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Adherence to Adjuvant Endocrine Therapy for Breast Cancer: Importance in Women with Low Income

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Abstract

There are wide disparities in breast cancer–specific survival by patient sociodemographic characteristics. Women of lower income, for instance, have higher relapse and death rates from breast cancer. One possible contributing factor for this disparity is low use of adjuvant endocrine therapy—an extremely efficacious therapy in women with early stage, hormone receptor positive breast cancer, the most common subtype of breast cancer. Alone, adjuvant endocrine therapy decreases breast cancer recurrence by 50% and death by 30%. Data suggest that low use of adjuvant endocrine therapy is a potentially important and modifiable risk factor for poor outcome in low-income breast cancer patients.

Introduction

In the past several decades, advances in breast cancer care have led to earlier diagnoses and better treatment, with mortality from breast cancer decreasing and the number of women surviving after the diagnosis of breast cancer growing.[1] Among the major contributions to the improvements in breast cancer care has been the use of adjuvant endocrine therapy. Well over half of breast cancers possess hormone receptors[2] and are, therefore, susceptible to an effect from endocrine therapies, making adjuvant endocrine therapy an extremely important component of treatment for breast cancer, with proportional benefits larger than those seen with chemotherapy (Table 1). Prescription adjuvant endocrine therapy for women with hormone receptor positive breast cancer reduces recurrence, prolongs survival, and is standard of care.[3,4] Five years of adjuvant endocrine therapy with tamoxifen in women with hormone receptor positive breast cancer, for instance, leads to decreases in annual events of 41% for recurrence and 34% for death from breast cancer.[3] Furthermore, recent evidence suggests that extending the duration of adjuvant endocrine therapy, by either continuing tamoxifen to 10 years[5,6] or changing to an aromatase inhibitor for an additional 2–5 years after 5 years of tamoxifen,[7] yields even lower breast cancer recurrence rates.

Despite these advances, multiple studies using individual and area-based socioeconomic measures have consistently shown that low socioeconomic status (SES) is a risk factor for worse breast cancer survival, regardless of the tumor's hormone receptor status.[8–24] The reasons for this disparity are not fully understood. Possible explanations include differences in where patients live and where they receive care,[25,26] access to early diagnosis and screening,[27] stage at diagnosis,[28] tumor biology,[9,14,28–31] and access to optimal treatment.[14,31–34] Low use of adjuvant endocrine therapy is a problem across socioeconomic groups, with rates of discontinuation in clinical trials ranging from 23% to 40% over the prescribed time period.[35–37] Though not pertinent to outcome among women with ER-negative breast cancer, because ER-positive breast cancers are more common in general, we believe that lack of use and/or adherence to adjuvant endocrine therapy may account for some of the disparity in breast cancer outcome by SES. We therefore performed a review of the literature in order to explore issues pertinent to the association between use of adjuvant endocrine therapy and disparity in breast cancer outcomes.

Drug Adherence

Medication adherence is defined as the extent to which a patient's behavior, with respect to taking medication, corresponds with recommendations from a health care provider, and includes therapy initiation, persistence, and execution (typically defined as the medication/possession ratio or what percent of pills the person took over a prespecified time). Nonadherence to chronic oral medication has implications for overall health care and health outcomes. Nonadherence can contribute greatly to the variability observed in a drug's

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Table 1. Benefits of Adjuvant Systemic Therapies for Hormone Receptor Positive, Early Stage Breast Cancer

Therapy	*RR for 0–4 year breast cancer recurrence*	*RR for 5–10 year breast cancer recurrence*	*RR 10+ year breast cancer mortality*
Chemotherapies			
Any anthracycline-based chemotherapy (vs. no chemotherapy)[72]	0.69 (SE 0.04)	0.89 (SE 0.07)	0.92 (SE 0.11)
Taxane + anthracycline (vs. anthracycline alone)[72]	0.84 (SE 0.04)	0.85 (SE 0.07)[b]	0.82 (SE 0.07)[b]
Endocrine therapies			
Tamoxifen[73]	0.54 (SE 0.03)	0.68 (SE 0.06)	0.71 (0.05)
Aromatase inhibitors (vs. tamoxifen)[74]	0.82 (SE 0.08)[a]	0.83 (SE 0.10)[b]	1.02 (SE 0.13)[b]
Aromatase inhibitors after tamoxifen (vs. continuing tamoxifen[c])	0.92 (SE 0.11)[a]	0.85 (SE 0.27)[b]	0.65 (SE 0.34)[b]

