Clinicopathological factors predicting early and late distant recurrence in estrogen receptor-positive, HER2-negative breast cancer

Hiroko Yamashita[1*], Akiko Ogiya[2], Tadahiko Shien[3], Yoshiya Horimoto[4], Norikazu Masuda[5], Touko Inao[6], Tomofumi Osako[7], Masato Takahashi[8], Yumi Endo[9], Mitsuchika Hosoda[1], Naoko Ishida[1], Rie Horii[10], Kieko Yamazaki[2], Yuichiro Miyoshi[3], Hiroyuki Yasojima[5], Nobumoto Tomioka[8]; Collaborative Study Group of Scientific Research of the Japanese Breast Cancer Society

[1] Breast Surgery, Hokkaido University Hospital, Sapporo, Japan

[2] Breast Surgical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

[3] Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan

[4] Department of Breast Oncology, Juntendo University School of Medicine, Tokyo, Japan

[5] Department of Surgery, Breast oncology, NHO Osaka National Hospital, Osaka, Japan

[6] Department of Breast & Endocrine Surgery, Graduate School of Medical Science Kumamoto University, Kumamoto, Japan

[7] Department of Breast and Endocrine Surgery, Kumamoto City Hospital, Kumamoto, Japan†

†Present address: Kumamoto Shinto General Hospital, Kumamoto, Japan

[8] Department of Breast Surgery, NHO Hokkaido Cancer Center, Sapporo, Japan

[9] Department of Oncology, Immunology and Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

[10] Division of Pathology, Cancer Institute of the Japanese Foundation for Cancer Research, Tokyo, Japan

***Corresponding author:** Hiroko Yamashita

Breast Surgery, Hokkaido University Hospital, Kita 14, Nishi 5, Kita-ku, Sapporo 060-8648, Japan

Tel: +81-11-706-7381, **Fax:** +81-11-706-7384

E-mail: hirokoy@huhp.hokudai.ac.jp

Key words: breast cancer, late recurrence, early recurrence, estrogen receptor-positive, HER2-negative

Abstract

Background: Most studies analyzing prognostic factors for late relapse have been performed in postmenopausal women who received tamoxifen or aromatase inhibitors as adjuvant endocrine therapy for estrogen receptor (ER)-positive breast cancer.

Methods: A total of 223 patients (108 premenopausal and 115 postmenopausal) with early distant recurrence and 149 patients (62 premenopausal and 87 postmenopausal) with late distant recurrence of ER-positive, HER2-negative breast cancer who were given their initial treatment between 2000 and 2004 were registered from nine institutions. For each late recurrence patient, approximately two matched control patients without relapse for more than ten years were selected. Clinicopathological factors and adjuvant therapies were compared among the three groups by menopausal status and age.

Results: Factors predicting early recurrence in premenopausal women were large tumor size, high lymph node category and high tumor grade, whereas predictors for late recurrence were large tumor size and high lymph node category. In postmenopausal women under 60 years of age, factors predicting early recurrence were bilateral breast cancer, large tumor size, high lymph node category, low PgR expression and high Ki67 labeling index (LI), while predictors for late recurrence were large tumor size and high lymph node category. On the other hand, in postmenopausal women aged 60 years or older, factors predicting early recurrence were bilateral breast cancer, large tumor size, high lymph node category, high tumor grade, low ER expression and high Ki67 LI, whereas predictors for late recurrence were high lymph node

category, low ER expression and short duration of adjuvant endocrine therapy.

Conclusion: Predictors of early and late distant recurrence might differ according to menopausal status and age.

Abbreviations

ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor type 2; Ki67 LI, Ki67 labeling index; IHC, immunohistochemistry

Introduction

Adjuvant therapies for early breast cancer have had a substantial beneficial effect on disease outcome [1-3]. Adjuvant chemotherapy has proven to be effective in reducing the risk of recurrence within the first 5 years after diagnosis [3]. However, women with estrogen receptor (ER)-positive breast cancer remain at particular risk of late recurrence which is defined as relapse more than 5 years after initial treatment [4]. Recent studies demonstrated that extended adjuvant endocrine therapy reduces late recurrence [5, 6]. Therefore, accurate and reliable estimates of the risk of recurrence after five years of endocrine therapy are necessary to enable appropriate decisions regarding extended endocrine therapy. It has been considered that the risk of long-term relapse is related to the number of positive lymph nodes and large size of invasive tumors [7]. Furthermore, multi-parameter molecular assays, including IHC4, OncotypeDX, EndoPredict, PAM50 and Breast Cancer Index, have been developed for predicting early and/or late distant recurrence [7], [8].

In addition to tumor biology, host factors, such as menopausal status, age or body mass index, and adjuvant therapies may influence disease prognosis [9]. Moreover, host factors may influence tumor biology. To date, most studies analyzing prognostic factors for early and late relapse have been performed in postmenopausal women, mainly using patients and samples in adjuvant aromatase inhibitor trials [10-13], in which patients received tamoxifen or aromatase inhibitors as adjuvant endocrine therapy. Kennecke and colleagues retrospectively analyzed risk of early [14] and late recurrence [15] among postmenopausal

women with ER-positive early breast cancer treated with adjuvant tamoxifen. However, prognostic factors for especially late relapse might differ between patients who received adjuvant tamoxifen and those who were treated with aromatase inhibitors. Furthermore, there are few studies on prognostic factors for early and late recurrence in premenopausal ER-positive breast cancer.

The present study was a multi-institutional joint study carried out as Scientific Research of the Japanese Breast Cancer Society. We retrospectively collected data from ER-positive, HER2-negative breast cancer patients with early and late distant relapse and patients who remained relapse-free for more than ten years. All patients were given their initial treatment between 2000 and 2004. Clinicopathological factors and adjuvant therapies were compared among patients with early and late distant recurrence and patients without recurrence by menopausal status and age.

Patients and methods

Patients and breast cancer samples

A total of 223 consecutive patients with early distant recurrence and 149 consecutive patients with late distant recurrence of ER-positive, HER2-negative breast cancer who had undergone breast surgery or neoadjuvant chemotherapy between January 2000 and December 2004 were registered from nine institutions, joining a multi-institutional joint study titled ‘Analysis on biological characteristics and factors predicting late recurrence in breast cancer’, carried out as Scientific Research of the Japanese Breast Cancer Society. Early recurrence was defined as relapse within 5 years, and late recurrence was defined as relapse more than 5 years after initial treatment. For each late recurrence patient, approximately two age-matched control patients without relapse for more than ten years were randomly selected using RAND in combination with Excel software at each institution. Clinicopathological factors and adjuvant therapies were compared among the three groups. The study protocol was approved by the institutional review board and conformed to the guidelines of the 1996 Declaration of Helsinki in all nine institutions.

Immunohistochemical evaluation of ER, PgR, HER2 and Ki67 expression

Expression of ER, progesterone receptor (PgR), HER2 and Ki67 was centrally assessed by immunohistochemistry (IHC). Primary antibodies included monoclonal mouse anti-human ERα antibody (1D5, DAKO, Glostrup, Denmark) at 1:100 dilution, monoclonal

mouse anti-human PgR antibody (636, DAKO) at 1:100 dilution and monoclonal mouse anti-human Ki67 antibody (MIB-1, DAKO) at 1:200 dilution. ER was considered positive if there was ≥ 1 % positive nuclear staining. The Ki67 labeling index (LI) was assessed as the percentage of tumor cells showing definite nuclear staining among >1,000 invasive tumor cells. Immunostaining of HER2 was evaluated using the HercepTest (DAKO). Tumors with a score of 2+ were tested for gene amplification by in situ hybridization (ISH). Tumors were considered HER2-positive if IHC staining was 3+ or ISH-positive. HER2-positive tumors were excluded from this study.

Statistical analysis

The chi-squared test and Student's *t*-test were used to compare clinicopathological characteristics and treatments among patients with early and late recurrence and without recurrence. The differences between expression levels of ER and PgR, and Ki67 LI corresponding to menopausal status and age were compared by one-way ANOVA followed by Scheffe's test.

Results

We collected data from a total of 223 women (108 premenopausal and 115 postmenopausal) with early distant recurrence, 149 women (62 premenopausal and 87 postmenopausal) with late distant recurrence and 321 women (150 premenopausal and 171 postmenopausal) without relapse for more than ten years with ER-positive, HER2-negative breast cancer.

