, 76% of cases and 70% of controls agreed. Among the 1,179 postmenopausal women included in these analyses, as shown in Table 1, there was a significant difference in age between the 576 cases and 603 controls. Cases and controls did not, however, differ on race, marital status or education. Similar to what would be expected among women with invasive breast cancer, fewer pregnancies, no births or older age at birth of first child, breast cancer in a first degree relative, history of breast biopsy, and a greater number of mammography screenings were associated with increased risk of DCIS. All covariates in Table 1 that were significantly associated with the outcome were included in the multivariable models, coded as shown in that table.

Table 2 presents the adjusted ORs and CIs for associations between HT and DCIS. Among all postmenopausal women (Analysis 1), in relation to women who had never used HT, we found no evidence of increased risk of DCIS with ever use of any HT preparations (adjusted OR: 0.85, 95% CI: 0.65-1.11). For estrogen alone, the adjusted OR was 0.93 (95 % CI: 0.68-1.29), while for those who had used estrogen and progesterone, the adjusted OR was 0.75 (95% CI: 0.52-1.08). Moreover, neither continuous nor sequential use of combined estrogen and progesterone had a significant impact. In addition, among current users of these HT preparations, we found no increased risk of DCIS: adjusted OR = 0.87; 95 % CI: 0.64-1.18 (any HT); adjusted OR = 0.98; 95% CI: 0.66-1.41 (estrogen only); adjusted OR=0.78; 95 % CI: 0.52-1.16 (estrogen and progesterone). In addition, we found no significant associations between DCIS and any category of duration of use of: 1) any HT; 2) estrogen; and 3) combined estrogen and progesterone (Table 2). Tests for trend by duration of any HT, estrogen only, and estrogen and progesterone use were also not significant. In addition, the interactions of HT and each category of BMI were non-significant.

When we repeated these analyses on the subset of women with known age at menopause (Table 2, Analysis 2), we found no association between any form of HT use and DCIS, whether examined as ever use, as current use, or by duration of use.

4. Discussion

We found that use of any HT, estrogen alone, and progesterone and estrogen combined were not associated with DCIS among ever users or current users. In addition, none of the categories of duration of use of these hormones were significantly associated with DCIS, nor was there evidence of increased risk with longer duration of use. This held for the analysis that included all women, as well as that restricted to women with known age at menopause.

Notwithstanding the relatively large sample size of this case control study, power was limited for some of the analyses. In particular, though current use of HT has been more strongly associated with breast cancer than ever use [10], we had less power to examine current than ever use in our study. An additional limitation is that we gathered hormone data by self-report. One [13] study found good agreement between self reported HT data (obtained from a mailed questionnaire) and prescription information, though the questionnaire under-estimated short-term use [20]. However, non-differential misclassification and recall bias are always potential problems in studies where data is collected retrospectively and by self-report. Our first analysis included women with unknown age at menopause for whom we imputed age values, based on widely used

conventions [18, 21]. However, some have raised concerns that imputing age may produce biased estimates [15, 22]. Thus, a strength of this study is the conduct of a second analysis that included only those women with known age at menopause. Further strengths of this work include the use of population-based cases and controls, relatively high participation among invited subjects, and detailed assessment of hormone use. In addition, we were able to obtain information on a range of covariables that could impact the association between HT and DCIS, notably time since menopause and use of mammography screening.

We had fairly detailed information on screening behavior: i.e., whether women were not receiving screening mammograms or were receiving mammograms: 1) less often than once a year; 2) once a year; or 3) more often than once per year. We found that this mammography screening variable had more impact on the relationship between HT and DCIS than any covariable in the dataset, reducing the estimated risk by nearly 11%. Thus, studies that are unable to control for mammography screening, or do so with sufficient precision (e.g., ever had a screening mammogram) may inflate the impact of postmenopausal hormone use. Because in situ cancers that might otherwise go undetected can be found on screening [23], controlling for this variable may be even more important in studies of in situ than invasive breast cancer.

We offer these results as part of a small, but developing, literature on HT and non-invasive breast cancer. We located fifteen studies [4, 11, 15, 24-35] that examined this association (Table 3). These include one randomized trial [25], seven prospective studies [11, 26, 28, 30-33], and seven case control studies [4, 15, 24, 27, 29, 34, 35]. The one clinical trial, an analysis of Women's Health Initiative data, did not find an association between combined estrogen and progesterone use and DCIS, but few DCIS cases were included (n=84) [25]. The larger prospective studies by Reeves and colleagues with 1,913 BCIS cases [31]; Kerlikowske and colleagues with 583 DCIS cases [28]; and Lyytinen et al. with 404 in situ cases [11], all found that HT was associated with BCIS. Reeves found a stronger risk of DCIS, and especially of LCIS, with current than past use. The Lyytinen group found increasing risk with greater duration of use, with a standardized incidence ratio (SIR) of 2.28 after 10 or more years. However, the latter study was not able to control for important potential confounders, including mammography screening. The Kerlikowske study was based on mammography registry data and accounted for time between screenings, while the Reeves study, based on data from the Million Women Study, recruited participants at the time they [L4] attended a routine screening.