[a]Years 2–4.
[b]Years 5+.
[c]Postmenopausal women only.
RR, recurrence and death rate ratio; SE, standard error.

therapeutic effect, with the clinician possibly incorrectly attributing a patient's worsening condition to an absence of drug activity when the patient is actually not taking the prescribed medication.[38] Suboptimal adherence can compromise the patient–provider relationship, as misconceptions about the effects of a therapy on the part of either the patient or the provider may lead to a breakdown in communication and negatively affect the patient's views about care.[39] Identification of those at risk for nonadherence, therefore, has the potential to improve patient care and improve outcome.

There are inconsistencies in the literature with regard to the influence of demographic factors (such as age, gender, and socioeconomic status) on adherence to oral medications, with some studies reporting no relationship and others showing a direct relationship between SES and medication adherence.[40] Longer duration of treatment, however, is associated with decreased adherence;[41,42] the highest risk of discontinuing chronic therapy is within the first year.[43–46] These general risk factors for nonadherence to oral medications are likely to apply to adjuvant endocrine therapy for breast cancer as well.

Nonadherence to adjuvant endocrine therapy approximates 20% within the first year and increases by 7%–10% with each subsequent year of therapy.[47,48] The reasons for nonadherence to adjuvant endocrine therapy are multifaceted. Side effects, or the fear thereof, are thought to be the main cause.[43,46,49,50] As is true of adherence to other chronic therapies, demographic factors are important; for adjuvant endocrine therapy, associations have been found between lower adherence rates and nonwhite ethnicity, married status, lower SES, lower education level, and extremes of age.[34,47,48,51,52] The influence of these demographic factors is probably multifactorial but mediated by health beliefs, such as the positive or negative belief in the prescribed medication or the perceived importance of health and/or their ability of modify it, health literacy, the relationship with and ability to communicate with health care providers, and other social and cultural factors.[43,53–58] Longer pill-refill intervals and lower cost are associated with better adherence to adjuvant endocrine therapies.[48,59,60] Current smoking and alcohol use, other medication use, and comorbidities also play roles.[61] With respect to interventions aimed to improve adherence to adjuvant endocrine therapy, however, provision of educational material and reminders does not seem to improve adherence.[62,63]

Here, we will expand on studies related to adjuvant endocrine therapy for breast cancer in low-income populations.

Use of Adjuvant Endocrine Therapy in Low SES Populations

Use of adjuvant endocrine therapy has been studied in Medicaid-insured women—who are, by definition, low income to qualify for Medicaid—in two studies. Using data from New Jersey's Medicaid or Pharmaceutical Assistance to the Aged and Disabled programs, Partridge and colleagues described nonadherence to tamoxifen as adjuvant breast cancer therapy between 1990 and 1996.[47] In this study of 2,378 women with a mean age of 75 years, only 77% had a medication possession ratio (MPR) of ≥80% during the first year of treatment and thus were considered adherent to treatment. By the fourth year of therapy, the overall adherence decreased to 50%. Another study used the North Carolina Central Cancer Registry and NC Medicaid claims identified 1,491 Medicaid-insured women with invasive, nonmetastatic breast cancer in 1998–2002 and data on prescribed endocrine therapy.[34] In this group only 70% of women who were eligible for adjuvant endocrine therapy filled initial prescriptions, 88% of which were for tamoxifen. Of those that filled initial prescriptions, adherence and persistence rates were low. Within the first year of filling the first prescription, only 60% were adherent, defined as 80% or greater medication possession ratio, and 80% were persistent, defined as no gaps in fills ≥90 days. This rate is lower than that found in other studies, possibly because it specifically examined women of low SES.