Prognostic factors for early and late distant recurrence in premenopausal women

Premenopausal women with both early and late recurrence had larger clinical tumor size ($p < 0.0001$ and $p < 0.0001$, respectively) and higher clinical lymph node category ($p < 0.0001$ and $p < 0.0001$, respectively) than those without recurrence (Table 1). Tumor grade ($p = 0.0079$) was significantly higher in patients with early recurrence, but not in patients with late recurrence ($p = 0.18$), compared with those without recurrence. On the other hand, expression levels of ER and PgR, and Ki67 LI did not differ between premenopausal women with early and late recurrence and those without recurrence (Table 1).

Adjuvant treatment in premenopausal women

Among women with distant recurrent tumors, 64.8% with early recurrence and 66.1% with late recurrence received both endocrine therapy and chemotherapy, while among patients without recurrence, 50.0% received endocrine therapy alone and 36.0% received both

endocrine therapy and chemotherapy ($p < 0.0001$ and $p = 0.007$, respectively, Table 2). Among patients with early recurrence who received adjuvant or neoadjuvant chemotherapy, 26.9% received anthracyclines and 36.1% received both anthracyclines and taxanes. Similarly, 25.8% of women with late recurrence received anthracyclines and 35.5% received both anthracyclines and taxanes. In contrast, among patients without recurrence, 12.0% of women received anthracyclines and 16.7% received both anthracyclines and taxanes. Thus, more of the patients with early and late distant recurrence had received adjuvant or neoadjuvant chemotherapies, including anthracyclines and/or taxanes. Among patients who had received neoadjuvant chemotherapy, no tumors in patients with early or late recurrence achieved pathological complete response (pCR), whereas one patient without recurrence achieved pCR (Table 2).

Prognostic factors for early and late distant recurrence in postmenopausal women

Postmenopausal women with early and late recurrence had significantly more incidences of bilateral breast cancer ($p = 0.0001$ and $p < 0.0001$, respectively), larger tumor size ($p < 0.0001$ and $p = 0.0097$, respectively) and higher lymph node category ($p < 0.0001$ and $p = 0.0006$, respectively) than those of control patients (Table 3). Tumor grade ($p = 0.001$) and Ki67 LI ($p = 0.0006$) were significantly higher, and expression levels of PgR ($p = 0.005$) were significantly lower in patients with early recurrence, but not in patients with late recurrence, compared with controls (Table 3).

Adjuvant treatment in postmenopausal women

Of the patients with distant recurrence, 42.6% of women with early recurrence and 34.5% of women with late recurrence received both endocrine therapy and chemotherapy, whereas in patients without recurrence 64.9% received endocrine therapy alone and 25.1% received both endocrine therapy and chemotherapy ($p < 0.0001$ and $p = 0.033$, respectively, Table 4). Among patients with early recurrence who received adjuvant or neoadjuvant chemotherapy, 12.2% received anthracyclines and 37.4% received both anthracyclines and taxanes, whereas in patients with late recurrence 20.7% of women received anthracyclines and 14.9% received both anthracyclines and taxanes. In contrast, among patients without recurrence, 12.9% received anthracyclines and 9.9% received both anthracyclines and taxanes. Thus similar to the findings in premenopausal women, more of the patients with early recurrence had received adjuvant or neoadjuvant chemotherapies, including anthracyclines and/or taxanes.

Difference between two age groups (<60 years and ≥60 years) in postmenopausal women in terms of predicting early and late distant recurrence

Anderson and colleagues demonstrated the existence of early-onset (progressing before menopause) and late-onset (progressing after menopause) breast cancers [16], and we suggest that the mechanisms of development and estrogen-dependent growth of ER-positive

breast cancer might differ according to menopausal status [17, 18]. Although most cases of ER-positive breast cancer in postmenopausal women aged 60 years or older are likely to be late-onset, both early-onset and late-onset breast cancers are included in postmenopausal breast cancer diagnosed under 60 years of age. Therefore, we next analyzed postmenopausal patients in the two age groups (<60 years and ≥60 years) separately. In both age groups, women with early recurrence had significantly more incidences of bilateral breast cancer (p = 0.0087 and p = 0.0035, respectively), larger tumor size (p = 0.0009 and p < 0.0001, respectively), higher clinical lymph node category (p < 0.0001 and p < 0.0001, respectively) and higher Ki67 LI (p = 0.039 and p = 0.0077, respectively) compared with women without recurrence (Tables 5 and 6). On the other hand, PgR expression was significantly lower (p = 0.019, Table 5) in patients with early recurrence under 60 years of age, but not in patients aged 60 years or older (Table 6), compared with controls. Tumor grade was significantly higher (p = 0.0017, Table 6) and expression levels of ER were significantly lower (p = 0.0037, Table 6) in patients with early recurrence aged 60 years or older, but not in patients under 60 years of age (Table 5), compared with controls.

In patients with late recurrence, women in both age groups had significantly higher lymph node category (p = 0.023 and p = 0.0062, respectively) compared with women without recurrence (Tables 5 and 6). However, although tumor size was significantly larger (p = 0.015, Table 5) in patients under 60 years of age, it was not in patients aged 60 years or older (p = 0.10, Table 6), compared with controls. ER expression was significantly lower (p = 0.0025,

Table 6) in patients aged 60 years or older, but not in patients under 60 years of age (p = 0.20, Table 5), compared with controls. There were fewer patients with late recurrence among those who had received adjuvant aromatase inhibitors for more than two, three or four years in the group of postmenopausal women aged 60 years or older (p = 0.042, p = 0.0095, and p = 0.0003, respectively, Table 6), but not in postmenopausal women under 60 years of age (Table 5).

Expression levels of ER and PgR, and Ki67 LI in patients without recurrence by menopausal status and age

We compared expression levels of ER and PgR and Ki67 LI in patients without recurrence among 4 groups defined by menopausal status and age (Fig. 1). ER expression was significantly higher in postmenopausal women compared with that in premenopausal women, although there was no difference between the two age groups of each menopausal status (<40 years and ≥40 years in premenopausal women and <60 years and ≥60 years in postmenopausal women, Fig. 1a). In contrast, PgR expression was significantly higher in premenopausal women compared with that in postmenopausal women (Fig. 1b). Ki67 LI in postmenopausal women aged 60 years or older was significantly lower than that in premenopausal women under 40 years of age (p = 0.006, Fig. 1c). Mean Ki67 LI was 9.1% in postmenopausal women aged 60 years or older and 19.7% in premenopausal women under 40 years of age. These results suggested that clinical roles or cutoffs of PgR and Ki67 in

ER-positive breast cancer might differ between pre- and postmenopausal women.

Discussion

We investigated clinicopathological factors and adjuvant therapies predicting early and late distant recurrence in ER-positive, HER2-negative breast cancer by menopausal status and age. Our results demonstrated that factors predicting early recurrence in premenopausal women were large tumor size, high lymph node category and high tumor grade, whereas predictors for late recurrence in premenopausal women were large tumor size and high lymph node category. In postmenopausal women under 60 years of age, factors predicting early recurrence were bilateral breast cancer, large tumor size, high lymph node category, low PgR expression and high Ki67 LI, while predictors for late recurrence were large tumor size and high lymph node category. On the other hand, in postmenopausal women aged 60 years or older, factors predicting early recurrence were bilateral breast cancer, large tumor size, high lymph node category, high tumor grade, low ER expression and high Ki67 LI, whereas predictors for late recurrence were high lymph node category, low ER expression and short duration of adjuvant endocrine therapy (especially, aromatase inhibitors).