The case control studies that assessed the relationship between HT use and BCIS did adjust for multiple covariables, though they varied in which covariables were included, and in the precision of covariable measurement. Four of the seven case control studies showed modestly elevated risk with estrogen and/or progesterone use in some analyses [4, 15, 24, 29], usually stronger with current use or longer duration, though one of these studies found decreasing risk with longer use [4]. Of these four studies, one adjusted for number of mammograms [29], one included a less precise measure of screening (ever use) [4], one did not appear to have adjusted for screening [15], and one included participants in the Breast Cancer Detection Demonstration Project and did account for time in the program [24]. Three case control studies had negative findings, though two of these studies included very few subjects with in situ disease [27, 34]. However, the present analysis, which included more in situ cases (n=573) than the prior case control studies we identified, also yielded a null result.

Differences in exposure measures may have contributed to inconsistent findings across studies. For example, risk may differ for estrogen only and estrogen-progesterone regimens [15]. Combining all HT medications in one analysis, as did some investigators [4, 26, 31, 32], may have obscured differences in the effect of these preparations on BCIS. Our study

did examine use of any HT, but we also examined estrogen alone and combined estrogen and progesterone use. Although not significant, the impact of type of HT on DCIS did differ in our study. However, across studies, even when examined by type of hormone, results varied. Some investigators found increased risk with estrogen only [15, 24, 29, 30] whereas other did not [28, 34]. Results of studies that examined combined estrogen and progesterone use were similarly inconsistent. This suggests that it may not be enough to examine specific hormones; more refined analyses may be needed. For example, studies of breast cancer and HT conducted in Finland [11] and Germany [36] suggest that different types of progestins used in combined regimens may impact risk differently. Among subjects in our study, medroxyprogesterone acetate was most frequently prescribed, but others were also used. With regard to estrogens, subjects in our study reported use of conjugated equine estrogens and esterified estrogens, among others. Not distinguishing among these forms of estrogen and progesterone may have obscured some differences in risk of DCIS by HT regimen within our study and may have also contributed to differences across studies, especially when comparing findings conducted across countries where commonly prescribed regimens may differ. For example, though medroxyprogesterone acetate was the most common progestin reported in our study conducted in the United States, norethisterone acetate was more common in the Finnish study noted above. Large studies of in situ breast cancer with sufficient power will be needed to undertake analyses that can meaningfully assess risk of BCIS associated with specific forms of estrogen and progesterone.

Pattern of use may also impact risk and should be considered. As reviewed by Lyytinen [11], several, but not all, investigators found that continuous use of progesterone in combined regimens put women at higher risk of invasive breast cancer than sequential use. Only our study and a study by Ross et al. [15] report on continuous and sequential hormone use in relation to in situ cancers, but small numbers prohibit drawing definitive conclusions. An additional factor to consider is that HT dosage and preparation may impact BCIS risk. Since the Women's Health Initiative findings were made public in 2002, there has been a decrease in overall HT use and in standard dose oral HT use, but there has been an increase in lower dose oral medications and an increase in use of vaginal preparations [37]. These products may impact BCIS differently, but the studies reviewed here did not report on, and presumably did not have the data and/or power to conduct, such analyses, nor did we. Future studies will need to account for these changes in prescribing patterns over time.

Across studies, there were also differences in the outcomes investigated. The majority reported on non-specific BCIS [11, 15, 24, 25, 27, 29, 30, 32-34], whereas others reported on DCIS [26, 28, 31, 35] or LCIS [4, 31] separately. Because there is some evidence that HT may be more strongly associated with lobular than ductal lesions in invasive disease [14, 38, 39], and in situ cancers [31], reporting on BCIS without examining specific histology may have missed important distinctions. Our study's focus specifically on DCIS is an improvement over the more generic BCIS studies. Yet, it may be necessary to even more precisely examine outcome; for example, by DCIS subtype [40]. A recent study by Phillips and colleagues [35] is, to our knowledge, the first to examine HT use in relation to comedo and non-comedo DCIS, in addition to examining the effect on DCIS overall (shown in Table 3) and on invasive breast cancer. Among the subset of postmenopausal women in that study, the impact of HT on DCIS did not differ by DCIS subtype, but numbers of women in each group were small. Additional factors to consider in the assessment of BCIS outcomes include the expression of hormone receptors and other biomarkers. We do know that in situ tumors express receptors for estrogen and progesterone [41], but to our knowledge, the assessment of HT in relation to BCIS by hormone receptor status and other common markers has yet to be undertaken. Breast cancers may include distinct entities that can be differentiated based on specific tumor characteristics, including hormone receptor status, and HT may differentially affect the development of these tumors [42]. Combining, for

example, estrogen receptor (ER) positive and ER negative DCIS tumors as one outcome could, potentially, obscure a significant association if HT contributes primarily to the development of DCIS that is ER positive.