Lack of ability to pay for prescriptions and/or high prescription costs are associated with higher nonadherence rates. Copayment amount, for instance, was found to be associated with endocrine therapy use in a retrospective cohort study of patients filling 90-day prescriptions through Medco Health Solutions, a large pharmacy benefits manager in the United States, between 2007 and 2008.[59] Nonpersistence was based on insurance claims data and defined as a gap of more than 45 days without prescription refill. Regardless of age, higher copayment

was significantly associated with nonadherence. Among women who were pre-Medicare (<age 63 years; $n=8,110$), nonpersistence rates were 20.4% with copay $0.00–$29.99 (reference group), compared with 20.8% with copay $30.00–$89.99 (odds ratio [OR] 0.93, 95% confidence interval [CI] 0.81–1.06) and 22.7% with copay $90 or greater (OR 0.82, 95% CI 0.72–0.94). Among women with Medicare (age 63 and older; n=14,050), nonpersistence rates were 22% with copay $0.00–$29.99 (reference group), compared with 27.5% with copay $30.00–$89.99 (OR 0.69, 95% CI 0.52–0.75) and 26.8% with copay $90 or greater (OR 0.7, 95% CI 0.0.65–0.80). In this study, income level did not predict nonpersistence, but all patients received some form of prescription coverage and a 90-day supply, so data may not be representative of the low income population in general. Another German retrospective analysis studied adjuvant endocrine therapy discontinuation, defined as 90 days without a prescription refill or alternative endocrine therapy (aromatase inhibitor) in breast cancer patients prescribed tamoxifen prior to switching to a rebate pharmaceutical program.[60] Of the 3,620 patients in the cohort, 1,712 (47.3%) converted to a rebate product. Within 3 years of follow-up, the discontinuation rates increased to 51.5% for switched patients and 46.3% for patients who did not switch ($p<0.01$). Thus, in this population, the rebate plan had negative impact on adherence to adjuvant endocrine therapy.

Contrary to this finding are study results analyzing adherence before and after aromatase inhibitors became generic in the United States. Using a deidentified pharmacy and claims database and studying adherence among 5511 women over age 50, investigators found that use of generic versus brand-name drugs was associated with greater adherence (OR 1.53, 95% CI 1.22–1.99) and lower discontinuation rates (hazard ratio [HR] 0.69, 95% CI 0.57–0.84).[64] The median monthly cost for brand-name aromatase inhibitor was $33.30 and for generic was $9.04. This group subsequently studied the association of household net worth and adherence.[65] The relationship was linear, such that women with higher household net worth were more likely to be adherent (OR 1.29, 95% CI 1.15–1.43, for medium and OR 1.59, 95% CI 1.36–1.84, for high, compared with low household net worth) and less likely to discontinue (HR 0.82, 95% CI 0.76–0.90, for medium and 0.67, 95% CI 0.59–0.75, for high, compared with low household net worth) endocrine therapy. Economic factors, therefore, should be considered in studies of adherence to adjuvant endocrine therapy for breast cancer.

Another large study of 662,117 women in the National Cancer Database who were diagnosed with breast cancer from 1998 to 2005, examined differences in care when patients were stratified by insurance type.[66] In multivariate analysis, compared with those who had private insurance, receipt of adjuvant endocrine therapy was less likely in those with no insurance (OR 0.85, 95% CI 0.80–0.91), Medicaid (OR 0.89, 95% CI 0.85–0.94), Medicare and age 64 or lower (OR 0.85, 95% CI 0.84–0.94), and unknown status (OR 0.83, 95% CI 0.72–0.97). In this study, black race also predicted lower rate of endocrine therapy use compared with white race (OR 0.91, 95% CI 0.88–0.94). There was a trend for lower endocrine therapy use in lower SES groups, by median income in zip code of residence. This suggests that being poor and/or disabled is a risk factor for not receiving endocrine therapy.

An Australian study of 1684 breast cancer patients additionally addressed the role of education, which correlates directly with SES, in endocrine therapy receipt through questionnaires concerning patients' receipt of therapy, level of formal education, and knowledge about their own tumor's hormone receptor status. [67] Lower level of education was associated with lower level of knowledge regarding hormone receptor status of their tumor; for instance, women with no formal education or only finishing primary school had an odds ratio of 9.3 (95% CI 4.4 – 19.5) of not knowing their tumor's hormone receptor status. Correct knowledge of the tumor's hormone receptor predicted receipt of endocrine therapy (OR 1.00, 95% CI 1.4–2.9). Long-term adherence to endocrine therapy once received was not addressed. Further investigation into this relationship could highlight an important and potentially addressable risk factor for endocrine therapy use.