To date, most studies analyzing predictive or prognostic factors in ER-positive breast cancer have been performed in postmenopausal women, mainly using patients and samples in adjuvant aromatase inhibitor trials [8]. In contrast, even the clinical roles of PgR and Ki67 have been little analyzed so far in premenopausal women, although testing of PgR and Ki67 by IHC has become routine [19, 20]. Recent studies indicated that plasma estradiol levels are related to expression levels of estrogen-responsive genes, including PgR, in ER-positive

breast cancer tissues in both pre- and postmenopausal women [21, 22]. We previously analyzed expression levels of estrogen-responsive genes and Ki67 in ER-positive, HER2-negative breast cancer, and suggested that clinical roles of PgR and Ki67 might differ between pre- and postmenopausal women [17]. In this study, we demonstrate that expression levels of ER and PgR, and Ki67 LI in patients without recurrence differ between pre- and postmenopausal women. It was recently reported that comparing ER-positive pre- and postmenopausal breast cancer by analyzing gene expression, copy number, methylation, somatic mutation and reverse-phase protein array data using TCGA and METABRIC databases revealed that ER-positive premenopausal tumors have distinct molecular characteristics compared to ER-positive postmenopausal tumors, particularly with respect to integrin/laminin and EGFR signaling [23]. We previously analyzed genetic and environmental factors, endogenous hormones and growth factors to identify risk factors for ER-positive breast cancer, and showed that risk factors differ between women of different menopausal status [18]. It has been demonstrated that there are bimodal pre- and postmenopausal breast cancer populations divided by Clemmesen's menopausal hook, and the etiology of pre- and postmenopausal breast cancer is therefore likely to be different [16, 24, 25]. Consequently, the mechanisms of development and estrogen-dependent growth of ER-positive breast cancer might differ according to menopausal status. We suggest that the definition of "luminal A-like" and "luminal B-like" in the St Gallen International Expert Consensus [19] would be appropriate for postmenopausal women, but whether the definition is suitable for

premenopausal ER-positive breast cancer should be determined by further study.

Our results further show that predictors of early and late distant recurrence differ between postmenopausal women under 60 years of age and postmenopausal women aged 60 years or older. Specifically, patients with both early and late recurrence had significantly lower ER expression compared with controls in postmenopausal women aged 60 years or older, but not in women under 60 years of age. This suggests that most ER-positive breast cancer might be late-onset in postmenopausal women aged 60 years or older. In contrast, both early-onset and late-onset breast cancers are included in postmenopausal breast cancer diagnosed under 60 years of age [16]. Thus, a biological difference between the two age groups (<60 years and ≥60 years) might become apparent in postmenopausal ER-positive breast cancer.

Previous studies reported that tumor grade and Ki67 expression were predictive only of recurrence in the first 5 years after diagnosis [7, 12]. The present study also indicated that tumor grade and/or Ki67 LI were predictors of early recurrence, but not of late recurrence in both pre- and postmenopausal women. Furthermore, more of the patients with early recurrence had received adjuvant or neoadjuvant chemotherapies, including anthracyclines and/or taxanes in our analysis. This may not be surprising because patients with early recurrence had larger tumor size, higher lymph node category and higher tumor grade or higher Ki67 LI compared with patients without recurrence. Approximately two thirds of both pre- and postmenopausal patients who relapsed within 5 years had received anthracyclines

and/or taxanes as adjuvant or neoadjuvant chemotherapy. Thus, these standard chemotherapies might not be enough for prevention of early relapse in many patients regardless of high tumor grade or high Ki67 LI. Standard adjuvant chemotherapy regimens should be reconsidered, especially for ER-positive HER2-negative breast cancer.

This study has some limitations; it is a retrospective study without validation, and approximately two age-matched control patients without relapse were randomly selected for each late recurrence patient. However, almost 80% of postmenopausal women received aromatase inhibitors as adjuvant endocrine therapy, and the duration of adjuvant aromatase inhibitor therapy was a predictive factor for late recurrence in postmenopausal women aged 60 years or older. Furthermore, anthracyclins and/or taxanes were used as adjuvant chemotherapy, because patients in our analysis had undergone initial treatments between 2000 and 2004.

In conclusion, our study demonstrates that predictors of early and late distant recurrence differ between patients of different menopausal status, and between those postmenopausal women under 60 years of age and those aged 60 years or older. Menopausal status and age as well as tumor biology should be taken into account when planning the care of ER-positive, HER2-negative breast cancer.

Acknowledgments

This study was supported by Grant-in-Aid for Scientific Research from the Japanese Breast Cancer Society.

Conflict of interest statement

The authors have no conflict of interest.

