Comparison of pathological characteristics between self-detected and screen-detected invasive breast cancers in Chinese women: a retrospective study

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Background: In China, there is insufficient evidence to support that screening programs can detect breast cancer earlier and improve outcomes compared with patient self-reporting. Therefore, we compared the pathological characteristics at diagnosis between self-detected and screen-detected cases of invasive breast cancer at our institution and determined whether these characteristics were different after the program’s introduction (versus [vs] prior to).

Methods: Three databases were selected (breast cancer diagnosed in 1995–2000, 2010, and 2015), which provided a total of 3,014 female patients with invasive breast cancer. The cases were divided into self-detected and screen-detected groups. The pathological characteristics were compared between the two groups and multiple imputation and complete randomized imputation were used to deal with missing data.

Results: Compared with patient self-reporting, screening was associated with the following factors: a higher percentage of stage T1 tumors (75.0% vs 17.1%, P = 0.109 in 1995–2000; 66.7% vs 40.4%, P < 0.001 in 2010; 67.8% vs 35.7%, P < 0.001 in 2015); a higher percentage of tumors with stage N0 lymph node status (67.3% vs 48.4%, P = 0.007 in 2010); and a higher percentage of histologic grade I tumors (22.9% vs 13.9%, P = 0.017 in 2010).

Conclusions: Screen-detected breast cancer was associated with a greater number of favorable pathological characteristics. However, although screening had a beneficial role in early detection in China, we found fewer patients were detected by screening in this study compared with those in Western and Asian developed countries.
Comparison of pathological characteristics between self-detected and screen-detected invasive breast cancers in Chinese women: a retrospective study

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Abstract

Background: In China, there is insufficient evidence to support that screening programs can detect breast cancer earlier and improve outcomes compared with patient self-reporting. Therefore, we compared the pathological characteristics at diagnosis between self-detected and screen-detected cases of invasive breast cancer at our institution and determined whether these characteristics were different after the program’s introduction (versus [vs] prior to).

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Results: Compared with patient self-reporting, screening was associated with the following factors: a higher percentage of stage T1 tumors (75.0% vs 17.1%, \( P = 0.109 \) in 1995–2000; 66.7% vs 40.4%, \( P < 0.001 \) in 2010; 67.8% vs 35.7%, \( P < 0.001 \) in 2015); a higher percentage of tumors with stage N0 lymph node status (67.3% vs 48.4%, \( P = 0.007 \) in 2010); and a higher percentage of histologic grade I tumors (22.9% vs 13.9%, \( P = 0.017 \) in 2010).

Conclusions: Screen-detected breast cancer was associated with a greater number of favorable pathological characteristics. However, although screening had a beneficial role in early detection in China, we found fewer patients were detected by screening in this study compared with those in Western and Asian developed countries.
1. Introduction

Breast cancer has become the major cause of death in Chinese women [1, 2]. According to Chinese urban cancer registries, the overall incidence of breast cancer has increased at a rate of 2%–5% annually, with a peak incidence at an age of approximately 50 years [3–5, 2]. Early tumor detection, before symptoms appear, could significantly improve survival [6–9].

The National Health and Family Planning Commission of the People’s Republic of China organized a three-year breast cancer screening program for women aged 35 to 69 years between 2009 and 2011, with a second phase of screening launched in 2012 [5]. The first phase of the program screened 1.2 million women and detected 440 cases with early-stage lesions, giving a diagnostic rate of 48.0 per 100,000 women [5]. Concurrently, in 2009, the All-China Women’s Federation and the National Health and Family Planning Commission organized a screening program that offered free screening for breast and cervical cancer to women in rural China. As of 2014, about 48.35 million women in rural China had received free tests since the program’s inception. The guidelines for breast cancer screening in China, which were first published in 2007 and updated in 2015, recommend women at average risk of breast cancer are encouraged to have mammography combined with clinical breast examination after age 40 years. Even though, there is no national organized screening program [10]. Zhu et al reported the long-term prognosis of breast cancers has been improved during the past 40 years [11]. This article was aimed to observe whether the distribution of pathological characteristics at diagnosis had differed since the introduction of limited screening programs.