In this analysis, we examined HT use during the postmenopausal period, in keeping with prior work and allowing for comparison across studies. However, examining the potential risk of HT at different points in a woman's life cycle may be indicated. An intriguing study by Shantakumar and colleagues found that premenopausal HT, which may be prescribed to treat a range of gynecological problems, had a greater impact on breast cancer risk (invasive and in situ combined) than postmenopausal use [21]. In a post hoc analysis, compared with the postmenopausal women in this analysis, we, too, found a higher, albeit non-significant, risk of DCIS among women in the original study who had used HT and who were pre- or perimenopausal, or whose menopausal status was unknown. Thus, to fully assess risk, future studies should account for all HT use over a woman's lifetime.

Future studies that include large numbers of subjects will be needed to examine lifetime hormone use by more precise BCIS outcomes and exposures. In the meanwhile, a careful meta-analysis that thoughtfully examines and parses out the different exposures and outcomes captured by current studies may yield analyses with adequate power to draw more definitive conclusions regarding postmenopausal HT and in situ breast cancers. To ensure that the meta-analysis is free of publication bias, it is critical that both positive and null study results, such as these, are published and made available.

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References

- [1]. Allegra C, Aberle D, Ganschow P, Hahn S, Lee C, Millon-Underwood S, et al. National Institutes of Health State-of-the-Science Conference statement: Diagnosis and Management of Ductal Carcinoma In Situ September 22-24, 2009. *Journal of the National Cancer Institute*. 102(3):161–169. [PubMed: 20071686]
- [2]. Altekruse, SFKC.; Krapcho, M.; Neyman, N.; Aminou, R.; Waldron, W.; Ruhl, J.; Howlander, N.; Tatalovich, Z.; Cho, H.; Mariotto, A.; Eisner, MP.; Lewis, DR.; Cronin, K.; Feuer, EJ.; Stinchcomb, DG.; Edwards, BK., editors. *SEER Cancer Statistics Review, 1975-2007*. National Cancer Institute; Bethesda, MD:
- [3]. Warnberg F, Yuen J, Holmberg L. Risk of subsequent invasive breast cancer after breast carcinoma in situ. *Lancet*. 2000; 355(9205):724–725. [PubMed: 10703809]
- [4]. Trentham-Dietz A, Newcomb PA, Storer BE, Remington PL. Risk factors for carcinoma in situ of the breast. *Cancer Epidemiology, Biomarkers and Prevention*. 2000; 9(7):697–703.
- [5]. Wohlfahrt J, Rank F, Kroman N, Melbye M. A comparison of reproductive risk factors for CIS lesions and invasive breast cancer. *International journal of cancer*. 2004; 108(5):750–753.

