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EPIDEMIOLOGY

# Medication use trajectories of postmenopausal breast cancer survivors and matched cancer-free controls

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**Abstract** While adverse medical sequelae are associated with breast cancer therapies, information on breast cancer impact on medication use is limited. Therefore, we compared medication use before and after diagnosis of early stage breast cancer to medication use in matched, cancer-free controls. Of 68,132 Women's Health Initiative participants, 3726 were diagnosed with breast cancer and, after exclusions, in 1731 breast cancer cases, medication use before and >3 years after diagnosis (mean 5.3 ± 2.1 SD) was compared to use in 1731 cancer-free matched controls on similar inventory dates. The medication category number at follow-up inventory was the primary study outcome. Medication category use (*n*, mean, SD) was comparable at baseline and significantly increased at follow-up in both cases (2.48 ± 1.66 vs. 4.15 ± 2.13, baseline vs follow-up, respectively, $P < .0001$) and controls (2.44 ± 1.67 vs. 3.95 ± 2.13, respectively, $P < .0001$), with clinically marginal but statistically significant additional medication category use by cases (0.20 ± 2.40, $P < .0001$). Tamoxifen users used somewhat more selected medication categories at follow-up assessment (mean 3.40 ± 1.89 vs. 3.21 ± 1.99, respectively, $P = 0.05$), while aromatase inhibitor users used more medication categories (mean 4.85 ± 2.10 vs. 4.44 ± 1.94, respectively, $P = 0.02$). No increase in medication category was seen in cases who were not current endocrine therapy users. Breast cancer survivors having only a clinically marginal increase in medication use compared to cancer-free controls. These findings highlight the importance of incorporation of control populations in studies of cancer survivorship.

**Keywords** Breast cancer · Medication · Survivorship · Control group · Women's Health Initiative · Comorbidity

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## Introduction

For most women with localized breast cancer, the prognosis is favorable, with 2.9 m breast cancer survivors reported in the United States in 2012 [1]. As a result, there is a growing population experiencing the immediate and long-term sequelae of cancer therapy [2].

Adverse health outcomes associated with breast cancer and breast cancer therapy include anxiety and depression

[3] osteoporosis and fracture [4, 5], venous thromboembolism [6], menopausal symptoms and sexual dysfunction [7, 8], cataracts [9], cardiovascular disease and stroke [10–12], local or regional pain [13], neuropathy [14], pulmonary dysfunction [15], second malignancies [16] and, less commonly, thyroid dysfunction [17].

The well-documented adverse influence of breast cancer therapies on health outcomes appears discordant with recent reports indicating that severe non-cancer comorbidities, as quantified by the Charlson comorbidity index, are similar among breast cancer patients and cancer-free controls [18, 19]. In exploring this discordance, we postulated that potential adverse influences of cancer therapy on health outcomes were being prevented and/or treated by targeted medications such as bisphosphonates and statins. As a result, we hypothesized that medication use would substantially increase following a breast cancer diagnosis. However, to our review, reports of medication use after breast cancer are limited [20, 21] and no published study has comprehensively assessed medication use in breast cancer survivors before and after diagnosis and compared findings to that of a matched cancer-free population.

The large, well-characterized population of postmenopausal participants in the Women's Health Initiative (WHI) clinical trials with serial, medication inventory collection provides a unique opportunity to address the issue of medication use before and after breast cancer diagnosis in comparison to age-matched controls studied over a comparable interval.

## Methods

Details of the WHI clinical trial designs and adjudication procedures have been previously described [22]. Eligible were postmenopausal women among 50–79 years with estimated survival of $\geq$3 years and no prior breast cancer history. Women were recruited at 40 US Clinical Centers from 1993 to 1998. Participants could be randomized to one, two, or three clinical trials (one of two hormone therapy trials and trials of dietary modification and calcium and vitamin D supplementation). At baseline, participants completed questionnaires regarding demographic characteristics, smoking, lifestyle, and medical history. Height and weight were measured at baseline, and body mass index (BMI) was computed as weight divided by height squared (kg/m$^2$).