Studies worldwide have indicated that screen-detected patients have more favorable survival outcomes compared with the patients with self-discovered breast cancer (i.e., self-detected cancer) [12–14]. Screen-detected cancers tend to be of a smaller size, to have better differentiation, and to be at an earlier stage [15]. In a study carried out in a private hospital in
Hong Kong, patients with screen-detected breast cancer had greater numbers of favorable pathological characteristics than a self-detected group [16]. Therefore, the second aim of this study was to compare the pathological characteristics of the self-detected (symptomatic) and screen-detected (asymptomatic) invasive breast cancer in Tianjin, China.

2. Materials and Methods

2.1 Information of database and subjects

This was a retrospective cohort study conducted at the Tianjin Medical University Cancer Institute and Hospital. Since 1995, all cases of breast cancer treated in this hospital have been recorded in a structured database. We identified cases for 1995–2000 (paper documentation), 2010 (half paper and half electronic documentation), and 2015 (electronic documentation), taking care to exclude those cases with ductal carcinoma in situ and bilateral breast cancer. The study was approved by the Ethics Committee in Tianjin Medical University Cancer Institute and Hospital.

2.2 Data extraction

Clinical histories and pathological characteristics were obtained from the three databases by two authors individually (Zhang Q. and Ding L.), including the age of patients at initial diagnosis and the cancer detection method. Different records between authors were re-checked. Pathological characteristics included tumor size staging and lymph node staging and histologic grade based, respectively, on the tumor-node-metastasis classification system of the American Joint Committee on Cancer [17] and the World Health Organization classification of tumors [18].

2.3 Methods of detection

Cases were divided into two groups, based on method of detection: a self-detected group and a screen-detected group. Patients in the screen-detected group were primarily screened by
population-based or opportunistic screening with mammography, ultrasound, or clinical breast examination. Patients in the self-detected group were defined as those with obvious clinical symptoms at presentation, including nipple discharge, pain, a palpable axillary lump, a palpable breast lump, or a combination of those symptoms.

2.4 Statistical analysis

Descriptive statistics were used to show the demographic and pathological characteristics of the patients. Pearson’s chi-square or Fisher’s exact test was used to analyze categorical variables, and the Mann–Whitney U test was used to analyze ordinal variables. Multinomial logistic regression analyses were used to analyze associations between method of detection and pathological characteristics. The tumor size (T1, T2 and T3-4), node lymph stage (N0, N1 and N2-3) and histologic grade (I, II and III) were treated as the outcome variables. The category “T1”, “N0” and “I” was used as the reference category in tumor size model, node lymph stage model and histologic grade model respectively. The variable “age” was divided into four categories: cases younger than 40, 40 to 49, 50 to 59, and aged 60 and older. The variable “method of detection” and “age” was included in these models. The null hypothesis was that there would be no significant difference between variables. A significance level of 0.05 was used for two-tailed P values.

2.5 Techniques of dealing with missing data

To maximize the likelihood of comparability and equivalence, four methods were used to deal with missing data based on a missing-at-random assumption. These were as follows: (A) multiple imputation by chained equation (five times) (by R Project, version 3.3.2) [19, 20], with age group, T stage, N stage, histologic grade and detection modes included into multivariate regression model; (B) complete randomized imputation (five times), stratified by year [21]; (C)
arbitrarily replacing all missing values for the detection methods into the self-detected mode and
deleting other missing values in the group; (D) arbitrarily replacing a missing mode of detection
into the screen-detected mode and deleting other missing values in the group.

3. Results

3.1 Pathological characteristics of breast cancer patients

We identified 1,086, 1,053, and 1,047 female cases from databases in 1995–2000, 2010, and
2015, respectively. From these, we excluded 172 women with ductal carcinoma in situ or
bilateral breast cancer. The final study therefore included 3,014 cases of invasive breast cancer:
1,060 in 1995–2000, 946 in 2010, and 1,008 in 2015. The median (range) ages at presentation
were 48.0 (19–80) years in 1995–2000, 51.0 (22–82) years in 2010, and 52.0 (18–82) years in
2015. The general pathological characteristics of the cancers, including T stage, N stage, and
histologic grade, are shown in Table 1 for each period.