- [6]. Kerlikowske K. Epidemiology of ductal carcinoma in situ. *Journal of the National Cancer Institute. Monographs.* 2010; (41):139–141. [PubMed: 20956818]
- [7]. Claus EB, Stowe M, Carter D. Breast carcinoma in situ: risk factors and screening patterns. *Journal of the National Cancer Institute.* 2001; 93(23):1811–1817. [PubMed: 11734598]
- [8]. Kabat GC, Kim MY, Woods NF, Habel LA, Messina CR, Wactawski-Wende J, et al. Reproductive and menstrual factors and risk of ductal carcinoma in situ of the breast in a cohort of postmenopausal women. *Cancer Causes Control.* Jul 13.2011 [Epub ahead of print].
- [9]. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet.* 1997; 350(9084): 1047–1059. [PubMed: 10213546]
- [10]. Collins J, Blake J, Crosignani P. Breast cancer risk with postmenopausal hormonal treatment. *Human Reproduction Update.* 2005; 11(6):545–560. [PubMed: 16150813]
- [11]. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. *Obstetrics and gynecology.* 2009; 113(1):65–73. [PubMed: 19104361]
- [12]. Leonard G, Swain S. Ductal carcinoma in situ, complexities and challenges. *Journal of the National Cancer Institute.* 2004; 96(12):906–920. [PubMed: 15199110]
- [13]. Virnig B, Tuttle T, Shamliyan T, Kane R. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. *Journal of the National Cancer Institute.* 2010; 102(3):170–178. [PubMed: 20071685]
- [14]. Daling J, Malone K, Doody D, Voigt L, Bernstein L, Coates R, et al. Relation of regimens of combined hormone replacement therapy to lobular, ductal, and other histologic types of breast carcinoma. *Cancer.* 2002; 95(12):2455–2464. [PubMed: 12467057]
- [15]. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *Journal of the National Cancer Institute.* 2000; 92(4):328–332. [PubMed: 10675382]
- [16]. Gadducci A, Cosio S, Genazzani A. Ovarian function and childbearing issues in breast cancer survivors. *Gynecological endocrinology.* 2007; 23(11):625–631. [PubMed: 17926162]
- [17]. Minisini A, Menis J, Valent F, Andreetta C, Alessi B, Pascoletti G, et al. Determinants of recovery from amenorrhea in premenopausal breast cancer patients receiving adjuvant chemotherapy in the taxane era. *Anti-cancer drugs.* 2009; 20(6):503–507. [PubMed: 19339872]
- [18]. Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *New England Journal of Medicine.* 1995; 332(24):1589–1593. [PubMed: 7753136]
- [19]. Li C, Malone K, Daling J. Interactions between body mass index and hormone therapy and postmenopausal breast cancer risk (United States). *CCC. Cancer causes & control.* 2006; 17(5): 695–703.
- [20]. Sandini L, Pentti K, Tuppurainen M, Krger H, Honkanen R. Agreement of self-reported estrogen use with prescription data: an analysis of women from the Kuopio Osteoporosis Risk Factor and Prevention Study. *Menopause.* 2008; 15(2):282–289. [PubMed: 17998884]
- [21]. Shantakumar S, Terry M, Paykin A, Teitelbaum S, Britton J, Moorman P, et al. Age and menopausal effects of hormonal birth control and hormone replacement therapy in relation to breast cancer risk. *American Journal of Epidemiology.* 2007; 165(10):1187–1198. [PubMed: 17337757]
- [22]. Pike MC, Ross RK, Spicer DV. Problems involved in including women with simple hysterectomy in epidemiologic studies measuring the effects of hormone replacement therapy on breast cancer risk. *American Journal of Epidemiology.* 1998; 147(8):718–721. [PubMed: 9554412]
- [23]. Malmgren JA, Atwood MK, Kaplan HG. Increase in mammography detected breast cancer over time at a community based regional cancer center: a longitudinal cohort study 1990-2005. *BMC Cancer.* 2008; 8(131)
- [24]. Brinton LA, Hoover R, Fraumeni JF. Menopausal oestrogens and breast cancer risk: an expanded case-control study. *British Journal of Cancer.* 1986; 54(5):825–832. [PubMed: 3801275]