In-person medication inventories were obtained by review of participants' pill containers at baseline and at years 1, 3, 6, 9, prior to 2005, the original study end date. Information on dietary supplements, including multivitamins, was similarly collected. Participants who consented to participation in the WHI extension study (2005–2010) also provided information on medication and supplement use by mailed questionnaire during year 5 of the extension. All reported medications were matched to the master drug database (MDDB, Medi-Span, Indianapolis, IN). All protocols received Institutional Review Board approval from the WHI Clinical Centers and all participants provided written informed consent.

Information regarding health outcomes including cancers was collected semi-annually. Reported invasive breast cancers were initially verified by medical record and pathology report review at the local Clinical Centers by trained physician adjudicators [23] with final adjudication and coding for stage and tumor characteristics at the WHI Clinical Coordinating Center using Surveillance, Epidemiology, and End Results (SEER) criteria [24]. Information on endocrine adjuvant therapy use was available from the medication inventories. Information regarding other breast cancer therapy is currently limited to self-report from a mailed questionnaire returned by 872 of the breast cancer participants.

Breast cancer cases were selected based on the following criteria: no prior history of breast cancer or other invasive cancer (except non-melanoma skin cancer), locoregional stage, medication inventory done prior to breast cancer diagnosis and repeated $\geq$3 years following diagnosis, and available health status at time of second medication inventory. Women with triple-negative breast cancer and those with primary tumor >5 cm or with $\geq$10 positive lymph nodes were excluded due to higher risk of recurrence. Controls were selected based on the following criteria: no history of breast cancer or other invasive cancer (except non-melanoma skin cancer), medication inventory done during two points in time at an interval matching that of a case, and available health status at time of second medication inventory.

Each breast cancer case was matched with one control using the following criteria: age at initial medication inventory ($\pm$5 years), date of initial medication inventory ($\pm$3 years), number of medication categories at initial inventory (exact), number of years between initial and second medication assessment ($\pm$3 years), BMI ($\pm$5), current smoker at initial inventory (yes/no), and randomization assignment in the hormone therapy and dietary modification trials. As localized breast cancer commonly presents without symptoms, the medication inventory done closest in time prior to the breast cancer diagnosis was used for the pre-diagnosis inventory for cases. The 3-, 6-, 9-year medication inventory, or extension study inventory, whichever most closely approximated $\geq$3 years following breast cancer diagnosis, was used for the post-diagnosis inventory.

As of September 2013, 3726 of 68,132 participants had developed invasive breast cancer. Excluded from the

current analyses were triple-negative cases ($n = 230$), those with distant or unknown stage ($n = 88$), tumor size >5 cm or with ≥10 positive lymph nodes ($n = 248$). Of these, 1738 cases had a medication inventory prior to breast cancer diagnosis and a subsequent inventory at ≥1090 days after diagnosis. Four additional cases were excluded due to unknown BMI or smoking status, leaving 1734 cases. Of these, 1731 were able to be matched to controls and represent the final case number. For 981 of the 1731 case–control pairs, the post-diagnosis inventory was derived from the extension study inventory.

Based on prior reports of health-related consequences of breast cancer therapy, we prospectively identified 10 specific medication classes likely to increase disproportionately in breast cancer cases relative to controls (anti-hypertensives, anti-hyperlipidemics, cardiovascular, analgesics, anti-depressants, anti-anxiety agents, bisphosphonates, calcium and vitamin D, thyroid agents, and diabetes agents). The number of the "selected medication categories" utilized at baseline was used for case–control matching.

Change in the number of selected medication categories was the primary study outcome. The study hypothesis was that, based on established effects of breast cancer and related therapies, the number of the selected medicine categories (excluding endocrine adjuvant therapy) used by breast cancer survivors (cases) would be significantly greater than in matched, cancer-free controls.