3.2 Pathological differences between the self-detected and screen-detected groups

The screen-detected group had a higher proportion of stage T1 tumors than the self-detected
group in each database (75.0% vs 17.1%, P = 0.109 in 1995–2000; 66.7% vs 40.4%, P < 0.001 in
2010; and 67.8% vs 35.7%, P < 0.001 in 2015) (Table 2 and Fig.1-a). The proportion with
negative lymph nodes (N0) was also slightly higher in the screen-detected group than in the self-
detected group in each database (50.0% vs 47.4%, 67.3% vs 48.4%, and 55.2% vs 48.5% in
1995–2000, 2010, and 2015, respectively), although statistical significance was only reached for
2010 (P = 0.007) (Table 2 and Fig.1-b). The percentages of histologic grade I tumors were
significant higher in screen-detected group than that in self-detected group (22.9% vs 13.9%, P =
0.017 in 2010) (Table 2 and Fig.1-c). The age distribution showed no significant difference
between self-detected and screen-detected group (Table 2 and Fig.2). After adjusting for age,
self-detected group had increased T2 stage cases in 2010 (T2 vs T1, OR = 2.817, P = 0.001) and 2015 (T2 vs T1, OR = 3.820, P < 0.001), increased N2-3 stage cases in 2010 (N2-3 vs N0, OR = 2.775, P = 0.017) and increased histologic grade III in 2010 (grade III vs I, OR = 5.763, P = 0.026) significantly, compared with screen-detected group (Table 3).

4. Discussion

In this study, we retrospectively compared the differences in pathological characteristics between self-detected and screen-detected breast cancer. The proportion of cases identified by the screening program increased significantly before the introduction of screening. The screen-detected group had smaller tumor sizes and tended to have less lymph node involvement and lower histologic grades compared with the self-detected group.

The coverage of the breast cancer screening remains low in Chinese population. From 2009 to 2011, a breast cancer screening program, which was launched by the Chinese Anti-Cancer Association with the permission of the Chinese government, only covered 1.46 million women and only 631 with breast cancer [5]. As of 2014, the total number of screened women had risen to 48.35 million, but this still accounts for less than 5% of the population. Another possible explanation for the low percentage of screen-detected cancer may relate to the theory and technology underpinning existing screening programs and guidelines, typically relying on a lack of indigenous studies. Moreover, the Chinese guidelines for breast cancer screening were not published by the Chinese Anti-Cancer Association, Committee of Breast Cancer Society until 2007 [22] and have been updated four times over the last decade. These guidelines recommend that women at average risk of breast cancer only undergo opportunistic screening mammography. However, ultrasound and parallel clinical breast examination are the primary screening tools in second-generation screening programs [5].
Consistent with the findings of previous studies from Japan, Singapore, Korea, and some Western countries, we confirmed the benefits of screening when seeking to detect breast cancer at an early stage [13–15, 23, 24]. Specifically, we identified the prognostic advantages, based on pathological findings at diagnosis, for asymptomatic patients with screen-detected cancers. Comparable to our results (66.7%–75.0% vs 17.1%–40.4%), higher proportions of screen-detected patients were reported to have stage T1 cancer compared with self-detected groups in studies in both Korea (59.2% vs 31.7%) [14] and Hong Kong (44.7% vs 33.4%) [16]. A study in Singapore also indicated that screening was an independent factor for better clinical staging at presentation, after adjusting for race and menopausal status [12]. However, although there were trends, we did not find any statistically significant difference for lymph node status or histologic grade between the groups in this study. Mammography was not popular yet as the modality of breast cancer screening in China [5, 10]. Breast cancer examination was used in most of the screening program which might limit the performance of screening and results unsatisfied tumor stage.