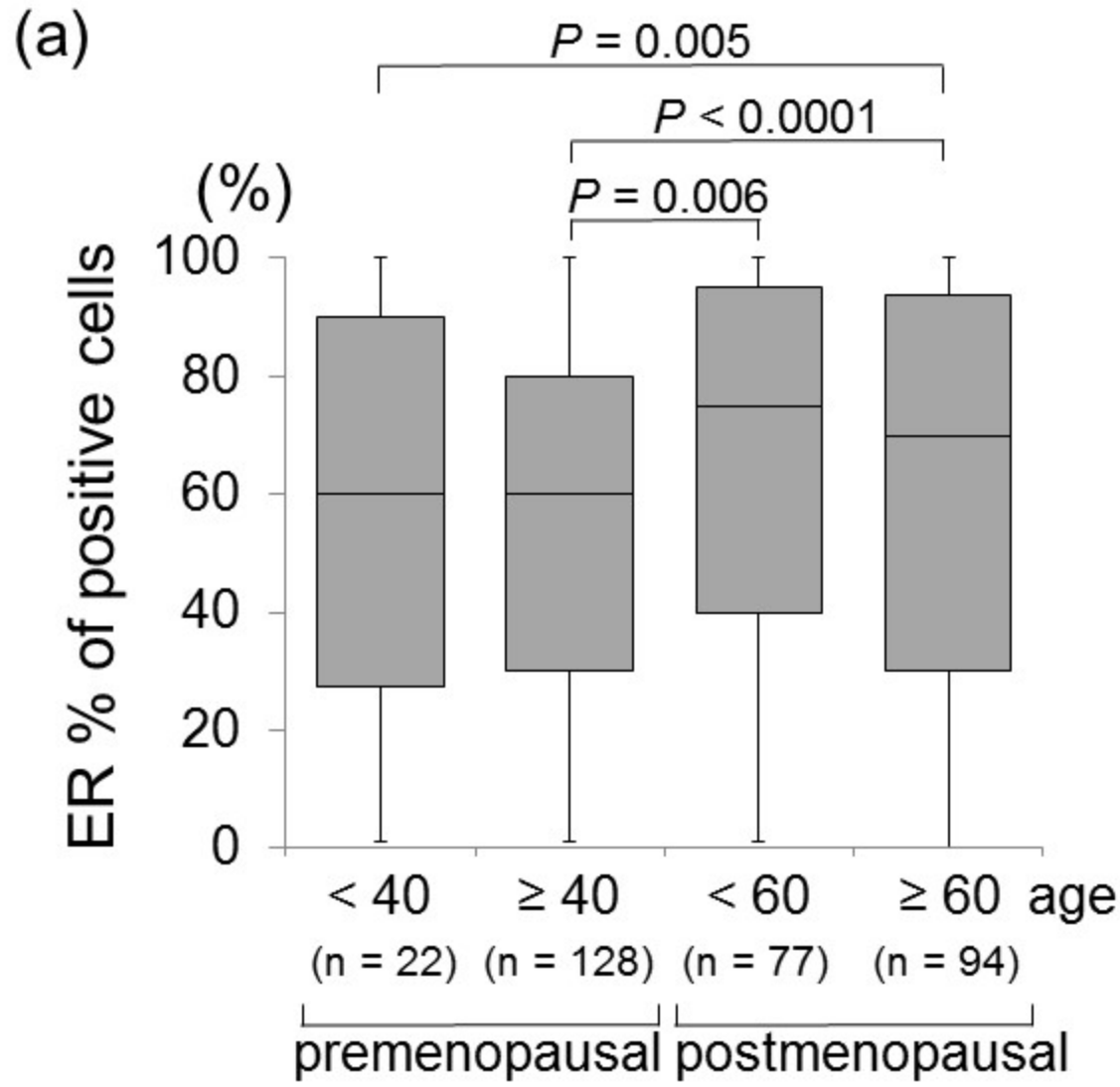
References

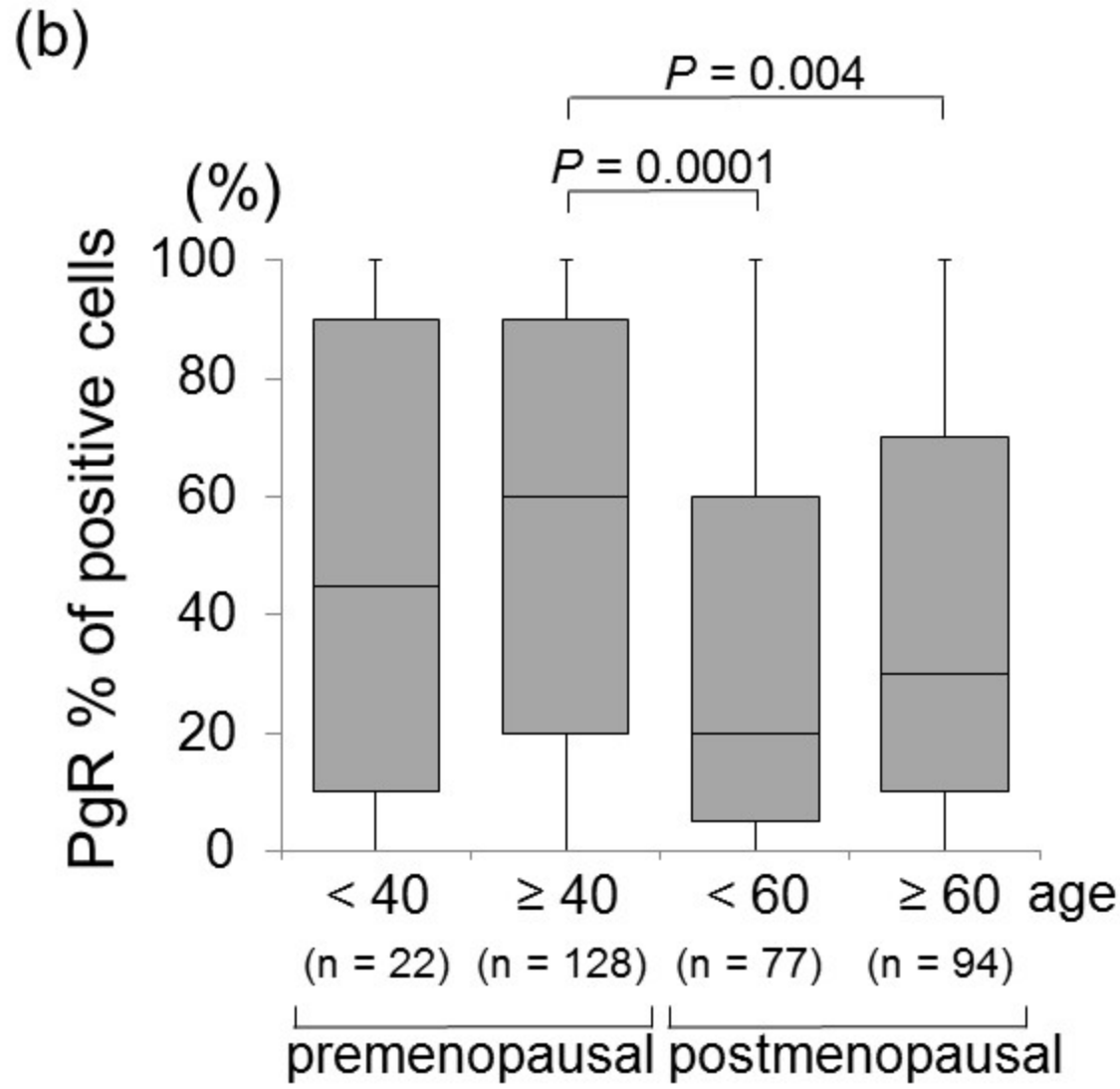
1. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet, 2015;
2. Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet, 2011;378:771-84.
3. Palmieri C, Jones A. The 2011 EBCTCG polychemotherapy overview. Lancet, 2012;379:390-2.
4. Jatoi I, Anderson WF, Jeong JH, Redmond CK. Breast cancer adjuvant therapy: time to consider its time-dependent effects. J Clin Oncol, 2011;29:2301-4.
5. Goss PE, Ingle JN, Pater JL, Martino S, Robert NJ, Muss HB, et al. Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. J Clin Oncol, 2008;26:1948-55.
6. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, 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;381:805-16.
7. Sestak I, Cuzick J. Markers for the identification of late breast cancer recurrence. Breast Cancer Res, 2015;17:10.
8. Hayes DF. Clinical utility of genetic signatures in selecting adjuvant treatment: Risk stratification for early vs. late recurrences. Breast, 2015;
9. Yamashita H, Iwase H, Toyama T, Takahashi S, Sugiura H, Yoshimoto N, et al. Estrogen receptor-positive breast cancer in Japanese women: trends in incidence, characteristics, and prognosis. Ann Oncol, 2011;22:1318-25.
10. Dowsett M, Sestak I, Buus R, Lopez-Knowles E, Mallon E, Howell A, et al. Estrogen Receptor Expression in 21-Gene Recurrence Score Predicts Increased Late Recurrence for Estrogen-Positive/HER2-Negative Breast Cancer. Clin Cancer Res, 2015;21:2763-70.
11. Dubsky P, Filipits M, Jakesz R, Rudas M, Singer CF, Greil R, et al. EndoPredict improves the prognostic classification derived from common clinical guidelines in ER-positive, HER2-negative early breast cancer. Ann Oncol, 2013;24:640-7.
12. Sestak I, Dowsett M, Zabaglo L, Lopez-Knowles E, Ferree S, Cowens JW, et al. Factors predicting late recurrence for estrogen receptor-positive breast cancer. J Natl Cancer Inst, 2013;105:1504-11.
13. Sgroi DC, Sestak I, Cuzick J, Zhang Y, Schnabel CA, Schroeder B, et al. Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. Lancet Oncol, 2013;14:1067-76.
14. Kennecke H, McArthur H, Olivotto IA, Speers C, Bajdik C, Chia SK, et al. Risk of early recurrence among postmenopausal women with estrogen receptor-positive early breast

cancer treated with adjuvant tamoxifen. Cancer, 2008;112:1437-44.
15. Kennecke HF, Olivotto IA, Speers C, Norris B, Chia SK, Bryce C, et al. Late risk of relapse and mortality among postmenopausal women with estrogen responsive early breast cancer after 5 years of tamoxifen. Ann Oncol, 2007;18:45-51.
16. Anderson WF, Chatterjee N, Ershler WB, Brawley OW. Estrogen receptor breast cancer phenotypes in the Surveillance, Epidemiology, and End Results database. Breast Cancer Res Treat, 2002;76:27-36.
17. Hosoda M, Yamamoto M, Nakano K, Hatanaka KC, Takakuwa E, Hatanaka Y, et al. Differential expression of progesterone receptor, FOXA1, GATA3, and p53 between pre- and postmenopausal women with estrogen receptor-positive breast cancer. Breast Cancer Res Treat, 2014;144:249-61.
18. Yoshimoto N, Nishiyama T, Toyama T, Takahashi S, Shiraki N, Sugiura H, et al. Genetic and environmental predictors, endogenous hormones and growth factors, and risk of estrogen receptor-positive breast cancer in Japanese women. Cancer Sci, 2011;102:2065-72.
19. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies-improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol, 2015;26:1533-46.
20. Yamamoto Y, Yamamoto-Ibusuki M, Iwase H. Menopausal status should be taken into consideration for patients with luminal a breast cancer in terms of the effect of differential biology on prognosis. J Clin Oncol, 2013;31:2516.
21. Haynes BP, Viale G, Galimberti V, Rotmensz N, Gibelli B, A'Hern R, et al. Expression of key oestrogen-regulated genes differs substantially across the menstrual cycle in oestrogen receptor-positive primary breast cancer. Breast Cancer Res Treat, 2013;138:157-65.
22. Dunbier AK, Anderson H, Ghazoui Z, Folkerd EJ, A'Hern R, Crowder RJ, et al. Relationship between plasma estradiol levels and estrogen-responsive gene expression in estrogen receptor-positive breast cancer in postmenopausal women. J Clin Oncol, 2010;28:1161-7.
23. Liao S, Hartmaier RJ, McGuire KP, Puhalla SL, Luthra S, Chandran UR, et al. The molecular landscape of premenopausal breast cancer. Breast Cancer Res, 2015;17:104.
24. Anderson WF, Jatoi I, Sherman ME. Qualitative age interactions in breast cancer studies: mind the gap. J Clin Oncol, 2009;27:5308-11.
25. Kurebayashi J, Miyoshi Y, Ishikawa T, Saji S, Sugie T, Suzuki T, et al. Clinicopathological characteristics of breast cancer and trends in the management of breast cancer patients in Japan: Based on the Breast Cancer Registry of the Japanese Breast Cancer Society between 2004 and 2011. Breast Cancer, 2015;22:235-44.