## Statistical methods

We compared breast cancer cases and breast cancer-free controls with respect to several demographic and clinical characteristics at their randomization into the WHI clinical trials. Mean values and standard deviations were calculated for the numbers of medication categories and total numbers of medications in the pre-diagnosis and post-diagnosis inventories by each group. We separately calculated the proportions of breast cancer cases and controls with medications in the inventories that pertained to medication categories of interest in this study. Case–control differences in categorical variables were tested using conditional logistic regression models that stratified on each case–control matched pair. Paired t-tests were used to evaluate differences between the number of medication categories used by breast cancer cases prior to diagnosis versus ≥3 years following diagnosis. Paired t-tests were also used to evaluate differences between the number of medication categories used by breast cancer cases versus matched postmenopausal women. A sensitivity analysis also compared the total number of medications used by cases and controls during the same intervals. Analyses that stratified breast cancer cases on adjuvant endocrine therapy retained the case–control matching and utilized paired t-tests to test case–control differences in the number of selected medication categories used.

All analyses were conducted using SAS software, version 9.4 (SAS Institute Cary, NC). All statistical tests were two sided.

## Results

Baseline characteristics of breast cancer cases and controls are outlined in Table 1. Reflecting the matching criteria, the cases and controls were closely comparable in terms of age, smoking status, history of diabetes, cardiovascular disease, and fracture. Women with breast cancer were more likely to be White (88.8 vs. 82.8 %, $P < 0.001$, respectively) and had somewhat greater BMI than women without cancer. However, mean BMI was closely comparable in the two groups ($29.15 \pm 5.72$ vs. $29.11 \pm 5.39$, for breast cancer cases and controls, respectively, $P = 0.343$). As regular screening mammography and clinical breast exam were mandated in the clinical trials (annually in the two hormone therapy trials and bi-annually in the dietary modification trial), the characteristics of the breast cancers reflected those of a screened population. The cancers were 73 % node negative and 85 % estrogen receptor positive with a mean tumor size of $1.35 \pm 0.85$ cm (Table 2). Among the subset ($n = 872$) with self-reported treatment information, 74 % reported receiving radiation therapy, 71 % received endocrine adjuvant therapy, and 30 % received adjuvant chemotherapy, again reflecting the relatively favorable stage at diagnosis.

Also reflecting the matching criteria, the number of total and prospectively selected medication categories (categories judged to be potentially influenced by breast cancer diagnosis and therapy) used at baseline by women in the breast cancer and control groups was closely comparable (Table 3). The most common individual categories of medications used by women were also similar between breast cancer and control groups (Table 4). In descending order of frequency, they included analgesics, multivitamins, calcium/vitamin D, anti-hypertensives, and anti-hyperlipidemics. Compared to controls, women with breast cancer were more likely to have been users of estrogen plus progestin ($P < 0.001$) and were only slightly more likely than controls to have been users of unopposed estrogen ($P = 0.08$) at baseline before diagnosis. At the follow-up assessment, some breast cancer patients were receiving adjuvant endocrine therapy with 24.6 % using tamoxifen and 19.1 % using aromatase inhibitors. One control using tamoxifen was excluded from analyses that stratified on endocrine therapy. By study design, adjuvant endocrine therapy use is excluded from medication analyses.

