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 group. 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.

1 Comparison of pathological characteristics between self-detected and screen-detected invasive

2 breast cancers in Chinese women: a retrospective study

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23   **Abstract**

24   **Background**: In China, there is insufficient evidence to support that screening programs can

25   detect breast cancer earlier and improve outcomes compared with patient self-reporting.

26   Therefore, we compared the pathological characteristics at diagnosis between self-detected and

27   ~~screen~~-detected cases of invasive breast cancer at our institution and determined whether these

28   characteristics were different after the program's introduction (versus [vs] prior to).

29   **Methods**: Three databases were selected (breast cancer diagnosed in 1995–2000, 2010, and

30   2015), which provided a total of 3,014 female patients with invasive breast cancer. The cases

31   were divided into self-detected and screen-detected ~~group.~~ The pathological characteristics were

32   compared between the two groups and multiple imputation and complete randomized imputation

33   were used to deal with missing data.

34   **Results**: Compared with patient self-reporting, screening was associated with the following

35   factors: a higher percentage of stage T1 tumors (75.0% vs 17.1%, P = 0.109 in 1995–2000; 66.7%

36   vs 40.4%, P < 0.001 in 2010; 67.8% vs 35.7%, P < 0.001 in 2015); a higher percentage of tumors

37   with stage N0 lymph node status (67.3% vs 48.4%, P = 0.007 in 2010); and a higher percentage

38   of histologic grade I tumors (22.9% vs 13.9%, P = 0.017 in 2010).

39   **Conclusions**: ~~Screen~~-detected breast cancer was associated with a greater number of favorable

40   pathological characteristics. However, although screening had a beneficial role in early detection

41   in China, we found fewer patients were detected by screening in this study compared with those

42   in Western and Asian developed countries.

1. Introduction

43
44   Breast cancer has become the major cause of death in Chinese women [1, 2]. According to

45   Chinese urban cancer registries, the overall incidence of breast cancer has increased at a rate of 2%–

46   5% annually, with a peak incidence at an age of approximately 50 years [3–5, 2]. Early tumor

47   detection, before symptoms appear, could significantly improve survival [6–9].

48   The National Health and Family Planning Commission of the People's Republic of China

49   organized a three-year breast cancer screening program for women aged 35 to 69 years between

50   2009 and 2011, with a second phase of screening launched in 2012 [5]. The first phase of the

51   program screened 1.2 million women and detected 440 cases with early-stage lesions, giving a

52   diagnostic rate of 48.0 per 100,000 women [5]. Concurrently, in 2009, the All-China Women's

53   Federation and the National Health and Family Planning Commission organized a screening

54   program that offered free screening for breast and cervical cancer to women in rural China. As of

55   2014, about 48.35 million women in rural China had received free tests since the program's

56   inception. The guidelines for breast cancer screening in China, which were first published in

57   2007 and updated in 2015, recommend women at average risk of breast cancer are encouraged to

58   have mammography combined with clinical breast examination after age 40 years. Even though,

59   there is no national organized screening program [10]. Zhu et al reported the long-term prognosis

60   of breast cancers has been improved during the past 40 years [11]. This article was aimed to

61   observe whether the distribution of pathological characteristics at diagnosis had differed since

62   the introduction of limited screening programs.

63   Studies worldwide have indicated that screen-detected patients have more favorable survival

64   outcomes compared with the patients with self-discovered breast cancer (i.e., self-detected

65   cancer) [12–14]. Screen-detected cancers tend to be of a smaller size, to have better

66   differentiation, and to be at an earlier stage [15]. In a study carried out in a private hospital in

67   Hong Kong, patients with screen-detected breast cancer had greater numbers of favorable

68   pathological characteristics than a self-detected group [16]. Therefore, the second aim of this

69   study was to compare the pathological characteristics of the self-detected (symptomatic) and

70   screen-detected (asymptomatic) invasive breast cancer in Tianjin, China.