Figure legends

Fig. 1: Expression levels of ER (a) and PgR (b), and Ki67 LI (c) in patients without recurrence by menopausal status and age.


(a)
P = 0.005
P < 0.0001
P = 0.006
(%)
ER % of positive cells
100
80
60
40
20
0
< 40
≥ 40
< 60
≥ 60
age
(n = 22)
(n = 128)
(n = 77)
(n = 94)
premenopausal
postmenopausal


(b)
P = 0.004
P = 0.0001
(%)
PgR % of positive cells
100
80
60
40
20
0
< 40
≥ 40
< 60
≥ 60
age
(n = 22)
(n = 128)
(n = 77)
(n = 94)
premenopausal
postmenopausal

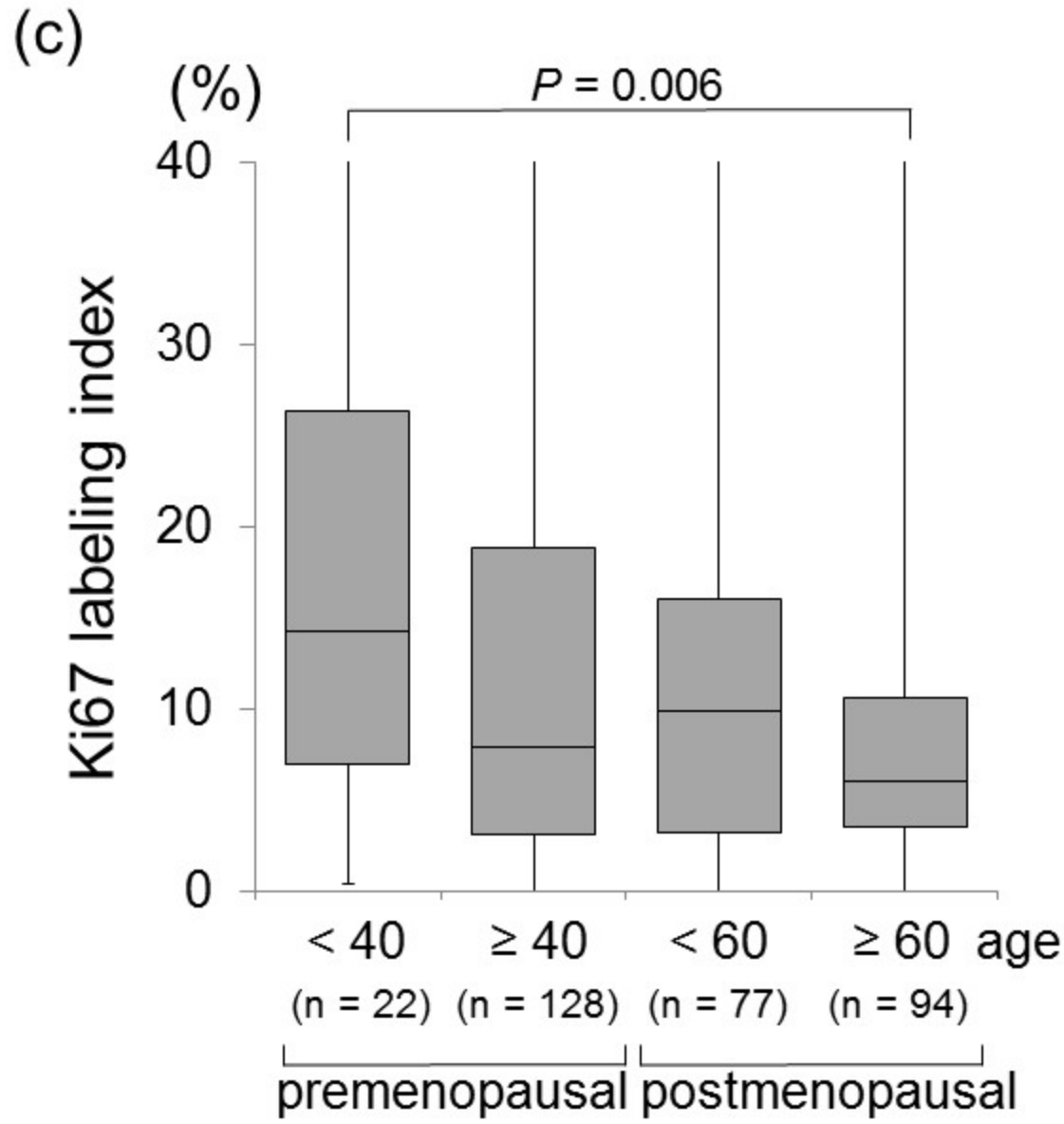

(c)
(%)
P = 0.006
40
30
20
10
0
Ki67 labeling index
< 40
≥ 40
< 60
≥ 60
age
(n = 22)
(n = 128)
(n = 77)
(n = 94)
premenopausal
postmenopausal

Table 1. Clinicopathlogical characteristics of patients and breast tumors according to recurrence pattern in premenopausal women

	Early recurrence (n=108)	Late recurrence (n=62)	Controls (n=150)	*P*-values Early vs. controls	*P*-values Late vs. controls	*P*-values Early vs. Late
Family history of breast cancer						
Yes	13 (12.0%)	7 (11.3%)	28 (18.7%)	0.15	0.19	0.88
No	95 (88.0%)	55 (88.7%)	122 (81.3%)			
Bilateral breast cancer						
Yes	5 (4.8%)	2 (3.2%)	2 (1.3%)	0.11	0.36	0.66
No	103 (95.4%)	60 (96.8%)	148 (98.7%)			
Body mass index, mean ± SD	21.9 ± 3.6	22.7 ± 4.1	22.5 ± 3.5	0.19	0.84	0.25
Tumor category (clinical)						
T0	2 (1.9%)	0	1 (0.7%)	<0.0001*	<0.0001*	0.34
T1 (≤2 cm)	18 (16.7%)	15 (24.2%)	90 (61.2%)			
T2 (2.1-5.0 cm)	53 (49.1%)	34 (54.8%)	47 (32.0%)			
T3 (>5.0 cm)	22 (20.4%)	9 (14.5%)	5 (3.4%)			
T4	13 (12.0%)	4 (6.5%)	4 (2.7%)			
unknown	0	0	3			
Tumor category (pathological)†						
pT1 (≤2 cm)	30 (36.6%)	23 (45.1%)	104 (75.4%)	<0.0001*	0.0002*	0.63
pT2 (2.1-5.0 cm)	34 (41.5%)	21 (41.2%)	31 (22.5%)			
pT3 (>5.0 cm)	15 (18.3%)	6 (11.8%)	2 (1.4%)			
pT4	3 (3.7%)	1 (2.0%)	1 (0.7%)			
unknown	2	1	1			
Lymph node category (clinical)						
N0	48 (44.4%)	28 (45.2%)	121 (80.7%)	<0.0001*	<0.0001*	0.37
N1	46 (42.6%)	31 (50.0%)	27 (18.0%)			
N2	8 (7.4%)	2 (3.2%)	2 (1.3%)			
N3	6 (5.6%)	1 (1.6%)	0			
Number of positive lymph nodes (pathological)†, mean ± SD	5.1 ± 6.7	2.9 ± 4.7	0.81 ± 1.9	<0.0001*	0.0026*	0.041*
0	21 (25.0%)	16 (30.8%)	85 (62.5%)	<0.0001*	0.0001*	0.17
1-3	30 (35.7%)	25 (48.1%)	43 (31.6%)			
4-9	16 (19.0%)	6 (11.5%)	7 (5.1%)			
≥10	17 (20.2%)	5 (9.6%)	1 (0.7%)			
unknown	0	0	3			
Stage (clinical)						
0	3 (2.8%)	0	1 (0.7%)	<0.0001*	<0.0001*	0.19
1	15 (13.9%)	13 (21.0%)	90 (60.0%)			
2	58 (53.7%)	37 (59.7%)	51 (34.0%)			
3	32 (29.6%)	12 (19.4%)	8 (5.3%)			