**Table 1** Descriptive characteristics of participants at WHI randomization, by breast cancer status

| | Breast cancer case ($n = 1731$) | | Control ($n = 1731$) | | $P$ value |
|---|---|---|---|---|---|
| | $N$ | (%) | $N$ | (%) | |
| Age group at screening (10-year intervals) | | | | | |
| 50–59 | 595 | 34.4 | 569 | 32.9 | 0.10 |
| 60–69 | 836 | 48.3 | 871 | 50.3 | |
| 70–79 | 300 | 17.3 | 291 | 16.8 | |
| Race/ethnicity | | | | | |
| White | 1537 | 88.8 | 1434 | 82.8 | <0.001 |
| Black | 106 | 6.1 | 169 | 9.8 | |
| Hispanic | 40 | 2.3 | 58 | 3.4 | |
| American Indian | 3 | 0.2 | 6 | 0.3 | |
| Asian/Pacific Islander | 32 | 1.8 | 36 | 2.1 | |
| Unknown | 13 | 0.8 | 28 | 1.6 | |
| Years since menopause | | | | | |
| <5 years | 225 | 14.1 | 219 | 13.5 | 0.03 |
| 5–9 years | 346 | 21.6 | 301 | 18.5 | |
| 10–14 years | 343 | 21.4 | 342 | 21.0 | |
| ≥15 years | 687 | 42.9 | 765 | 47.0 | |
| Body mass index (kg/m$^2$), baseline (categories) | | | | | |
| <25 | 443 | 25.7 | 426 | 24.7 | 0.004 |
| 25–<30 | 596 | 34.5 | 668 | 38.8 | |
| ≥30 | 687 | 39.8 | 629 | 36.5 | |
| Smoking status | | | | | |
| Never | 846 | 49.3 | 872 | 50.8 | 0.13 |
| Past | 765 | 44.6 | 724 | 42.2 | |
| Current | 104 | 6.1 | 119 | 6.9 | |
| Treated diabetes (pills or shots) | | | | | |
| No | 1662 | 96.0 | 1654 | 95.6 | 0.49 |
| Yes | 69 | 4.0 | 77 | 4.4 | |
| History of high cholesterol requiring pills | | | | | |
| No | 1361 | 88.7 | 1322 | 86.4 | 0.008 |
| Yes | 174 | 11.3 | 208 | 13.6 | |
| Treated for hypertension or BP ≥ 140/90 mm Hg | | | | | |
| No | 1041 | 60.1 | 1094 | 63.2 | 0.04 |
| Yes | 690 | 39.9 | 637 | 36.8 | |
| History of MI | | | | | |
| No | 1702 | 98.3 | 1706 | 98.6 | 0.58 |
| Yes | 29 | 1.7 | 25 | 1.4 | |
| History of angina | | | | | |
| No | 1654 | 95.9 | 1654 | 95.9 | 1.000 |
| Yes | 70 | 4.1 | 70 | 4.1 | |
| History of CABG/PTCA | | | | | |
| No | 1697 | 99.0 | 1688 | 98.7 | 0.41 |
| Yes | 18 | 1.0 | 22 | 1.3 | |
| History of stroke | | | | | |
| No | 1718 | 99.2 | 1723 | 99.5 | 0.28 |
| Yes | 13 | 0.8 | 8 | 0.5 | |
| History of DVT or PE | | | | | |
| No | 1678 | 97.0 | 1679 | 97.0 | 1.00 |
| Yes | 52 | 3.0 | 52 | 3.0 | |

**Table 1** continued

| | Breast cancer case ($n = 1731$) | | Control ($n = 1731$) | | $P$ value |
|---|---|---|---|---|---|
| | $N$ | (%) | $N$ | (%) | |
| History of fracture age 55+ | | | | | |
| No | 1095 | 86.4 | 1091 | 85.0 | 0.40 |
| Yes | 173 | 13.6 | 192 | 15.0 | |
| First-degree female relative had breast cancer | | | | | |
| No | 1272 | 80.0 | 1376 | 86.4 | <0.0001 |
| Yes | 319 | 20.0 | 217 | 13.6 | |

$P$ values are from conditional logistic regression models

The number of the prospectively selected medication categories (judged likely to be influenced by breast cancer) used at baseline and after 5.3 years mean follow-up in the two groups is outlined in Table 3. Compared to baseline, the number of selected medication categories significantly increased at the follow-up assessment in both breast cancer cases (2.48 ± 1.66 vs. 4.15 ± 2.13, mean + SD for selected medication categories used at baseline and follow-up, respectively, $P < 0.0001$) and controls (2.44 ± 1.67 vs. 3.95 ± 2.1, respectively, $P < 0.0001$). With regard to the increase in number of medication categories over time, the difference between the breast cancer and control groups was clinically marginal but statistically significant (an increase of 0.20 ± 2.40 of a medication category increase, $P = 0.0005$).