71

72   **2. Materials and Methods**

73   2.1 Information of database and subjects

74   This was a retrospective cohort study conducted at the Tianjin Medical University Cancer

75   Institute and Hospital. Since 1995, all cases of breast cancer treated in this hospital have been

76   recorded in a structured database. We identified cases for 1995–2000 (paper documentation),

77   2010 (half paper and half electronic documentation), and 2015 (electronic documentation),

78   taking care to exclude those cases with ductal carcinoma in situ and bilateral breast cancer. The

79   study was approved by the Ethics Committee in Tianjin Medical University Cancer Institute and

80   Hospital.

81   2.2 Data extraction

82   Clinical histories and pathological characteristics were obtained from the three databases by

83   two authors individually (Zhang Q. and Ding L.), including the age of patients at initial diagnosis

84   and the cancer detection method. Different records between authors were re-checked.

85   Pathological characteristics included tumor size staging and lymph node staging and histologic

86   grade based, respectively, on the tumor-node-metastasis classification system of the American

87   Joint Committee on Cancer [17] and the World Health Organization classification of tumors [18].

88   2.3 Methods of detection

89   Cases were divided into two groups, based on method of detection: a self-detected group and

90   a screen-detected group. Patients in the screen-detected group were primarily screened by

91   population-based or opportunistic screening with mammography, ultrasound, or clinical breast

92   examination. Patients in the self-detected group were defined as those with obvious clinical

93   symptoms at presentation, including nipple discharge, pain, a palpable axillary lump, a palpable

94   breast lump, or a combination of those symptoms.

95   2.4 Statistical analysis

96   Descriptive statistics were used to show the demographic and pathological characteristics of

97   the patients. Pearson's chi-square or Fisher's exact test was used to analyze categorical variables,

98   and the Mann–Whitney U test was used to analyze ordinal variables. Multinomial logistic

99   regression analyses were used to analyze associations between method of detection and

100   pathological characteristics. The tumor size (T1, T2 and T3-4), node lymph stage (N0, N1 and

101   N2-3) and histologic grade (I, II and III) were treated as the outcome variables. The category

102   "T1", "N0" and "I" was used as the reference category in tumor size model, node lymph stage

103   model and histologic grade model respectively. The variable "age" was divided into four

104   categories: cases younger than 40, 40 to 49, 50 to 59, and aged 60 and older. The variable

105   "method of detection" and "age" was included in these models. The null hypothesis was that

106   there would be no significant difference between variables. A significance level of 0.05 was used

107   for two-tailed P values.

108   2.5 Techniques of dealing with missing data

109   To maximize the likelihood of comparability and equivalence, four methods were used to

110   deal with missing data based on a missing-at-random assumption. These were as follows: (A)

111   multiple imputation by chained equation (five times) (by R Project, version 3.3.2) [19, 20], with

112   age group, T stage, N stage, histologic grade and detection modes included into multivariate

113   regression model; (B) complete randomized imputation (five times), stratified by year [21]; (C)

114   arbitrarily replacing all missing values for the detection methods into the self-detected mode and

115   deleting other missing values in the group; (D) arbitrarily replacing a missing mode of detection

116   into the screen-detected mode and deleting other missing values in the group.

117

118   **3. Results**

119   3.1 Pathological characteristics of breast cancer patients

120   We identified 1,086, 1,053, and 1,047 female cases from databases in 1995–2000, 2010, and

121   2015, respectively. From these, we excluded 172 women with ductal carcinoma in situ or

122   bilateral breast cancer. The final study therefore included 3,014 cases of invasive breast cancer:

123   1,060 in 1995–2000, 946 in 2010, and 1,008 in 2015. The median (range) ages at presentation

124   were 48.0 (19–80) years in 1995–2000, 51.0 (22–82) years in 2010, and 52.0 (18–82) years in

125   2015. The general pathological characteristics of the cancers, including T stage, N stage, and

126   histologic grade, are shown in Table 1 for each period.