From a statewide survey of women age 18 years and older, newly diagnosed with breast cancer, and enrolled in the California Breast and Cervical Cancer Treatment Program (BCCTP), there is information about patient–physician communication and adherence to adjuvant endocrine therapy.[55] The BCCTP is funded in part by Medicaid and the state of California to provide treatment for breast and cervical cancer for un- and under-insured low income women (less than or equal to 200% federal poverty level). From the 921 survey participants, there were 303 women with stage 1–3 breast cancer who had initiated endocrine therapy. This study's measure of adherence was the self-reported use of endocrine therapy at 36 months after diagnosis, which was relatively high at 88%. In their multivariate analysis of the survey data, barriers to adherence included having no health insurance ($p=0.001$), experiencing side effects ($p=0.003$), lack of coexisting medical diagnoses ($p=0.03$), and lower scores of patient-centered communication ($p=0.006$), by the Consumer Assessment of Healthcare Providers and Systems and patients' self-efficacy in patient–physician interactions. These authors concluded that measures to improve patient–provider communication might improve adherence and, thereby, improve outcomes in low-income populations.

Impact of Nonadherence to Adjuvant Endocrine Therapy on Risk of Breast Cancer Relapse and Death

Until recently, the only data to support the idea that adherence to adjuvant endocrine therapy was important for survival was indirectly derived from clinical trials. Data from the Early Breast Cancer Trialists' Collaborative Group showed that women who complete 5 years of tamoxifen had a significantly lower risk of breast cancer recurrence and mortality than women who completed 1–2 years.[3] With 15 years of follow-up, compared with placebo, the ratio of annual event rates for recurrence and death from breast cancer in women with hormone receptor positive disease who took 5 years of adjuvant tamoxifen were 0.59 (standard error [SE] 0.03) and 0.69 (SE 0.04), respectively, translating to a 15 year gain of 11.8% for recurrence and 9.2% for breast cancer mortality. These rates were statistically better than for only 1–2 years of therapy; for 5 versus 1–2 years of therapy, the ratio of annual events was 0.82 (SE 0.03) and 0.92 (SE 0.04), respectively. This emphasized the importance of completing 5 years of daily oral medication, even though it provided only indirect information about actual adherence.

In the past several years, the association of adherence and outcome in terms of survival has been confirmed in epidemiologic studies using prescription fill information. The first of these was a retrospective cohort of 1,633 women with incident breast cancer between 1993 and 2002 in which 2,080 (79%) women were prescribed adjuvant tamoxifen for a median 2.42 years (interquartile range 1.04–4.89 years).[68] The median adherence to tamoxifen was 93% (interquartile range 84%–100%). Decreased duration of tamoxifen and lower adherence to tamoxifen were both significantly associated with reduced survival from breast cancer. Similarly, a restrospective study of 1,962 women in the Netherlands found decreased adherence during the first year of tamoxifen to be associated with a lower breast cancer event free time, when median adherence was 93%.[69] When dichotomized to above and below 90% adherence, and with adjustment for tumor size, nodal status, and diagnostic year, they identified a HR of 0.67 (95% CI 0.48–0.93; $p = 0.016$). Hershman and colleagues investigated the impact of early discontinuation of either tamoxifen or aromatase inhibitors (AIs) in 8,769 women in the Kaiser Permanente health system in Northern California.[70] Among women with stage 1–3 breast cancer diagnosed between 1997 and 2007, 31% prematurely discontinued therapy and only 49% completed the full duration of therapy. Of the women who did complete therapy, only 72% did not have gaps in therapy. The estimated 10-year survival was 80.7% for those who continued therapy and 73.6% for those who discontinued early ($p < 0.001$). Of those who continued, 10-year survival was 81.7% and 77.8% for women who did and did not adhere to endocrine therapy, respectively ($p < 0.001$). In multivariate analysis, in addition to use of endocrine therapy, higher SES predicted better survival. Women in the highest quintile of income had a HR of mortality of 0.77 (95% CI 0.61–0.98) compared with the lowest quintile. The interaction between endocrine therapy use and SES was not explored.

At the same time, not all studies have found poor adherence to correlate with cancer recurrence or decreased survival. A cohort study of 857 women with breast cancer from 1998 to 2002 in North Carolina did not find an association between adherence, evaluated by MPR, and cancer-related death or recurrence.[71] The mean MPR in this study was 77% during the first year, and had decreased to 58% by the fifth year of treatment. This low average may explain the lack of association between adherence and outcome. Additionally, this was a study of Medicaid patients, who are by definition of low SES and at risk for worse breast cancer outcomes, which could mask any effect of adherence on outcome.