The difference in the number of medication categories used, in the follow-up inventory minus baseline inventory for breast cancer cases minus controls is illustrated in Fig. 1. A similar pattern for some increase over time as age increases is seen with little difference between cases and controls.

In a sensitivity analysis, the total number of medication categories used by cases and controls was compared (Table 3). At baseline assessment, breast cancer cases used 4.09 ± 2.69 total medication categories, whereas controls used 3.88 ± 2.55 total categories; at follow-up, the number of total medication categories increased to 6.40 ± 3.21 and 5.86 ± 3.28, for cases and controls. There also was a modest but statistically significant increase in the number of total medication categories for the breast cancer cases at follow-up compared to controls (0.54 ± 3.83, $P < 0.0001$).

In terms of specific medication categories, at follow-up more breast cancer cases used anti-depressants (15.3 vs. 12.2 %, $P = 0.006$) and bisphosphonates and/or calcium/vitamin D (62.2 vs. 54.8 %, $P < 0.001$). Use of statins (32.4 vs. 36.0 %, $P = 0.02$), as well as use of both estrogen alone (0.1 vs. 1.5 %, $P < 0.001$) and especially use of estrogen plus progestin (0.3 vs. 11.3 %, $P < 0.001$) was lower in women in the breast cancer group. Use of the following medication categories did not differ between groups: anti-diabetic, cardiovascular, anti-anxiety, and narcotic and non-narcotic analgesics (Online Appendix).

When examined by adjuvant endocrine therapy use, among women with breast cancer, tamoxifen users were younger (70.3 ± 6.4 years, mean + SD) than both aromatase inhibitor users (74.9 ± 6.1 years) and breast cancer cases not on endocrine therapy (74.4 ± 7.0 years) ($P < 0.0001$). Tamoxifen users used somewhat more selected medication categories at follow-up assessment (mean 3.40 ± 1.89 vs. 3.21 ± 1.99, respectively, for selected medication category use, $P = 0.05$) compared to cancer-free controls (Table 4), while aromatase inhibitor users used more medication categories (mean 4.85 ± 2.10 vs. 4.44 ± 1.94, respectively, for selected medication category use, $P = 0.002$). No increase in medication category was seen in the 975 cases who were not current endocrine therapy users, a population which included 536 former tamoxifen or aromatase inhibitor users.

## Discussion

In postmenopausal women participating in the WHI clinical trials, the trajectory of medication use was that of significant increase over time in both breast cancer survivors and cancer-free controls, likely reflecting age-related comorbidities. The number of medication categories used by breast cancer cases on tamoxifen and on aromatase inhibitors was greater than in controls. Overall, breast cancer impact on medication use was limited with breast cancer survivors using less than one additional medication category compared to cancer-free controls.

While our primary study hypothesis was supported, in that a statistically significant increase in medication use was seen in the breast cancer survivors, the small increase was of marginal clinical significance. It is clear that a breast cancer diagnosis and associated therapies not uncommonly result in medical sequelae not shared by