In this study, long-term information of 3,014 breast cancer patients from Tianjin Medical University Cancer Institute and Hospital were collected. Because the breast cancer patients at our hospital came from all over the country of China, this database represent a trend of Chinese breast cancer. However, this study has two main limitations. The first is that it was retrospective and that approximately 12% of values were missing in the detection mode due to the use of electronic documentation. Hence, four imputation methods were used to ascertain whether major differences occurred on the comparison of pathological characteristics between self-detected and screen-detected breast cancer. When using multiple imputation by chained equations, the missing values were completed depending on the interdependency between values [19]. In this regard,
more preferable results tended to be classified into the screen-detected group. When using completely randomized imputation stratified by year, no tendency was seen in either direction. When the missing detection mode values were replaced by “self-detected,” the pathological advantage of the screen-detected group was attributed to the self-detected group. The differences between the two groups may therefore have been underestimated. When the missing detection mode values were replaced by “screen-detected,” the disadvantage in the self-detected group was attributed to the screen-detected group, also potentially leading to an underestimation of the differences between the two groups. The second limitation is that there was no information about the follow-up or survival status of the patients, for which further studies would be required. A study from the UK reported that the impact of introducing such a screening program on survival was small but significant, and that most of the improved survival was due to a shift in the Nottingham Prognostic Index (used to determine prognosis following surgery for breast cancer) [25]. Similar shifts in pathologic characteristics of prognosis were identified both in this retrospective investigation and in previous studies [26].

5. Conclusion

This study indicates that the breast cancers detected by screening had more favorable clinicopathologic characteristics than those detected by themselves. We also found fewer patients were detected by screening in this study compared with those in Western and Asian developed countries.

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References

[1] Li T, Mello-Thoms C, Brennan PC. 2016. Descriptive epidemiology of breast cancer in China: incidence, mortality, survival and prevalence. *Breast cancer research and treatment* 159(3):395-406.

[2] Yang L, Parkin DM, Ferlay J, Li L, Chen Y. 2005. Estimates of cancer incidence in China for 2000 and projections for 2005. *Cancer epidemiology, biomarkers & prevention* 14(1):243-50.

[3] Anderson BO, Yip CH, Smith RA, Shyyan R, Sener SF, Eniu A, Carlson RW, Azavedo E, Harford J. 2008. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. *Cancer* 113(8 Suppl): 2221-43.

[4] P. Porter. 2008. "Westernizing" women's risks? Breast cancer in lower-income countries. *New England Journal of Medicine* 358(3):213-6.

[5] Song QK, Wang XL, Zhou XN, Yang HB, Li YC, Wu JP, Ren J, Lyerly HK. 2015. Breast cancer challenges and screening in China: Lessons from current registry data and population screening studies. *The oncologist* 20(7):773-9.

[6] Tabar L, Vitak B, Chen HH, Yen MF, Duffy SW, Smith RA. 2001. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer* 91(9):1724-31.

[7] Duffy SW, Tabar L, Chen HH, Holmqvist M, Yen MF, Abdsalah S, Epstein B, Frodis E, Ljungberg E, Hedborg-Melander C, Sundbom A, Tholin M, Wiege M, Akerlund A, Wu HM, Tung TS, Chiu YH, Chiu CP, Huang CC, Smith RA, Rosen M, Stenbeck M, Holmberg L. 2002. The impact of organized mammography service screening on breast carcinoma mortality in seven Swedish counties. *Cancer* 95(3):458-69.

[8] de Gelder R, Heijnsdijk EAM, Fracheboud J, Draisma G, de Koning HJ. 2015. The effects of population-based mammography screening starting between age 40 and 50 in the presence of adjuvant systemic therapy. *International Journal of Cancer* 137(1):165-172.

[9] Sankatsing VDV, van Ravesteyn NT, Heijnsdijk EAM, Looman CWN, van Luijt PA, Fracheboud J, den Heeten GJ, Broeders MJM, de Koning HJ. 2017. The effect of population-based mammography screening in Dutch municipalities on breast cancer mortality: 20 years of follow-up. *International Journal of Cancer* doi:10.1002/ijc.30754.

[10] Chinese Anticancer Association Breast Cancer Society. 2015. Clinical practice guidelines in...
breast cancer. China Oncology 25(9):692-754.

[11] Zhu J, Chen JG, Chen YS, Zhang YH, Ding LL, Chen TY. Female breast cancer survival in Qidong, China, 1972-2011: a population-based study. BMC cancer 2014;14:318.

[12] Wang WV, Tan SM, Chow WL. 2011. The impact of mammographic breast cancer screening in Singapore: a comparison between screen-detected and symptomatic women. Asian Pacific Journal of Cancer Prevention 12(10):2735-40.