Conclusions

Given the known association between SES and breast cancer outcome, and the growing data showing worse outcomes with adjuvant endocrine therapy nonadherence, it follows that improving adherence to adjuvant endocrine therapy for breast cancer in this population will improve outcome. If low-income women are not prescribed or are under-accessing this effective therapy, then educational and health systems interventions, interventions to improve patient–provider communication, and attention to those at risk in order to design interventions may be needed to improve care quality and promote optimal cancer outcomes.

Low-income women may face barriers to filling monthly prescriptions such as transportation difficulties or Medicaid plans that require co-payment, as well as lower education levels. States are decreasing the amount of coverage for Medicaid and many states are planning to increase copayment for prescription medications. The extent to which such changes will adversely affect medication adherence is unexplored. Cost-effective interventions focused on patient education are an additional area for further investigation.

Author Disclosure Statement

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References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71–96.
2. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst 2000;92:550.
3. Abe O, Abe R, Enomoto K, et al. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 2005;365:1687.
4. Carlson RW, Brown E, Burstein HJ, et al. NCCN task force report: Adjuvant therapy for breast cancer. J Natl Compr Canc Netw 2006;4:S1–S26.
5. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381:805–816.
6. Gray RG, Rea D, Handley K, et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. J Clin Oncol 2013;31(Suppl):Abstract 5.
7. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349:1793.
8. Ayanian JZ, Guadagnoli E. Variations in breast cancer treatment by patient and provider characteristics. Breast Cancer Res Treat 1996;40:65.
9. Carnon AG, Ssemwogerere A, Lamont DW, et al. Relation between socioeconomic deprivation and pathological prognostic factors in women with breast cancer. BMJ 1994;309:1054.
10. Schrijvers CT, Mackenbach JP, Lutz JM, et al. Deprivation, stage at diagnosis and cancer survival. Int J Cancer 1995; 63:324–329.
11. Stavraky KM, Skillings JR, Stitt LW, et al. The effect of socioeconomic status on the long-term outcome of cancer. J Clin Epidemiol 1996;49:1155–1160.
12. Kogevinas M, Porta M. Socioeconomic differences in cancer survival: A review of the evidence. In: Kogevinas M, Pearce N, Susser M, et al., eds. Social inequalities in cancer survival. Lyon: Internation Agency for Research on Cancer, 1998:177–206.
13. Bradley CJ, Given CW, Roberts C. Disparities in cancer diagnosis and survival. Cancer 2001;91:178.