- [25]. Chlebowski R, Hendrix S, Langer R, Stefanick M, Gass M, Lane D, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA*. 2003; 289(24):3243–3253. [PubMed: 12824205]
- [26]. Gapstur SM, Morrow M, Sellers TA. Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study. *JAMA*. 1999; 281(22): 2091–2097. [PubMed: 10367819]
- [27]. Henrich JB, Kornguth PJ, Viscoli CM, Horwitz RI. Postmenopausal estrogen use and invasive versus in situ breast cancer risk. *Journal of clinical epidemiology*. 1998; 51(12):1277–1283. [PubMed: 10086820]
- [28]. Kerlikowske K, Miglioretti D, Ballard-Barbash R, Weaver D, Buist DSM, Barlow W, et al. Prognostic characteristics of breast cancer among postmenopausal hormone users in a screened population. *Journal of clinical oncology*. 2003; 21(23):4314–4321. [PubMed: 14645420]
- [29]. Longnecker MP, Bernstein L, Paganini-Hill A, Enger SM, Ross RK. Risk factors for in situ breast cancer. *Cancer Epidemiology, Biomarkers and Prevention*. 1996; 5(12):961–965.
- [30]. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstetrics and gynecology*. 2006; 108(6):1354–1360. [PubMed: 17138766]
- [31]. Reeves G, Beral V, Green J, Gathani T, Bull D. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol*. 2006; 7(11): 910–918. [PubMed: 17081916]
- [32]. Reinier K, Vacek P, Geller B. Risk factors for breast carcinoma in situ versus invasive breast cancer in a prospective study of pre- and post-menopausal women. *Breast Cancer Research and Treatment*. 2007; 103(3):343–348. [PubMed: 17063272]
- [33]. Schairer C, Byrne C, Keyl PM, Brinton LA, Sturgeon SR, Hoover RN. Menopausal estrogen and estrogen-progestin replacement therapy and risk of breast cancer (United States). *Cancer Causes & Control*. 1994; 5(6):491–500. [PubMed: 7827235]
- [34]. Stanford JL, Weiss NS, Voigt LF, Daling JR, Habel LA, Rossing MA. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. *JAMA*. 1995; 274(2):137–142. [PubMed: 7596001]
- [35]. Phillips L, Millikan R, Schroeder J, Barnholtz Sloan J, Levine B. Reproductive and hormonal risk factors for ductal carcinoma in situ of the breast. *Cancer Epidemiology, Biomarkers and Prevention*. 2009; 18(5):1507–1514.
- [36]. Flesch-Janys D, Slinger T, Mutschelknauss E, Kropp S, Obi N, Vettorazzi E, et al. Risk of different histological types of postmenopausal breast cancer by type and regimen of menopausal hormone therapy. *International Journal of Cancer*. 2008; 123(4):933–941.
- [37]. Tsai S, Stefanick M, Stafford R. Trends in menopausal hormone therapy use of US office-based physicians, 2000–2009. *Menopause*. 2010; 18(4) 000–000 [Epub ahead of print].
- [38]. Biglia N, Sgro L, Defabiani E, De Rosa G, Ponzzone R, Marengo D, et al. The influence of hormone replacement therapy on the pathology of breast cancer. *European journal of surgical oncology*. 2005; 31(5):467–472. [PubMed: 15922881]
- [39]. Phipps A, Li C, Kerlikowske K, Barlow W, Buist DSM. Risk factors for ductal, lobular, and mixed ductal-lobular breast cancer in a screening population. *Cancer Epidemiology, Biomarkers and Prevention*. 2010; 19(6):1643–1654.
- [40]. Millikan R, Dressler L, Geradts J, Graham M. The need for epidemiologic studies of in-situ carcinoma of the breast. *Breast Cancer Research and Treatment*. 1995; 35(1):65–77. [PubMed: 7612906]
- [41]. Lari SA, Kuerer HM. Biological Markers in DCIS and Risk of Breast Recurrence: A Systematic Review. *J Cancer*. 2(232–61)
- [42]. Chen W, Hankinson S, Schnitt S, Rosner B, Holmes M, Colditz G. Association of hormone replacement therapy to estrogen and progesterone receptor status in invasive breast carcinoma. *Cancer*. 2004; 101(7):1490–1500. [PubMed: 15378477]

Table 1

Selected characteristics of the study participants.

	Cases n (%)^a 576 (48.9%)	Controls n (%)^a 603 (51.1%)	P
Hormone therapy (any)			0.858
Ever used	222 (40.5)	238 (41.0)	
Never used	326 (59.5)	342 (59.0)	
Age			<0.001
Under age 50	33 (5.7)	41 (6.8)	
50-59	176 (30.6)	163 (27.0)	
60-69	169 (29.3)	248 (41.1)	
70 and over	198 (34.4)	151 (25.1)	
Race			0.902
White	539 (93.6)	563 (93.4)	
Black	31 (5.4)	32 (5.3)	
Other	6 (1.0)	8 (1.3)	
Marital status			0.346
Single	39 (6.8)	27 (4.5)	
Married/living as married	344 (59.6)	359 (59.5)	
Divorced/separated	74 (12.8)	86 (14.3)	
Widowed	120 (20.8)	131 (21.7)	
Education-college graduate			0.968
Yes	199 (34.6)	209 (34.7)	
No	377 (65.4)	394 (65.3)	
First degree relative with breast cancer			0.008
Yes	130 (22.6)	99 (16.4)	
No	446 (77.4)	504 (83.6)	
Hx breast biopsy			<0.001
Yes	296 (51.4)	144 (23.9)	
No	280 (48.6)	459 (76.1)	
Mammography screening			0.001
Never	23 (4.0)	53 (8.8)	
Less than once a year	154 (27.0)	254 (42.1)	
Once a year	371 (65.1)	293 (48.6)	
More than once a year	22 (3.9)	3 (0.5)	
Oral contraceptive use			0.150
Yes	185 (32.2)	218 (36.2)	
No	390 (67.8)	385 (63.8)	
Body Mass Index			0.952
<18.5	9 (1.6)	10 (1.7)	
18.5<25	337 (58.9)	358 (59.4)	
25<30	162 (28.3)	163 (27.0)	