Table 1. *Continued*

Histological type						
Invasive ductal carcinoma	103 (95.4%)	55 (88.7%)	137 (91.3%)	0.41	0.61	0.14
Invasive lobular carcinoma	3 (2.8%)	2 (3.2%)	6 (4.0%)			
Other	2 (1.9%)	5 (8.1%)	7 (4.7%)			
Tumor grade						
1	27 (25.0%)	20 (32.3%)	60 (40.3%)	0.0079*	0.18	0.60
2	54 (50.0%)	28 (45.2%)	70 (47.0%)			
3	27 (25.0%)	14 (22.6%)	19 (12.8%)			
unknown	0	0	1			
ER (%), mean ± SD	54.9 ± 31.9	53.1 ± 34.5	48.6 ± 31.0	0.11	0.35	0.74
PgR (%), mean ± SD	49.0 ± 33.9	53.4 ± 34.8	55.4 ± 34.9	0.14	0.70	0.43
Positive (≥1%)	99 (91.7%)	59 (95.2%)	139 (92.7%)	0.77	0.51	0.39
Negative (<1%)	9 (8.3%)	3 (4.8%)	11 (7.3%)			
Ki67 LI (%), mean ± SD	16.3 ± 11.7	14.7 ± 14.1	13.3 ± 14.8	0.085	0.51	0.46
<14%	53 (49.5%)	36 (60.0%)	97 (65.5%)	0.035*	0.71	0.35
14-30%	40 (37.4%)	16 (26.7%)	36 (24.3%)			
>30%	14 (13.1%)	8 (13.3%)	15 (10.1%)			
undeterminable	1	2	2			
Disease-free interval (months), mean ± SD	33.5 ± 15.6	93.4 ± 24.1				
Follow up periods (months), mean ± SD			129.4 ± 15.8			

† Patients who received neoadjuvant chemotherapy were excluded.

Ki67 LI Ki67 labeling index

Table 2. Treatments according to recurrence pattern in premenopausal women

	Early recurrence (n=108)	Late recurrence (n=62)	Controls (n=150)	*P*-values Early vs. controls	*P*-values Late vs. controls	*P*-values Early vs. Late
(Neo) Adjuvant systemic therapies						
None	3 (2.8%)	2 (3.2%)	16 (10.7%)	<0.0001*	0.0007*	0.50
Endocrine therapy alone	25 (23.1%)	17 (27.4%)	75 (50.0%)			
Chemotherapy alone	10 (9.3%)	2 (3.2%)	5 (3.3%)			
Combined	70 (64.8%)	41 (66.1%)	54 (36.0%)			
Adjuvant endocrine therapy						
None	13 (12.0%)	4 (6.5%)	21 (14.0%)			
TAM alone	41 (38.0%)	20 (32.3%)	41 (27.3%)			
LHRH agonist alone	4 (3.7%)	6 (9.7%)	0			
TAM + LHRH agonist	35 (32.4%)	21 (33.9%)	20 (13.3%)			
TAM → AI	8 (7.4%)	7 (11.3%)	25 (16.7%)			
TAM + LHRH agonist → AI	0	3 (4.8%)	34 (22.7%)			
AI	7 (6.5%)	1 (1.6%)	9 (6.0%)			
Duration of any endocrine therapy (months), mean ± SD		48.8 ± 28.2	51.7 ± 33.6		0.55	
Discontinuation or change according to the endocrine symptoms						
No	90 (94.7%)	55 (94.8%)	118 (91.5%)	0.35	0.42	0.98
Yes	5 (5.3%)	3 (5.2%)	11 (8.5%)			
(Neo) Adjuvant chemotherapy						
None	28 (25.9%)	19 (30.6%)	91 (60.7%)			
Anthracyclines	29 (26.9%)	16 (25.8%)	18 (12.0%)			
Taxanes	3 (2.8%)	5 (8.1%)	7 (4.7%)			
Anthracyclines + taxanes	39 (36.1%)	22 (35.5%)	25 (16.7%)			
CMF	9 (8.3%)	0	6 (4.0%)			
Others	0	0	3 (2.0%)			
Discontinuation according to the side effects						
No	79 (98.8%)	37 (86.0%)	55 (93.2%)	0.084	0.23	0.0037*
Yes	1 (1.3%)	6 (14.0%)	4 (6.8%)			

Table 2. *Continued*

Neoadjuvant chemotherapy						
No	84 (77.8%)	52 (83.9%)	139 (92.7%)	0.0006*	0.051	0.34
Yes	24 (22.2%)	10 (16.1%)	11 (7.3%)			
Clinical response to neoadjuvant chemotherapy						
CR	0	0	0	0.20	0.069	0.37
PR	15 (62.5%)	5 (55.6%)	10 (90.9%)			
SD	6 (26.0%)	4 (44.4%)	1 (9.1%)			
PD	3 (12.5%)	0	0			
unknown	0	1	0			
Pathological response to neoadjuvant chemotherapy						
Grade 3 (pCR)	0	0	1 (10.0%)	0.069	0.47	0.35
Grade 2	4 (21.1%)	0	0			
Grade 1	14 (73.7%)	6 (85.7%)	6 (60.0%)			
Grade 0	1 (5.3%)	1 (14.3%)	3 (30.0%)			
unknown	5	3	1			
Radiation therapy						
None	50 (46.3%)	43 (69.4%)	58 (38.7%)			
Whole breast	34 (31.5%)	14 (22.6%)	89 (59.3%)			
Chest wall and supraclavicular areas	24 (22.2%)	6 (9.7%)	3 (2.0%)			

TAM tamoxifen, *LHRH agonist* luteinizing hormone-releasing hormone agonist, *AI* aromatase inhibitor, *Anthracyclines* AC (doxorubicin and cyclophosphamide), EC (epirubicin and cyclophosphamide) or FEC (fluorouracil, epirubicin and cyclophosphamide), *Taxanes* docetaxel or paclitaxel, *CMF* cyclophosphamide, methotrexate and fluorouracil, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 3. Clinicopathlogical characteristics of patients and breast tumors according to recurrence pattern in postmenopausal women

	Early recurrence (n=115)	Late recurrence (n=87)	Controls (n=171)	*P*-values Early vs. controls	*P*-values Late vs. controls	*P*-values Early vs. Late
Family history of breast cancer						
Yes	10 (8.7%)	5 (5.7%)	24 (14.0%)	0.17	0.046*	0.43
No	105 (91.3%)	82 (94.3%)	147 (86.0%)			
Bilateral breast cancer						
Yes	10 (8.7%)	10 (11.5%)	0	0.0001*	<0.0001*	0.51
No	105 (91.3%)	77 (88.5%)	171 (100%)			
Body mass index, mean ± SD	23.5 ± 3.5	23.5 ± 3.2	22.8 ± 3.4	0.10	0.12	0.97
Tumor category (clinical)						
T0	0	2 (2.3%)	2 (1.2%)	<0.0001*	0.0097*	0.0003*
T1 (≤2 cm)	31 (27.0%)	27 (31.0%)	91 (53.2%)			
T2 (2.1-5.0 cm)	47 (40.9%)	52 (59.8%)	72 (42.1%)			
T3 (>5.0 cm)	12 (10.4%)	2 (2.3%)	4 (2.3%)			
T4	25 (21.7%)	4 (4.6%)	2 (1.2%)			
Tumor category (pathological)†						
pT1 (≤2 cm)	28 (32.2%)	39 (48.8%)	108 (64.7%)	<0.0001*	0.12	0.16
pT2 (2.1-5.0 cm)	51 (58.6%)	37 (46.3%)	54 (32.3%)			
pT3 (>5.0 cm)	5 (5.7%)	2 (2.5%)	3 (1.8%)			
pT4	3 (3.4%)	2 (2.5%)	2 (1.2%)			
unknown	2	1	0			
Lymph node category (clinical)						
N0	51 (44.3%)	55 (63.2%)	146 (85.4%)	<0.0001*	0.0006*	0.018*
N1	48 (41.7%)	29 (33.3%)	24 (14.0%)			
N2	11 (9.6%)	2 (2.3%)	1 (0.6%)			
N3	5 (4.3%)	1 (1.1%)	0			
Number of positive lymph nodes (pathological)†, mean ± SD	5.4 ± 8.1	3.6 ± 7.2	0.95 ± 3.2	<0.0001*	0.0002*	0.14
0	27 (31.0%)	36 (44.4%)	116 (69.9%)	<0.0001*	0.0001*	0.080
1-3	30 (34.5%)	30 (37.0%)	40 (24.1%)			
4-9	12 (13.8%)	4 (4.9%)	7 (4.2%)			
≥10	18 (20.7%)	11 (13.6%)	3 (1.8%)			
unknown	2	0	1			
Stage (clinical)						
0	4 (3.5%)	3 (3.4%)	2 (1.2%)	<0.0001*	0.0011*	0.0001*
1	25 (21.7%)	22 (25.3%)	83 (48.5%)			
2	45 (39.1%)	55 (63.2%)	82 (48.0%)			
3	41 (35.7%)	7 (8.0%)	4 (2.3%)			