**Table 2** Tumor characteristics of patients diagnosed with breast cancer

| | Breast cancer cases ($n = 1731$) | |
|---|---|---|
| | *n* | (%) |
| Histology | | |
| Ductal | 1148 | 66.3 |
| Lobular | 159 | 9.2 |
| Ductal and lobular | 237 | 13.7 |
| Tubular | 62 | 3.6 |
| Other | 125 | 7.2 |
| Morphology—grading | | |
| Well differentiated | 504 | 29.1 |
| Moderately differentiated | 693 | 40.0 |
| Poorly differentiated | 327 | 18.9 |
| Anaplastic | 28 | 1.6 |
| Unknown/not done | 179 | 10.3 |
| Tumor size (cm), mean (SD) | 1.35 ± 0.85 | |
| Lymph nodes positive | | |
| No | 1266 | 73.1 |
| Yes | 333 | 19.2 |
| Not examined | 132 | 7.6 |
| Summary stage (SEER) | | |
| Localized | 1383 | 79.9 |
| Regional | 348 | 20.1 |
| Estrogen receptor status | | |
| Positive | 1471 | 85.0 |
| Negative | 134 | 7.7 |
| Unknown/not done/missing | 123 | 7.1 |
| Progesterone receptor status | | |
| Positive | 1203 | 69.5 |
| Negative | 366 | 21.1 |
| Unknown/not done/missing | 147 | 8.5 |
| HER2/neu status | | |
| Positive | 206 | 11.9 |
| Negative | 894 | 51.6 |

Percentage less than 100 % reflects borderline or unknown status

women without a breast cancer history [25–28]. Nonetheless, overall quality of life in long-term breast cancer survivors remains quite favorable [7], consistent with our current finding of no substantial increase in medication use in breast cancer survivors. Thus, there remains the question of how breast cancer survivors, despite the documented adverse effects of cancer therapy, maintain a favorable quality of life without a substantial increase in medication use.

While some of the breast cancer therapy-associated sequelae have no truly effective therapy [26] or have potential therapies limited by cancer recurrence risk [8], a recent quality of life analysis [29] and associated commentary [30] regarding patient reported outcomes in the tamoxifen and exemestane trial (TEXT) and suppression of ovarian function trial (SOFT) trials affords a potential explanation. In these studies, while addition of tamoxifen or aromatase inhibitor to ovarian function inhibition resulted in considerable worsening of endocrine symptoms. However, serial measures of coping effort in these trials suggested that women were able to successfully adapt to the therapy-associated symptoms and maintain favorable quality of life [29]. Further studies are needed to better define the effect of patient coping strategies on quality of life.

While women on tamoxifen had some increase in medication category use and aromatase inhibitor users had a statistically significant increase in use, the absolute increase in both situations was modest. In addition, there was no difference in medication use comparing controls and breast cancer cases who were not current endocrine therapy users. Past tamoxifen or aromatase inhibitor use was common in those breast cancer cases, suggesting the increase in medication use in endocrine therapy users may dissipate over time.

There is emerging interest in the development of survivorship care plans and identification of unmet needs for breast cancer survivors. However, relatively few studies include cancer-free controls. In six recent reports in this area, four were cross-sectional [31–34] and two reported serial findings [35, 36] but none included a cancer-free control population. In this regard, two study authors (KP, RTC) reviewed published abstracts from a recent national Cancer Survivorship Symposium. Of 252 abstracts, only 4 compared findings in cancer survivors to cancer-free controls [37].

The current study findings highlight the importance of a control population in studies of breast cancer-related comorbidities and medication use. In older patients in particular, it can be difficult to differentiate the consequences of breast cancer therapy from the effects of aging. In this study, without the benefit of a matched control group, one might conclude that a breast cancer diagnosis would have substantial impact on a woman's health care as reflected in a need for use of nearly twice as many medication categories.

As medication use has been validated as a surrogate for comorbidity in patients with cancer [38], our results expand findings from studies which compared comorbidity burden between older breast cancer survivors and age-matched controls. Edwards and colleagues found that the prevalence of non-cancer comorbidities comprising the Charlson comorbidity index (CCI) was similar between older breast cancer patients (32.2 %) and cancer-free Medicare beneficiaries (31.8 %) [18]. Jordan and colleagues also