[13] Joensuu H, Lehtimaki T, Holli K, Elomaa L, Turpeenniemi-Hujanen T, Kataja V, Anttila A, Lundin M, Isola J, Lundin J. 2004. Risk for distant recurrence of breast cancer detected by mammography screening or other methods. JAMA 292(9):1064–73.

[14] Kim J, Lee S, Bae S, Choi MY, Lee J, Jung SP, Kim S, Choe JH, Kim JH, Kim JS, Lee JE, Nam SJ, Yang JH. 2012. Comparison between screen-detected and symptomatic breast cancers according to molecular subtypes. Breast Cancer Research and Treatment 131(2):527-40.

[15] Crispo A, Barba M, D'Aiuto G, De Laurentiis M, Grimaldi M, Rinaldo M, Caolo G, D'Aiuto M, Capasso I, Esposito E, Amore A, Di Bonito M, Botti G, Montella M. 2013. Molecular profiles of screen detected vs. symptomatic breast cancer and their impact on survival: results from a clinical series. BMC Cancer 13:15.

[16] Lau SS, Cheung PS, Wong TT, Ma MK, Kwan WH. 2016. Comparison of clinical and pathological characteristics between screen-detected and self-detected breast cancers: a Hong Kong study. Hong Kong Medical Journal 22(3):202-9.

[17] Edge SB, Compton CC. 2010. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Annals of Surgical Oncology 17(6):1471-4.

[18] Lakhani SR, Schnitt SJ, Tan PH, van de Vijver MJ. 2012. WHO classification of tumours of the breast. International Agency for Research on Cancer.

[19] Zhang Z. 2016. Multiple imputation with multivariate imputation by chained equation (MICE) package. Annals of Translational Medicine 4(2): 30.

[20] Eisemann N, Waldmann A, Katalinic A. 2011. Imputation of missing values of tumour stage in population-based cancer registration. BMC Medical Research Methodology 11:129.

[21] Pedersen AB, Mikkelsen EM, Cronin-Fenton D, Kristensen NR, Pham TM, Pedersen L, Petersen I. 2017. Missing data and multiple imputation in clinical epidemiological research. Clinical Epidemiology 9:57-166.
[22] Chinese Anticancer Association Breast Cancer Society. 2007. Clinical practice guidelines in breast cancer (Version 2007). *China Oncology* 17(5):410-428.

[23] Inari H, Shimizu S, Suganuma N, Yoshida T, Nakayama H, Yamanaka T, Yamanaka A, Rino Y, Masuda M. 2017. A comparison of clinicopathological characteristics and long-term survival outcomes between symptomatic and screen-detected breast cancer in Japanese women. *Breast Cancer (Tokyo, Japan)* 24(1):98-103.

[24] Chuwa EW, Yeo AW, Koong HN, Wong CY, Yong WS, Tan PH, Ho JT, Wong JS, Ho GH. 2009. Early detection of breast cancer through population-based mammographic screening in Asian women: a comparison study between screen-detected and symptomatic breast cancers. *The Breast Journal* 15(2):133-9.

[25] Wishart GC, Greenberg DC, Britton PD, Chou P, Brown CH, Purushotham AD, Duffy SW. 2016. Cancer screening barriers and facilitators for under and never screened populations: A mixed methods study. *Cancer epidemiology* 45:126-134.

[26] Zheng S, Bai JQ, Li J, Fan JH, Pang Y, Song QK, Huang R, Yang HJ, Xu F, Lu N, Qiao YL. 2012. The pathologic characteristics of breast cancer in China and its shift during 1999-2008: a national-wide multicenter cross-sectional image over 10 years. *International Journal of Cancer* 131(11):2622-31.
Table 1 (on next page)

Characteristics of the patients with breast cancer in Tianjin Medical University Cancer Institute and Hospital.