	Cases n (%)^a 576 (48.9%)	Controls n (%)^a 603 (51.1%)	P
30+	64 (11.2)	72 (11.9)	
Age at first menstrual period			0.149
Under age 11	45 (7.9)	51 (8.5)	
Age 11	65 (11.5)	62 (10.4)	
Age 12	150 (26.6)	126 (21.1)	
Age 13	167 (29.6)	183 (30.7)	
Age 14 and over	138 (24.4)	175 (29.3)	
Age at first live birth			<0.001
14<22 years	127 (22.0)	178 (29.5)	
22<30 years	290 (50.4)	310 (51.4)	
30+ years	57 (9.9)	54 (9.0)	
No births	102 (17.7)	61 (10.1)	
Number of pregnancies			<0.001
None	85 (14.8)	47 (7.8)	
1-2	196 (34.2)	170 (28.2)	
3-5	239 (41.7)	311 (51.7)	
6+	53 (9.3)	74 (12.3)	
Time since menopause			0.015
<10 years	209 (36.3)	200 (33.2)	
10<20 years	155 (26.9)	209 (34.7)	
20+ years	212 (36.8)	194 (32.2)	

^a n for selected characteristics may not sum to overall n for cases and controls due to missing values on some variables.

Table 2

Hormone therapy (HT) and ductal carcinoma in situ among all postmenopausal women (Analysis 1) and among women with known age at menopause (Analysis 2)

	<u>Analysis 1</u>			<u>Analysis 2</u>		
	Cases (n=569)	Controls (n=600)	Adjusted ^a OR (95% CI)	Cases (n=452)	Controls (n=474)	Adjusted ^a OR (95% CI)
Never use	326	342	reference	262	294	reference
Ever use						
Any HT	222	238	0.85 (0.65, 1.11)	170	161	1.01 (0.74, 1.38)
Estrogen only	127	131	0.93 (0.68, 1.29)	104	98	1.15 (0.79, 1.69)
Estrogen and progesterone	95	107	0.75 (0.52, 1.08)	66	63	0.83 (0.53, 1.29)
Continuous	36	38	0.84 (0.48, 1.45)	29	26	0.94 (0.50, 1.79)
Sequential	55	67	0.71 (0.45, 1.10)	34	35	0.72 (0.40, 1.30)
Missing	4	2		3	2	
Missing/don't know	28	23		20	19	
Current use						
Any HT	160	168	0.87 (0.65, 1.18)	117	109	0.97 (0.68, 1.74)
Estrogen only	86	83	0.97 (0.66, 1.41)	67	59	1.11 (0.71, 1.67)
Estrogen and progesterone	74	85	0.78 (0.52, 1.16)	50	50	0.82 (0.50, 1.34)
Missing/don't know	0	0		0	0	
Duration of use-Any HT						
< 1 year	46	58	0.90 (0.57, 1.43)	37	37	1.25 (0.72, 2.16)
1 to < 5 years	72	73	0.79 (0.52, 1.18)	54	50	0.88 (0.54, 1.42)
5 to < 10 years	36	44	0.77 (0.46, 1.29)	24	25	0.95 (0.49, 1.84)
10 years	65	61	0.93 (0.60, 1.43)	53	48	1.04 (0.63, 1.71)
Trend			0.95 (0.87, 1.05)			0.99 (0.89, 1.10)
Missing/don't know	3	2		2	1	
Duration of use-estrogen only						
< 1 year	30	25	1.55 (0.84, 2.87)	24	21	1.68 (0.84, 3.37)
1 to < 5 years	33	39	0.72 (0.41, 1.25)	28	28	1.02 (0.54, 1.92)
5 to < 10 years	16	22	0.84 (0.41, 1.74)	11	13	1.21 (0.49, 3.00)
10 years	47	43	0.93 (0.56, 1.55)	41	35	1.10 (0.62, 1.95)
Trend			0.96 (0.86, 1.08)			1.03 (0.91, 1.17)
Missing/don't know	1	2			0	1
Duration of use-estrogen and progesterone						
< 1 year	16	33	0.51 (0.26, 1.03)	13	16	0.78 (0.33, 1.87)
1 to < 5 years	39	34	0.85 (0.49, 1.48)	26	22	0.77 (0.39, 1.54)
5 to < 10 years	20	22	0.72 (0.36, 1.46)	13	12	0.76 (0.30, 1.93)
10 years	18	18	0.93 (0.44, 1.98)	12	13	0.86 (0.34, 2.17)gv
Trend			0.94 (0.81, 1.08)			0.93 (0.78, 1.10)
Missing/don't know	2	0		2	0	

^aAdjusted by age, number of pregnancies, age at first birth, time since menopause, breast cancer family history, breast biopsy, mammography use.