**Table 3** Medication category use by breast cancer status and assessment period

| Medication category | Baseline assessment* | Follow-up assessment* | Difference | Paired t-*t*est |
|---|---|---|---|---|
| Medication selected categories** | | | | |
| Breast cancer cases ($n = 1731$) | | | | |
| Selected Medication category ($n$), mean ± SD | 2.48 ± 1.66 (min = 0, max = 8) | 4.15 ± 2.13 (min = 0, max = 11) | 1.67 ± 1.88 | <.0001 |
| Controls ($n = 1731$) | | | | |
| Selected Medication category ($n$), mean ± SD | 2.44 ± 1.67 (min = 0, max = 10) | 3.95 ± 2.13 (min = 0, max = 11) | 1.51 ± 1.79 | <.0001 |
| Total medication categories | | | | |
| Breast cancer cases ($n = 1731$) | | | | |
| Medication category ($n$), mean ± SD | 4.09 ± 2.69 (min = 0, max = 15) | 6.40 ± 3.21 (min = 0, max = 17) | 2.31 ± 2.89 | <.0001 |
| Controls ($n = 1731$) | | | | |
| Medication category ($n$), mean ± SD | 3.88 ± 2.55 (min = 0, max = 16) | 5.86 ± 3.28 (min = 0, max = 19) | 1.98 ± 2.70 | <.0001 |

* Baseline assessment for breast cancer cases was before diagnosis, and follow-up assessment was ≥3 years after diagnosis. Baseline assessment for cancer-free controls was matched to cancer patient and follow-up assessment was ≥3 years later also matched to cases. Endocrine therapy (tamoxifen and aromatase inhibitor use) is excluded from all medication category analyses

** Selected medication classes contributing to count: non-insulin anti-diabetic group, insulin group, thyroid group, anti-anginal agents, beta blockers, calcium blockers, anti-arrhythmics, anti-hypertensive, diuretics, anti-anxiety agents, anti-depressants, analgesics—non-narcotic, analgesics—narcotic, analgesics—anti-inflammatory, bisphosphonates, calcium and/or vitamin D, and multivitamins with or without minerals

**Table 4** Medication category use at follow-up assessment for breast cancer cases and their matched controls, stratified by current endocrine treatment in cases

| | Breast cancer cases ($n = 1729$) | Controls ($n = 1729$) | $P$ value for paired $t$-test of case–control differences |
|---|---|---|---|
| | Current tamoxifen ($n = 425$) | Matched controls ($n = 425$) | |
| Selected medication categories*, mean ± SD | 3.40 ± 1.89 (min = 0, max = 10) | 3.21 ± 1.99 (min = 0, max = 10) | 0.05 |
| Total Medication categories (n), mean ± SD | 6.02 ± 3.02 (min = 1, max = 17) | 4.86 ± 3.14 (min = 0, max = 19) | <0.0001 |
| | Current aromatase inhibitor ($n = 331$) | Matched controls ($n = 331$) | |
| Selected medication categories*, mean ± SD | 4.85 ± 2.10 (min = 0, max = 10) | 4.44 ± 1.94 (min = 0, max = 9) | 0.002 |
| Total Medication categories ($n$), mean ± SD | 7.67 ± 2.99 (min = 1, max = 15) | 6.71 ± 3.15 (min = 0, max = 15) | <0.0001 |
| | No current endocrine therapy ($n = 975$) | Matched controls ($n = 975$) | |
| Selected medication categories*, mean ± SD | 4.23 ± 2.14 (min = 0, max = 11) | 4.11 ± 2.17 (min = 0, max = 11) | 0.12 |
| Total Medication categories ($n$), mean ± SD | 6.14 ± 3.25 (min = 0, max = 16) | 6.01 ± 3.29 (min = 0, max = 19) | 0.33 |

Follow-up assessment for breast cancer cases was ≥3 years after diagnosis. One control was matched to each case on age, baseline, and follow-up medication inventory dates, number of specific medication classes at baseline inventory, body mass index, and smoking

One breast cancer case with Fareston in the medication inventory and her matched control was excluded. One control with Tamoxifen in the medication inventory and her case was excluded

Sum of strata is more than total because two breast cancer cases had both Tamoxifen and AI in the inventory