Table 3. *Continued*

Histological type						
Invasive ductal carcinoma	105 (91.3%)	82 (94.3%)	162 (94.7%)	0.23	0.23	0.026*
Invasive lobular carcinoma	9 (7.8%)	1 (1.1%)	6 (3.5%)			
Other	1 (0.9%)	4 (4.6%)	3 (1.8%)			
Tumor grade						
1	34 (29.6%)	38 (43.7%)	76 (44.4%)	0.0010*	0.79	0.036*
2	45 (39.1%)	34 (39.1%)	71 (41.5%)			
3	36 (31.3%)	15 (17.2%)	24 (14.0%)			
ER (%), mean ± SD	63.9 ± 32.6	65.7 ± 30.5	71.0 ± 31.3	0.064	0.19	0.69
PgR (%), mean ± SD	25.4 ± 29.4	32.5 ± 31.8	36.5 ± 34.1	0.0050*	0.37	0.10
Positive (≥1%)	84 (73.0%)	75 (86.2%)	138 (80.7%)	0.13	0.27	0.024*
Negative (<1%)	31 (27.0%)	12 (13.8%)	33 (19.3%)			
Ki67 LI (%), mean ± SD	15.2 ± 11.8	10.4 ± 9.8	10.5 ± 10.9	0.0006*	0.98	0.0024*
<14%	58 (51.8%)	60 (69.0%)	126 (76.4%)	0.0001*	0.21	0.049*
14-30%	41 (36.6%)	21 (24.1%)	25 (15.2%)			
>30%	13 (11.6%)	6 (6.9%)	14 (8.5%)			
undeterminable	3	0	6			
Disease-free interval (months), mean ± SD (median, range)	30.8 ± 14.0	88.8 ± 24.6				
Follow up periods (months), mean ± SD			127.4 ± 16.2			

† Patients who received neoadjuvant chemotherapy were excluded.

Ki67 LI Ki67 labeling index

Table 4. Treatments according to recurrence pattern in postmenopausal women

	Early recurrence (n=115)	Late recurrence (n=87)	Controls (n=171)	*P*-values Early vs. controls	*P*-values Late vs. controls	*P*-values Early vs. Late
(Neo) Adjuvant systemic therapies						
None	12 (10.4%)	2 (2.3%)	15 (8.8%)	<0.0001*	0.033*	0.0074*
Endocrine therapy alone	43 (37.4%)	51 (58.6%)	111 (64.9%)			
Chemotherapy alone	11 (9.6%)	4 (4.6%)	2 (1.2%)			
Combined	49 (42.6%)	30 (34.5%)	43 (25.1%)			
Adjuvant endocrine therapy						
None	23 (20.0%)	6 (9.9%)	17 (9.9%)			
TAM alone	33 (28.7%)	18 (20.7%)	22 (12.9%)			
TAM + LHRH agonist	1 (0.9%)	0	1 (0.6%)			
TAM → AI	15 (13.0%)	31 (35.6%)	37 (21.6%)			
TAM + LHRH agonist → AI	1 (0.9%)	0	16 (9.4%)			
AI	42 (36.5%)	32 (36.8%)	78 (45.6%)			
Discontinuation or change according to the endocrine symptoms						
No	89 (96.7%)	77 (95.1%)	146 (94.8%)	0.48	0.93	0.58
Yes	3 (3.3%)	4 (4.9%)	8 (5.2%)			
(Neo) Adjuvant chemotherapy						
None	45 (39.1%)	41 (47.1%)	119 (69.6%)			
Anthracyclines	14 (12.2%)	18 (20.7%)	22 (12.9%)			
Taxanes	3 (2.6%)	3 (3.4%)	6 (3.5%)			
Anthracyclines + taxanes	43 (37.4%)	13 (14.9%)	17 (9.9%)			
CMF	8 (7.0%)	11 (12.6%)	7 (4.1%)			
Others	2 (1.7%)	1 (1.1%)	0			
Discontinuation according to the side effects						
No	68 (97.1%)	40 (87.0%)	48 (92.3%)	0.22	0.38	0.034*
Yes	2 (2.9%)	6 (13.0%)	4 (7.7%)			
Clinical response to neoadjuvant chemotherapy						
CR	1 (3.3%)	0	0			
PR	14 (53.8%)	2 (33.3%)	2 (50.0%)			
SD	9 (34.6%)	4 (66.7%)	2 (50.0%)			
PD	2 (7.7%)	0	0			

Table 4. *Continued*

Pathological response to neoadjuvant chemotherapy						
Grade 3 (pCR)	0	0	0			
Grade 2	2 (8.0%)	0	0			
Grade 1	21 (84.0%)	6 (100%)	3 (100%)			
Grade 0	2 (8.0%)	0	0			
unknown	1	0	1			
Radiation therapy						
None	65 (56.5%)	57 (65.5%)	92 (53.8%)			
Whole breast	25 (21.7%)	23 (26.4%)	74 (43.3%)			
Chest wall and supraclavicular areas	27 (23.5%)	8 (9.2%)	6 (3.5%)			
Oral bisphosphonate use for osteoporosis						
No	113 (99.1%)	80 (92.0%)	148 (86.5%)	0.0002*	0.20	0.010*
Yes	1 (0.9%)	7 (8.0%)	23 (13.5%)			

TAM tamoxifen, *LHRH agonist* luteinizing hormone-releasing hormone agonist, *AI* aromatase inhibitor, *Anthracyclines* AC (doxorubicin and cyclophosphamide), EC (epirubicin and cyclophosphamide) or FEC (fluorouracil, epirubicin and cyclophosphamide), *Taxanes* docetaxel or paclitaxel, *CMF* cyclophosphamide, methotrexate and fluorouracil, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 5. Clinicopathlogical characteristics and treatments according to recurrence pattern in postmenopausal women under 60 years of age

	Early recurrence (n=58)	Late recurrence (n=35)	Controls (n=77)	*P*-values Early vs. controls	*P*-values Late vs. controls	*P*-values Early vs. Late
Family history of breast cancer						
Yes	7 (12.1%)	3 (8.6%)	14 (18.2%)	0.33	0.19	0.60
No	51 (87.9%)	32 (91.4%)	63 (81.8%)			
Bilateral breast cancer						
Yes	5 (8.6%)	0	0	0.0087*	-	0.074
No	53 (91.4%)	35 (100%)	77 (100%)			
Tumor category (clinical)						
T0	0	0	2 (2.6%)	0.0009*	0.015*	0.099
T1 (≤2 cm)	14 (24.1%)	6 (17.1%)	37 (48.1%)			
T2 (2.1-5.0 cm)	29 (50.0%)	26 (74.3%)	35 (45.5%)			
T3 (>5.0 cm)	8 (13.8%)	1 (2.9%)	2 (2.6%)			
T4	7 (12.1%)	2 (5.7%)	1 (1.3%)			
Tumor category (pathological)†						
pT1 (≤2 cm)	14 (32.6%)	14 (46.7%)	43 (56.6%)	0.012*	0.64	0.29
pT2 (2.1-5.0 cm)	24 (55.8%)	15(50.0%)	31 (40.8%)			
pT3 (>5.0 cm)	5 (11.6%)	1 (3.3%)	1 (1.3%)			
pT4	0	0	1 (1.3%)			
unknown	0	1	0			
Lymph node category (clinical)						
N0	22 (37.9%)	22 (62.9%)	65 (84.4%)	<0.0001*	0.023*	0.080
N1	30 (51.7%)	12 (34.3%)	12 (15.6%)			
N2	4 (6.9%)	0	0			
N3	2 (3.4%)	1 (2.9%)	0			
Number of positive lymph nodes (pathological)†, mean ± SD	5.7 ± 9.3	3.5 ± 5.8	1.3 ± 4.4	0.0007*	0.033*	0.26
0	14 (32.6%)	12 (38.7%)	52 (68.4%)	0.0005*	0.020*	0.89
1-3	16 (37.2%)	12 (38.7%)	18 (23.7%)			
4-9	5 (11.6%)	3 (9.7%)	4 (5.3%)			
≥10	8 (18.6%)	4 (12.9%)	2 (2.6%)			
Stage (clinical)						
0	3 (5.2%)	0	2 (2.6%)	<0.0001*	0.0042*	0.016*
1	8 (13.8%)	5 (14.3%)	34 (44.2%)			
2	28 (48.3%)	27 (77.1%)	40 (51.9%)			
3	19 (32.8%)	3 (8.6%)	1 (1.3%)			

† Patients who received neoadjuvant chemotherapy were excluded.