127   3.2 Pathological differences between the self-detected and screen-detected groups

128   The screen-detected group had a higher proportion of stage T1 tumors than the self-detected

129   group in each database (75.0% vs 17.1%, $P = 0.109$ in 1995–2000; 66.7% vs 40.4%, $P < 0.001$ in

130   2010; and 67.8% vs 35.7%, $P < 0.001$ in 2015) (Table 2 and Fig.1-a). The proportion with

131   negative lymph nodes (N0) was also slightly higher in the screen-detected group than in the self-

132   detected group in each database (50.0% vs 47.4%, 67.3% vs 48.4%, and 55.2% vs 48.5% in

133   1995–2000, 2010, and 2015, respectively), although statistical significance was only reached for

134   2010 ($P = 0.007$) (Table 2 and Fig.1-b). The percentages of histologic grade I tumors were

135   significant higher in screen-detected group than that in self-detected group (22.9% vs 13.9%, $P =$

136   0.017 in 2010) (Table 2 and Fig.1-c). The age distribution showed no significant difference

137   between self-detected and screen-detected group (Table 2 and Fig.2). After adjusting for age,

138   self-detected group had increased T2 stage cases in 2010 (T2 vs T1, OR = 2.817, P = 0.001) and

139   2015 (T2 vs T1, OR = 3.820, P < 0.001), increased N2-3 stage cases in 2010 (N2-3 vs N0, OR

140   = 2.775, P = 0.017) and increased histologic grade III in 2010 (grade III vs I, OR = 5.763, P =

141   0.026) significantly, compared with screen-detected group (Table 3).

142

143   **4. Discussion**

144   In this study, we retrospectively compared the differences in pathological characteristics

145   between self-detected and screen-detected breast cancer. The proportion of cases identified by

146   the screening program increased significantly before the introduction of screening. The screen-

147   detected group had smaller tumor sizes and tended to have less lymph node involvement and

148   lower histologic grades compared with the self-detected group.

149   The coverage of the breast cancer screening remains low in Chinese population. From 2009

150   to 2011, a breast cancer screening program, which was launched by the Chinese Anti-Cancer

151   Association with the permission of the Chinese government, only covered 1.46 million women

152   and only 631 with breast cancer [5]. As of 2014, the total number of screened women had risen

153   to 48.35 million, but this still accounts for less than 5% of the population. Another possible

154   explanation for the low percentage of screen-detected cancer may relate to the theory and

155   technology underpinning existing screening programs and guidelines, typically relying on a lack

156   of indigenous studies. Moreover, the Chinese guidelines for breast cancer screening were not

157   published by the Chinese Anti-Cancer Association, Committee of Breast Cancer Society until

158   2007 [22] and have been updated four times over the last decade. These guidelines recommend

159   that women at average risk of breast cancer only undergo opportunistic screening mammography.

160   However, ultrasound and parallel clinical breast examination are the primary screening tools in

161   second-generation screening programs [5].

162   Consistent with the findings of previous studies from Japan, Singapore, Korea, and some

163   Western countries, we confirmed the benefits of screening when seeking to detect breast cancer

164   at an early stage [13–15, 23, 24]. Specifically, we identified the prognostic advantages, based on

165   pathological findings at diagnosis, for asymptomatic patients with screen-detected cancers.

166   Comparable to our results (66.7%–75.0% vs 17.1%–40.4%), higher proportions of screen-

167   detected patients were reported to have stage T1 cancer compared with self-detected groups in

168   studies in both Korea (59.2% vs 31.7%) [14] and Hong Kong (44.7% vs 33.4%) [16]. A study in

169   Singapore also indicated that screening was an independent factor for better clinical staging at

170   presentation, after adjusting for race and menopausal status [12]. However, although there were

171   trends, we did not find any statistically significant difference for lymph node status or histologic

172   grade between the groups in this study. Mammography was not popular yet as the modality of

173   breast cancer screening in China [5, 10]. Breast cancer examination was used in most of the

174   screening program which might limit the performance of screening and results unsatisfied tumor

175   stage.