* Selected medication classes contributing to count: non-insulin anti-diabetic group, insulin group, thyroid group, anti-anginal agents, beta blockers, calcium blockers, anti-arrhythmics, anti-hypertensive, diuretics, anti-anxiety agents, anti-depressants, analgesics—non-narcotic, analgesics—narcotic, analgesics—anti-inflammatory, bisphosphonates, calcium and/or vitamin D, and multivitamins with or without minerals

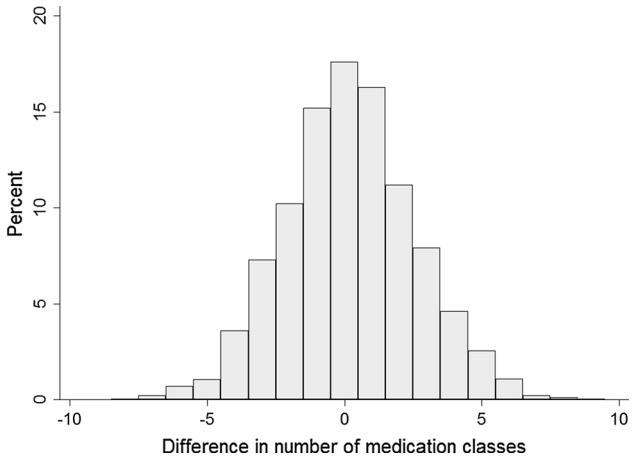


**Fig. 1** Distribution of differences in number of prospectively identified specific medication categories at follow-up inventory, breast cancer case minus matched control. Specific Medication categories = 10 specific medication categories judged likely to increase disproportionately in breast cancer cases relative to controls and included: anti-hypertensive, anti-hyperlipidemics, cardiovascular, analgesics, anti-depressants, anti-anxiety agents, bisphosphonates, calcium and vitamin D, thyroid agents, and diabetes agents

determined that 5-year breast cancer survivors aged 65 and older did not acquire incident comorbidities (as measured by a modified CCI) more often than age-matched cancer-free women (HR 1.0, 95 % CI 0.93–1.1) [19]. However, the CCI does not capture all potential sequelae of breast cancer therapy as, for example, anxiety, depression, osteoporosis, and pain are not CCI components. Thus, medication use may provide a more comprehensive assessment of health-related outcomes among breast cancer survivors.

Study strengths include the prospective cohort design, the large, diverse population of well-characterized women with breast cancer and controls matched on parameters including age and baseline medication category use, breast cancer cases verified by pathology report review, and information on serial medication inventories. Study limitations include incomplete information on cancer therapy. Our study examined medication use in the intermediate term following breast cancer diagnosis. As some breast cancer therapies may have long-term impact on health outcome, longer term evaluation of the same study question is needed. The findings reflect those in postmenopausal women volunteering for chronic disease prevention trials who are somewhat healthier than the general population [39]. Finally, despite the close matching of breast cancer cases and cancer-free controls, residual confounding could have influenced analyses.

In conclusion, reflecting age-related comorbidities, medication use significantly increases over time in both breast cancer survivors and matched cancer-free controls. Overall, despite known adverse medical sequelae of breast cancer therapy, breast cancer impact on medication use is limited, with breast cancer survivors having only a clinically marginal increase in use compared to similarly aged women without breast cancer. The findings are re-assuring and highlight the importance of incorporation of cancer-free control populations in studies of cancer survivorship.

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**Author contributions** KP and RTC wrote the analysis proposal and initial draft of the report. KP and RTC had full access to the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. RR undertook the statistical analysis. RTC, JEM, MLS, MSS, KCJ, JW, MJO, and RLP collected the data and obtained study funding. *Additional contributions*: We thank the Women's Health Initiative investigators, staff, and the trial participants for their outstanding dedication and commitment.

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**Compliance with ethical standards**

**Conflict of interest** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Chlebowski reported being a consultant for AstraZenea, Novartis, Amgen, Genomic Health and Novo Nordisk, receiving funding support from Amgen, and serving on the speaker's bureau for Novartis and Genentech.

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