14. Thomson CS, Hole DJ, Twelves CJ, et al. Prognostic factors in women with breast cancer: Distribution by socioeconomic status and effect on differences in survival. J Epidemiol Community Health 2001;55:308–315.
15. Polednak AP. Survival of breast cancer patients in Connecticut in relation to socioeconomic and health care access indicators. J Urban Health 2002;79:211–218.
16. Kaffashian F, Godward S, Davies T, et al. Socioeconomic effects on breast cancer survival: Proportion attributable to stage and morphology. Br J Cancer 2003;89:1693–1696.
17. Lagerlund M, Bellocco R, Karlsson P, et al. Socio-economic factors and breast cancer survival–A population-based cohort study (Sweden). Cancer Causes Control 2005;16:419–430.
18. Rutqvist LE, Bern A. Socioeconomic gradients in clinical stage at presentation and survival among breast cancer patients in the Stockholm area 1977–1997. Int J Cancer 2006; 119:1433–1439.
19. Bouchardy C, Verkooijen HM, Fioretta G. Social class is an important and independent prognostic factor of breast cancer mortality. Int J Cancer 2006;119:1145–1151.
20. Yabroff KR, Gordis L. Does stage at diagnosis influence the observed relationship between socioeconomic status and breast cancer incidence, case-fatality, and mortality? Soc Sci Med 2003;57:2265–2279.
21. Ansell D, Whitman S, Lipton R, et al. Race, income, and survival from breast cancer at two public hospitals. Cancer 1993;72:2974–2978.
22. Bassett MT, Krieger N. Social class and black-white differences in breast cancer survival. Am J Public Health 1986; 76:1400.
23. Sprague BL, Trentham-Dietz A, Gangnon RE, et al. Socioeconomic status and survival after an invasive breast cancer diagnosis. Cancer 2011;117:1542–1551.
24. Bauer KR, Brown M, Cress RD, et al. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: A population-based study from the California cancer Registry. Cancer 2007;109: 1721–1728.
25. Twelves CJ, Thomson CS, Gould A, et al. Variation in the survival of women with breast cancer in Scotland. The Scottish Breast Cancer Focus Group and The Scottish Cancer Therapy Network. Br J Cancer 1998;78:566–571.
26. Pollock AM, Vickers N. Deprivation and emergency admissions for cancers of colorectum, lung, and breast in southeast England: Ecological study. BMJ 1998;317:245–252.
27. Sprague BL, Trentham-Dietz A, Burnside ES. Socioeconomic disparities in the decline in invasive breast cancer incidence. Breast Cancer Res Treat 2010;122:873–878.
28. Macleod U, Ross S, Gillis C, et al. Socio-economic deprivation and stage of disease at presentation in women with breast cancer. Ann Oncol 2000;11:105–107.
29. Gordon NH. Association of education and income with estrogen receptor status in primary breast cancer. Am J Epidemiol 1995;142:796–803.
30. Gordon NH, Crowe JP, Brumberg DJ, et al. Socioeconomic factors and race in breast cancer recurrence and survival. Am J Epidemiol 1992;135:609–618.
31. Taylor A, Cheng KK. Social deprivation and breast cancer. J Public Health Med 200325:228–233.
32. Norredam M, Groenvold M, Petersen JH, et al. Effect of social class on tumour size at diagnosis and surgical treatment in Danish women with breast cancer. Soc Sci Med 1998;47:1659–1663.
33. Kimmick G, Camacho F, Foley KL, et al. Racial differences in patterns of care among Medicaid-enrolled breast cancer patients. J Oncol Pract 2006;2:205.
34. Kimmick G, Anderson R, Camacho F, et al. Adjuvant hormonal therapy use among insured, low-income women with breast cancer. J Clin Oncol 2009;27:3445–3451.
35. Fisher B, Costantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors [Prior annotation incorrect]. New Engl J Med 1989;320:479–484.
36. Controlled trial of tamoxifen as single adjuvant agent in management of early breast cancer. Analysis at six years by Nolvadex Adjuvant Trial Organisation. Lancet 1985;1:836.
37. Schumacher M, Bastert G, Bojar H, et al. Randomized 2×2 trial evaluating hormonal treatment and the duration of chemotherapy in node-positive breast cancer patients. German Breast Cancer Study Group. J Clin Oncol 1994;12: 2086–2093.
38. Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid-lowering medications: A cross-national study. JAMA 279:1458–1462.
39. Waterhouse DM, Calzone KA, Mele C, et al. Adherence to oral tamoxifen: A comparison of patient self-report, pill counts, and microelectronic monitoring. J Clin Oncol 1993; 11:1189–1197.
40. Horne R. Adherence to medication: A review of existing research. In: Myers LB, Midance K, ed. Adherence to treatment in medical conditions. Amsterdam: Hardwood Academic Publishers, 1998:285–310.
41. Pratt RJ, Robinson N, Loveday HP, et al. Adherence to antiretroviral therapy: Appropriate use of self-reporting in clinical practice. HIV Clin Trials 2001;2:146–159.
42. Bartlett JA. Addressing the challenges of adherence. J Acquir Immune Defic Syndr 2002;29:S2–S10.
43. Fink AK, Gurwitz J, Rakowski W, et al. Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor-positive breast cancer. J Clin Oncol 2004;22:3309.
44. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: Clinical applications. JAMA 2002;288:2880–2283.
45. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002;288:462–467.
46. Demissie S, Silliman RA, Lash TL. Adjuvant tamoxifen: Predictors of use, side effects, and discontinuation in older women. J Clin Oncol 2001;19:322.
47. Partridge AH, Wang PS, Winer EP, et al. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol 2003;21:602–606.
48. Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol 2010;28:4120–4128.
49. Hadji P, Jackisch C, Bolten W, et al. COMPliance and arthralgia in clinical therapy: The COMPACT trial, assessing the incidence of arthralgia, and compliance within the first year of adjuvant anastrozole therapy. Ann Oncol 2014;25:372–377.
50. Kyvernitakis I, Ziller V, Hars O, et al. Prevalence of menopausal symptoms and their influence on adherence in women with breast cancer. Climacteric 2013;17:252–259.
51. Owusu C, Buist DS, Field TS, et al. Predictors of tamoxifen discontinuation among older women with estrogen receptor-positive breast cancer. J Clin Oncol 2008;26:549–555.