Table 3

Studies of hormone therapy and breast carcinoma in situ

Authors (yr) [reference]	Design/n	Population/n	Exposure assessment	Lesions included	In situ cases (n)	Exposure	Classification of hormone use	Measure of association (CI or p- value)	Adjustment/matching/ stratification
Brinton et al. (1986) [22]	CC n=4218	Postmenopausal participants in the BCDDP	Home interview	Invasive and in situ	254	E	Ever use Duration (<5 yrs) Duration (5-9 yrs) Duration (10+ yrs)	OR=1.26(0.9-1.6) OR=0.90(p>0.05) OR=1.52(p<0.05) OR=1.90(p<0.05) Trend test (p<0.01)	Race, age, center, BCDDP enrollment date and time in program, type of menopause, time since oophorectomy
Chlebowski et al. (2003) [23]	RCT n=16,608	Postmenopausal Ages 50-79	n/a	Invasive and in situ	84	E+P	Intent-to-treat (mean f/up 5.6 yrs)	HR=1.18 (p=0.09)	Age, randomization assignment
Gapstur et al. (1999) [24]	PR n=37,105	Postmenopausal Ages 55-69	Mailed questionnaire	Invasive and DCIS	175	Any HT	Past use (5 yrs) (>5 yrs) Current (5 yrs) (>5 yrs)	RR=0.91(0.61-1.34) RR=0.29(0.07-1.18) RR=0.94(0.41-2.16) RR=1.35(0.77-2.36)	Age, BMI; waist-to-hip ratio; parity; family breast cancer hx; type of menopause, ETOH, and age at menarche, first birth, menopause.
Henrich et al. (1998) [25]	CC n=654	Postmenopausal Ages 45+	Screening mammogram questionnaire	Invasive and in situ	32	E or E+P	Use at age 45 years or older	OR=1.08(0.42-2.77)	Matched on age, mammography screening. Adjusted by family breast cancer hx, breast symptoms, hx of breast biopsy or hysterectomy
Kerlikowske et al. (2003) [26]	PR n=374,465	Postmenopausal Ages 50-79	Screening mammogram questionnaire	Invasive and DCIS	583	E+P E	Duration (5yrs) Ever use	RR=1.41(1.24-1.60) RR=0.98(0.89-1.07)	Age, family breast cancer hx, exam year, interval between screening mammograms, mammography registry.
Longnecker et al. (1996) [27]	CC n=4,493	Pre- and postmenopausal Ages 40 or younger and ages 55-64	Home interview	Invasive and in situ	233	E	Ever use-A Ever use-K Current Past use Duration (<4yrs) Duration (4yrs)	OR=1.43(0.97-2.12) OR=1.60 (1.00-2.58) OR=1.65(1.10-2.46) OR= 1.45(0.92-2.28) OR=1.13(0.72-1.77) OR=2.00(1.34-3.00)	Age, socioeconomic status, mammography, benign breast disease, family breast cancer hx, BMI, parity, age at first birth, age at menopause, age at menarche
Lyytinen et al. (2006) [28]	PR n=110,984	Ages over 50	Finnish medical reimbursement register	Invasive and in situ	141	E (oral or transdermal)	Ever use-A Ever use-K Duration (<5yrs) Duration (5yrs)	OR=1.75(1.10-2.80) OR=1.47(0.82-2.63) SIR=1.20 (0.78-1.76) SIR=2.43 (1.66-3.42)	None.
Lyytinen et al. (2009) [10]	PR n=221,551	Ages over 50	Finnish medical reimbursement register	Invasive and in situ	404	E+P (oral or transdermal)	Duration (6 m-<3 y) Duration (3 y-<5 y) Duration (5 y-<10 y) Duration (10+ y)	SIR=0.70 (0.62-1.00) SIR=1.32 (0.98-1.73) SIR=1.87 (1.35-2.52) SIR=2.28 (1.46-3.39)	None.