aT=tumor size staging, bN=lymph node staging.
| Characteristics                  | 1995–2000 (n=1,060) | 2010 (n=946) | 2015 (n=1,008) |
|---------------------------------|---------------------|--------------|----------------|
| Median age, years (range)       | 48.0 (19–80)        | 51.0 (22–82) | 52.0 (18–82)   |
| Detection mode, n (%)           |                     |              |                |
| Self-detected                   | 1,034 (97.5)        | 712 (75.3)   | 774 (76.8)     |
| Screen-detected                 | 4 (0.4)             | 60 (6.3)     | 76 (7.5)       |
| Unknown                         | 22 (2.1)            | 174 (18.4)   | 158 (15.7)     |
| T_1, n (%)                      |                     |              |                |
| T1                              | 168 (15.8)          | 330 (34.8)   | 299 (29.7)     |
| T2                              | 633 (59.7)          | 352 (37.2)   | 430 (42.6)     |
| T3                              | 127 (12.0)          | 45 (4.8)     | 46 (4.6)       |
| T4                              | 46 (4.3)            | 13 (1.4)     | 5 (0.5)        |
| Unknown                         | 86 (8.2)            | 206 (21.8)   | 228 (22.6)     |
| N_0, n (%)                      |                     |              |                |
| N0                              | 467 (44.1)          | 390 (41.2)   | 467 (46.4)     |
| N1                              | 397 (37.5)          | 184 (19.5)   | 243 (24.1)     |
| N2                              | 112 (10.6)          | 104 (11.0)   | 90 (8.9)       |
| N3                              | 4 (0.4)             | 82 (8.7)     | 124 (12.3)     |
| Unknown                         | 80 (7.4)            | 186 (19.6)   | 84 (8.3)       |
| Histologic grade, n (%)         |                     |              |                |
| I                               | 147 (13.9)          | 103 (10.9)   | 56 (5.5)       |
| II                              | 605 (57.1)          | 495 (52.3)   | 684 (67.9)     |
| III                             | 241 (22.7)          | 86 (9.1)     | 102 (10.1)     |
| Unknown                         | 67 (6.3)            | 262 (27.7)   | 166 (16.5)     |
Table 2 (on next page)

Comparison of differences in T stage, N stage, and histologic grade between self-detected and screen-detected patients.

a There was no data in the current group. b The P value was calculated by Fisher's exact test because the number of patients in the current group was less than 5.
| Characteristics | 1995–2000 | 2010 | 2015 |
|-----------------|-----------|------|------|
|                 | Self-detected | Screen-detected | Self-detected | Screen-detected | Self-detected | Screen-detected |
| T stage, n (%)  |           |      |      |           |      |      |
| T1              | 163 (17.1) | 3 (75.0) | 231 (40.4) | 34 (66.7) | 219 (35.7) | 40 (67.8) |
| T2              | 620 (65.0) | --a | 289 (50.5) | 15 (29.4) | 350 (57.1) | 17 (28.8) |
| T3-4            | 173 (17.9) | 1 (25.0) | 52 (9.1) | 2 (3.9) | 44 (7.2) | 2 (3.4) |
| **Mann-Whitney U** | 1113.000 | 10651.500 | 12256.000 |
| **P**           | 0.109b | <0.001 | <0.001 |
| N stage, n (%)  |           |      |      |           |      |      |
| N0              | 455 (47.4) | 2 (50.0) | 284 (48.4) | 35 (67.3) | 347 (48.5) | 37 (55.2) |
| N1              | 389 (40.6) | 2 (50.0) | 148 (25.2) | 10 (19.2) | 199 (27.8) | 16 (23.9) |
| N2-3            | 115 (12.0) | --a | 155 (26.4) | 7 (13.5) | 170 (23.7) | 14 (20.9) |
| **Mann-Whitney U** | 1754.000 | 12116.500 | 22349.000 |
| **P**           | 0.868b | 0.007 | 0.325 |
| Histologic grade, n (%) | | | | | | |
| I               | 143 (14.7) | 3 (75.0) | 72 (13.9) | 11 (22.9) | 38 (5.9) | 3 (4.6) |
| II              | 591 (60.8) | --a | 372 (71.8) | 35 (72.9) | 527 (81.6) | 57 (87.7) |
| III             | 238 (24.5) | 1 (25.0) | 74 (14.3) | 2 (4.2) | 81 (12.5) | 5 (7.7) |
| **Mann-Whitney U** | 1067.500 | 10388.000 | 20270.000 |
| **P**           | 0.100b | 0.017 | 0.491 |
| Age             |           |      |      |           |      |      |
| <40             | 138 (13.3) | 2 (50.0) | 87 (12.2) | 3 (5.0) | 78 (10.1) | 3 (3.9) |
| 40-49           | 428 (41.4) | --a | 218 (30.6) | 28 (46.7) | 233 (30.1) | 24 (31.6) |
| 50-64           | 259 (25.0) | 2 (50.0) | 257 (36.1) | 20 (33.3) | 390 (37.5) | 7 (35.6) |
| 65+             | 209 (20.2) | --a | 150 (21.1) | 9 (15.0) | 173 (22.4) | 22 (28.9) |
| **Mann-Whitney U** | 1529.000 | 20021.500 | 26602.000 |
| **P**           | 0.400b | 0.398 | 0.149 |
Table 3 (on next page)