52. Atkins L, Fallowfield L. Intentional and non-intentional non-adherence to medication amongst breast cancer patients. Eur J Cancer 2006;42:2271–2276.
53. Lash TL, Fox MP, Westrup JL, et al. Adherence to tamoxifen over the five-year course. Breast Cancer Res Treat, 2006;99:215–220.
54. Kahn KL, Schneider EC, Malin JL, et al. Patient centered experiences in breast cancer: Predicting long-term adherence to tamoxifen use. Med Care 2007;45:431–439.
55. Liu Y, Malin JL, Diamant AL, et al. Adherence to adjuvant hormone therapy in low-income women with breast cancer: The role of provider-patient communication. Breast Cancer Res Treat 2013;137:829–836.
56. Jacob Arriola KR, Mason TA, Bannon KA, et al. Modifiable risk factors for adherence to adjuvant endocrine therapy among breast cancer patients. Patient Educ Couns 2014; 95:98–103.
57. Kostev K, Waehlert L, Jockwig A, et al. Physicians' influence on breast cancer patient compliance. Ger Med Sci 2014;12:Doc03.
58. Hadji P. Improving compliance and persistence to adjuvant tamoxifen and aromatase inhibitor therapy. Crit Rev Oncol Hematol 2010;73:156–166.
59. Neugut AI, Subar M, Wilde ET, et al. Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. J Clin Oncol 2011;29:2534–2542.
60. Kostev K, May U, Hog D, et al. Adherence in tamoxifen therapy after conversion to a rebate pharmaceutical in breast cancer patients in Germany. Int J Clin Pharmacol Ther 2013;51:969–975.
61. Lin JH, Zhang SM, Manson JE. Predicting adherence to tamoxifen for breast cancer adjuvant therapy and prevention. Cancer Prev Res (Phila) 2011;4:1360–1365.
62. Hadji P, Blettner M, Harbeck N, et al. The Patient's Anastrozole Compliance to Therapy (PACT) program: A randomized, in-practice study on the impact of a standardized information program on persistence and compliance to adjuvant endocrine therapy in postmenopausal women with early breast cancer. Ann Oncol 2013;24:1505–1512.
63. Ziller V, Kyvernitakis I, Knoll D, et al. Influence of a patient information program on adherence and persistence with an aromatase inhibitor in breast cancer treatment–the COMPAS study. BMC Cancer 2013;13:407.
64. Hershman DL, Tsui J, Meyer J, et al. The change from brand-name to generic aromatase inhibitors and hormone therapy adherence for early-stage breast cancer. J Natl Cancer Inst 2014;106.
65. Hershman DL, Tsui J, Wright JD, et al. Household net worth, racial disparities, and hormonal therapy adherence among women with early-stage breast cancer. J Clin Oncol 2015;33:1053–1059.
66. Freedman RA, Virgo KS, He Y, et al. The association of race/ethnicity, insurance status, and socioeconomic factors with breast cancer care. Cancer 2011;117:180–189.
67. Bell RJ, Lijovic M, Fradkin P, et al. Lack of knowledge of hormone receptor status and use of endocrine therapy in invasive breast cancer. J Womens Health (Larchmt) 2009; 18:1975–1980.
68. McCowan C, Shearer J, Donnan PT, et al. Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. Br J Cancer 2008; 99:1763–1768.
69. Dezentje VO, van Blijderveen NJ, Gelderblom H, et al. Effect of concomitant CYP2D6 inhibitor use and tamoxifen adherence on breast cancer recurrence in early-stage breast cancer. J Clin Oncol 2010;28:2423–2429.
70. Hershman DL, Shao T, Kushi LH, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat 2011;126:529–537.
71. Weaver KE, Camacho F, Hwang W, et al. Adherence to adjuvant hormonal therapy and its relationship to breast cancer recurrence and survival among low-income women. Am J Clin Oncol 2013;36:181–187.
72. Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 2012;379:432–444.
73. Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378:771–784.
74. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol 2010;28:509–518.

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