176   In this study, long-term information of 3,014 breast cancer patients from Tianjin Medical

177   University Cancer Institute and Hospital were collected. Because the breast cancer patients at our

178   hospital came from all over the country of China, this database represent a trend of Chinese

179   breast cancer. However, this study has two main limitations. The first is that it was retrospective

180   and that approximately 12% of values were missing in the detection mode due to the use of

181   electronic documentation. Hence, four imputation methods were used to ascertain whether major

182   differences occurred on the comparison of pathological characteristics between self-detected and

183   screen-detected breast cancer. When using multiple imputation by chained equations, the missing

184   values were completed depending on the interdependency between values [19]. In this regard,

185   more preferable results tended to be classified into the screen-detected group. When using

186   completely randomized imputation stratified by year, no tendency was seen in either direction.

187   When the missing detection mode values were replaced by "self-detected," the pathological

188   advantage of the screen-detected group was attributed to the self-detected group. The differences

189   between the two groups may therefore have been underestimated. When the missing detection

190   mode values were replaced by "screen-detected," the disadvantage in the self-detected group was

191   attributed to the screen-detected group, also potentially leading to an underestimation of the

192   differences between the two groups. The second limitation is that there was no information about

193   the follow-up or survival status of the patients, for which further studies would be required. A

194   study from the UK reported that the impact of introducing such a screening program on survival

195   was small but significant, and that most of the improved survival was due to a shift in the

196   Nottingham Prognostic Index (used to determine prognosis following surgery for breast cancer)

197   [25]. Similar shifts in pathologic characteristics of prognosis were identified both in this

198   retrospective investigation and in previous studies [26].

199

200   **5. Conclusion**

201   This study indicates that the breast cancers detected by screening had more favorable

202   clinicopathologic characteristics than those detected by themselves. We also found fewer patients

203   were detected by screening in this study compared with those in Western and Asian developed

204   countries.

205   **Acknowledgments**

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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[a], 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[b], 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)

1

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		0.109[b]		<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		0.868[b]		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		0.100[b]		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-	428 (41.4)	--[a]	218 (30.6)	28 (46.7)	233 (30.1)	24 (31.6)
	50-	259 (25.0)	2 (50.0)	257 (36.1)	20 (33.3)	390 (37.5)	27 (35.6)
	60-	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		0.400[b]		0.398		0.149	

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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

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Figure 1(on next page)