Authors (yr) [reference]	Design/n	Population/n	Exposure assessment	Lesions included	In situ cases (n)	Exposure	Classification of hormone use	Measure of association (CI or p- value)	Adjustment/matching/ stratification
Phillips et al. (2009) [34]	CC n=4,276	Ages 20-74	In-person interviews	Invasive and DCIS	304 (post- meno- pausal)	Any HT	Ever use	OR=0.94 (0.66-1.32)	Age, race, offset term for sampling probabilities
Reeves et al. (2006) [29]	PR n=1,031,224	Postmenopausal Ages 50-64	Mailed questionnaire	Invasive and in situ (DCIS, LCIS, Other)	1,913 (DCIS, 1,443; LCIS, 86; other, 384)	Any HT	Past use -all in situ -DCIS -LCIS -other/unknown	RR=1.15 (1.01-1.31) RR=1.19 (1.03-1.38) RR=0.96 (0.45-2.07) RR=1.02 (0.77-1.37)	Age (stratified), geographical region, age at first birth, parity, years since menopause, deprivation index, BMI, family breast cancer hx; all participants had a routine mammo- graphy screening.
Reinier et al. (2007) [30]	PR N=61,844	Pre- and postmenopausal who received mammography	Screening mammogram questionnaire	Invasive and in situ	176 (post- meno- pausal)	Any post- menopausal HT	Current use -all in situ -DCIS -LCIS -other/unknown	RR=1.55 (1.40-1.72) RR=1.56 (1.38-1.75) RR=2.82 (1.72-4.63) RR=1.35 (1.07-1.70)	Age, family breast cancer hx, age at first birth, BMI, breast density
Ross et al. (2000) [16]	CC n=3,534	Postmenopausal Ages 55-72	Home interview	Invasive and in situ	186	Any HT E E+P E+P (continuous)	5 yrs of use 5 yrs of use 5 yrs of use 5 yrs of use	OR=1.36(1.15, 1.61) OR=1.41(1.18, 1.69) OR=1.10(0.76, 1.60) OR=1.14(0.69, 1.88)	Type of menopause, age at menopause, age at menarche, family breast cancer hx, benign breast disease, parity, age at first birth, OC use, body weight, ETOH
Schairer et al. (1994) [31]	PR n=49,017	Postmenopausal	Telephone interviews, mailed questionnaires	Invasive and in situ	154	E+P (sequential) E	5 yrs of use Ever use Duration (<5 y) Duration (5-9 y) Duration (10-14 y) Duration (15-19 y) Duration (20 y)	OR=1.07(0.64,1.79) RR=1.4(1.0-2.0) RR=1.1(0.7-2.0) RR=1.5(0.8-2.6) RR=2.1(1.2-3.7) RR=1.8(0.9-3.9) RR=2.0(0.9-4.5)	Age and education
Stanford et al. (1995) [32]	CC n=1,029	Ages 50-64	In-person interview	Invasive and in situ	87	E+P E	Ever use Duration (<2 yrs) Duration (2-3 yrs) Duration (4 yrs) Duration (1-3 m) Duration (4 m-2.9 y) Duration (3-4.9 y) Duration (5 y)	RR=2.3(1.3-3.9) RR=3.3(1.7-6.3) RR=3.9(1.5-9.7) RR=0.7(0.1-4.7) OR=1.8(0.5-6.9) OR=0.8(0.3-2.4) OR=1.3(0.4-5.0) OR=1.0(0.5-2.0)	Age, age at first birth, family breast cancer hx
						E+P	Duration (1-3 m) Duration (4 m-2.9 y)	OR=1.7(0.3-8.9) OR=1.7(0.8-3.6)	

Authors (yr) [reference]	Design/n	Population/n	Exposure assessment	Lesions included	In situ cases (n)	Exposure	Classification of hormone use	Measure of association (CI or p- value)	Adjustment/matching/ stratification
Trentham-Dietz et al. (2000) [4]	CC N=7,788	Ages 18-74 (postmenopausal women only in HRT analysis)	Telephone interview	Invasive and in situ (BCIS, LCIS, DCIS/ non- LCIS)	301 (total; 153 (post- meno- pausal?))	Postmeno- pausal E and/or P	Duration (3-4.9 y) Duration (5-7.9 y) Duration (8 y) BCIS Ever use Last use (<5 yrs) Last use (5-19 yrs) Last use (20 yrs) Duration (<2 yrs) Duration (2-4 yrs) Duration (5-9 yrs) Duration (10 yrs) LCIS Last use (<5 yrs) Last use (5 yrs) DCIS/non-LCIS Last use (<5 yrs) Last use (5 yrs)	OR=0.9(0.3-3.3) OR=2.3(0.6-8.1) OR=0.5(0.1-4.2) OR=1.9(1.3-2.7) OR=1.9(1.2-2.9) OR=1.7(1.0-3.0) OR=2.5(1.2-5.4) OR=2.4(1.5-1.9) OR=1.9(1.04-3.3) OR=1.6(0.8-3.3) OR=1.5(0.8-2.8) OR=1.63(0.7-3.9) OR=2.46(0.9-6.4) OR=2.03(1.2-3.3) OR=1.83(1.05-3.2)	Age, age at first birth, family breast cancer hx, age at menopause, education mammography

Abbreviations: CI: confidence interval; CC: case control; RCT: randomized controlled trial; PR: prospective; BCDDP: Breast cancer detection and prevention program; DCIS: ductal carcinoma in situ; LCIS, lobular carcinoma in situ; E: estrogen; P: progesterone; HT: hormone therapy; DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ; OR: odds ratio; HR: hazard ratio; RR: relative risk; SIR: standardized incidence ratio; A: all women; K: women with known age at menopause; OC: oral contraceptive; hx: history; ETOH: alcohol use; BMI: body mass index.