Relationship between pathological characteristics and method of detection of breast cancer patients after adjusting for age.

a OR=odds ratio values. The OR value and P value was calculated by using multinomial logistic regression model after adjusting for age. b There was no data in the current group. c P value indicates statistical significance at the 0.05 level.
| Characteristics | 1995–2000 | | | 2010 | | | 2015 | | |
|-----------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
|                 | OR\(^a\)  | 95\%CI    | P         | OR\(^a\)  | 95\%CI    | P         | OR\(^a\)  | 95\%CI    | P         |
| **T stage**     |           |           |           |           |           |           |           |           |           |
| T2 vs T1        | --\(^b\)  | --\(^b\)  | --\(^b\)  | 2.817     | 1.497 - 5.300 | 0.001\(^c\) | 3.820     | 2.111 - 6.915 | <0.001\(^c\) |
| T3-4 vs T1      | 2.961     | 0.303 - 28.926 | 0.351 | 0.023     | 0.888 - 16.397 | 0.072 | 3.835     | 0.891 - 16.498 | 0.071 |
| **N stage**     |           |           |           |           |           |           |           |           |           |
| N1 vs N0        | 0.851     | 0.119 - 6.078 | 0.872 | 1.832     | 0.882 - 3.806 | 0.105 | 1.339     | 0.726 - 2.469 | 0.351 |
| N2-3 vs N0      | --\(^b\)  | --\(^b\)  | --\(^b\)  | 2.775     | 1.203 - 6.400 | 0.017\(^c\) | 1.308     | 0.688 - 2.486 | 0.413 |
| **Histologic grade** |           |           |           |           |           |           |           |           |           |
| II vs I         | --\(^b\)  | --\(^b\)  | --\(^b\)  | 1.636     | 0.793 - 3.375 | 0.182 | 0.725     | 0.217 - 2.424 | 0.601 |
| III vs I        | 4.544     | 0.463 - 44.572 | 0.194 | 5.763     | 1.233 - 26.945 | 0.026\(^c\) | 1.251     | 0.284 - 5.517 | 0.767 |
Comparison of the difference between self-detected and screen-detected breast cancer patients in (a) T stage, (b) N stage, and (c) histologic grade in 1995–2000, 2010, and 2015.

Techniques of dealing with missing data included (R) complete-case analysis; (A1–5) multiple imputation by chained equations; (B1–5) completely randomized imputation; (C) arbitrarily replacing missing mode of detection into self-detected mode and deleting other missing values in the group; (D) arbitrarily replacing all missing detection method values into screen-detected mode and deleting other missing values in the group.
Figure 2 (on next page)

Frequency distribution at diagnosis, by detection mode in 1995–2000 (95-00), 2010 (10), and 2015 (15).

The age distribution of screen- and self-detected patients was constructed using the 2016 Excel software, while the patients with missing values of detection mode were deleted. Periods of self-detected patients included 1995 to 2000 in full line (Sel.1995-2000), 2010 in dotted dot line (Sel.2010) and 2015 in square dot line (Sel.2015). Periods of screen-detected patients included 1995 to 2000 in dash-dot line (Scr. 1995-2000), 2010 in long dashed line (Sel.2010) and 2015 in short dashed line (Sel.2015).