Table 5. *Continued*

Tumor grade						
1	16 (27.6%)	15 (42.9%)	28 (36.4%)	0.27	0.80	0.24
2	25 (43.1%)	14 (40.0%)	35 (45.5%)			
3	17 (29.3%)	6 (17.1%)	14 (18.2%)			
ER (%), mean ± SD	66.1 ± 31.3	72.7 ± 26.8	64.3 ± 34.3	0.75	0.20	0.30
PgR (%), mean ± SD	20.6 ± 25.4	29.8 ± 35.8	33.4 ± 34.1	0.019*	0.61	0.15
Positive (≥1%)	43 (74.1%)	26 (74.3%)	64 (83.1%)	0.20	0.28	0.99
Negative (<1%)	15 (25.9%)	9 (25.7%)	13 (16.9%)			
Ki67 LI (%), mean ± SD	16.3 ± 11.3	13.4 ± 12.1	12.1 ± 11.6	0.039*	0.59	0.24
<14%	25 (44.6%)	20 (57.1%)	50 (67.6%)	0.023*	0.56	0.44
14-30%	25 (44.6%)	11 (31.4%)	17 (23.0%)			
>30%	6 (10.7%)	4 (11.4%)	7 (9.5%)			
undeterminable	2	0	3			
Duration of AI therapy						
AI > 2 years						
Yes	15 (25.9%)	20 (57.1%)	46 (59.7%)		0.80	
No	43 (74.1%)	15 (42.9%)	31 (40.3%)			
AI > 3 years						
Yes		18 (51.4%)	43 (55.8%)		0.66	
No		17 (45.5%)	34 (44.2%)			
AI > 4 years						
Yes		16 (45.7%)	40 (51.9%)		0.54	
No		19 (54.3%)	37 (48.1%)			
Duration of any endocrine therapy (months), mean ± SD		42.2 ± 29.1	40.9 ± 29.6		0.84	
Disease-free interval (months), mean ± SD	29.8 ± 13.8	96.4 ± 25.4				
Follow up periods (months), mean ± SD			127.6 ± 15.3			

† Patients who received neoadjuvant chemotherapy were excluded.

Ki67 LI Ki67 labeling index, *AI* aromatase inhibitor

Table 6. Clinicopathlogical characteristics and treatments according to recurrence pattern in postmenopausal women aged 60 years or older

	Early recurrence (n=57)	Late recurrence (n=52)	Controls (n=94)	*P*-values Early vs. controls	*P*-values Late vs. controls	*P*-values Early vs. Late
Family history of breast cancer						
Yes	3 (5.3%)	2 (3.8%)	10 (10.6%)	0.25	0.15	0.72
No	54 (94.7%)	50 (96.2%)	84 (89.4%)			
Bilateral breast cancer						
Yes	5 (8.8%)	10 (19.2%)	0	0.0035*	<0.0001*	0.11
No	52 (91.2%)	42 (80.8%)	94 (100%)			
Tumor category (clinical)						
T0	0	2 (3.8%)	0	<0.0001*	0.10	0.0011*
T1 (≤2 cm)	17 (29.8%)	21 (40.4%)	54 (57.4%)			
T2 (2.1-5.0 cm)	18 (31.6%)	26 (50.0%)	37 (39.4%)			
T3 (>5.0 cm)	4 (7.0%)	1 (1.9%)	2 (2.1%)			
T4	18 (31.6%)	2 (3.8%)	1 (1.1%)			
Tumor category (pathological)†						
pT1 (≤2 cm)	14 (31.8%)	25 (50.0%)	65 (71.4%)	<0.0001*	0.067	0.22
pT2 (2.1-5.0 cm)	27 (61.4%)	22(44.0%)	23 (25.3%)			
pT3 (>5.0 cm)	0	1 (2.0%)	2 (2.2%)			
pT4	3 (6.8%)	2 (4.0%)	1 (1.1%)			
unknown	2	0	0			
Lymph node category (clinical)						
N0	29 (50.9%)	33 (63.5%)	81 (86.2%)	<0.0001*	0.0062*	0.12
N1	18 (31.6%)	17 (32.7%)	12 (12.8%)			
N2	7 (12.3%)	2 (3.8%)	1 (1.1%)			
N3	3 (5.3%)	0	0			
Number of positive lymph nodes (pathological)†, mean ± SD	5.1 ± 6.9	3.6 ± 8.0	0.69 ± 1.6	<0.0001*	0.0009*	0.36
0	13 (29.5%)	24 (48.0%)	64 (71.1%)	<0.0001*	0.0032*	0.038*
1-3	14 (31.8%)	18 (36.0%)	22 (24.4%)			
4-9	7 (15.9%)	1 (2.0%)	3 (3.3%)			
≥10	10 (22.7%)	7 (14.0%)	1 (1.1%)			
unknown	2	0	1			
Stage (clinical)						
0	1 (1.8%)	3 (5.8%)	0	<0.0001*	0.017*	0.0012*
1	17 (29.8%)	17 (32.7%)	49 (52.1%)			
2	17 (29.8%)	28 (53.8%)	42 (44.7%)			
3	22 (38.6%)	4 (7.7%)	3 (3.2%)			

Table 6. *Continued*

Tumor grade						
1	18 (31.6%)	23 (44.2%)	48 (51.1%)	0.0017*	0.48	0.14
2	20 (35.1%)	20 (38.5%)	36 (38.3%)			
3	19 (33.3%)	9 (17.3%)	10 (10.6%)			
ER (%), mean ± SD	61.6 ± 34.1	60.9 ± 32.1	76.5 ± 27.5	0.0037*	0.0025*	0.92
PgR (%), mean ± SD	30.1 ± 32.4	34.3 ± 29.1	39.0 ± 34.1	0.12	0.40	0.48
Positive (≥1%)	41 (71.9%)	49 (94.2%)	74 (78.7%)	0.34	0.014*	0.0022*
Negative (<1%)	16 (28.1%)	3 (5.8%)	20 (21.3%)			
Ki67 LI (%), mean ± SD	14.1 ± 12.2	8.4 ± 7.3	9.1 ± 10.1	0.0077*	0.67	0.0044*
<14%	33 (58.9%)	40 (76.9%)	76 (83.5%)	0.0025*	0.15	0.096
14-30%	16 (28.6%)	10 (19.2%)	8 (8.8%)			
>30%	7 (12.5%)	2 (3.8%)	7 (7.7%)			
undeterminable	1	0	3			
Duration of AI therapy						
AI > 2 years						
Yes	14 (24.6%)	29 (55.8%)	68 (72.3%)		0.042*	
No	43 (75.4%)	23 (44.2%)	26 (27.7%)			
AI > 3 years						
Yes		24 (46.2%)	64 (68.1%)		0.0095*	
No		28 (53.8%)	30 (31.9%)			
AI > 4 years						
Yes		18 (34.6%)	62 (66.0%)		0.0003*	
No		34 (65.4%)	32 (34.6%)			
Duration of any endocrine therapy (months), mean ± SD		38.3 ± 24.6	49.5 ± 34.8		0.043*	
Disease-free interval (months), mean ± SD	31.9 ± 14.2	83.8 ± 22.9				
Follow up periods (months), mean ± SD			127.2 ± 17.0			

† Patients who received neoadjuvant chemotherapy were excluded.

Ki67 LI Ki67 labeling index, *AI* aromatase inhibitor