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.
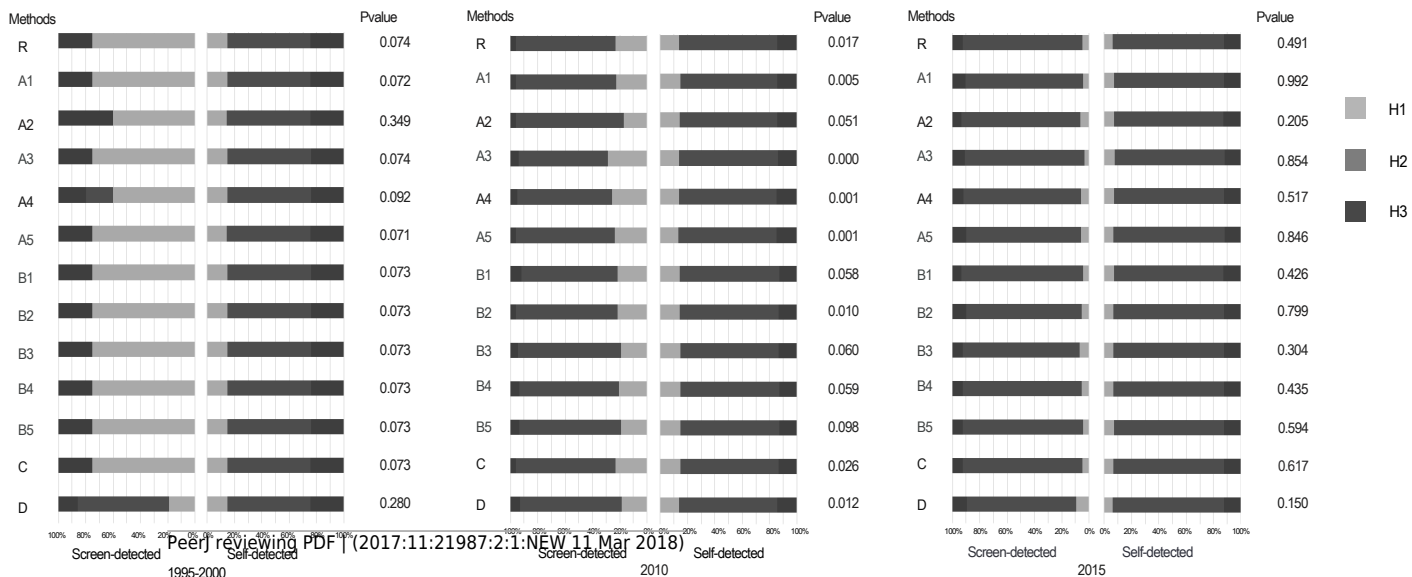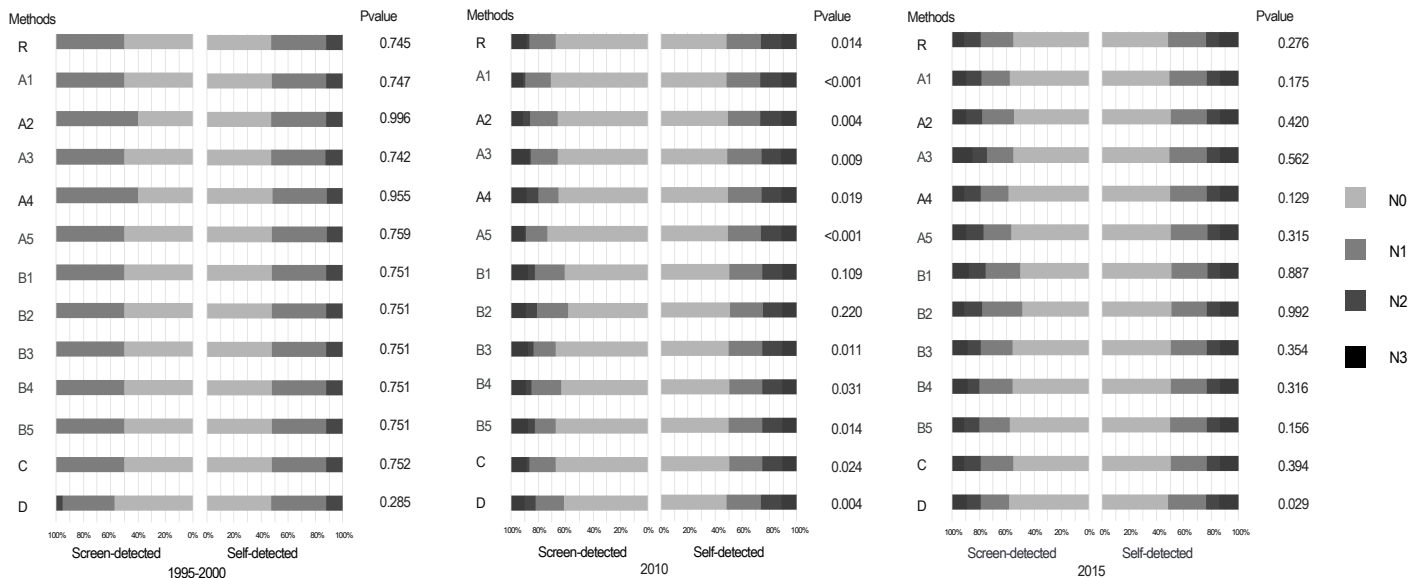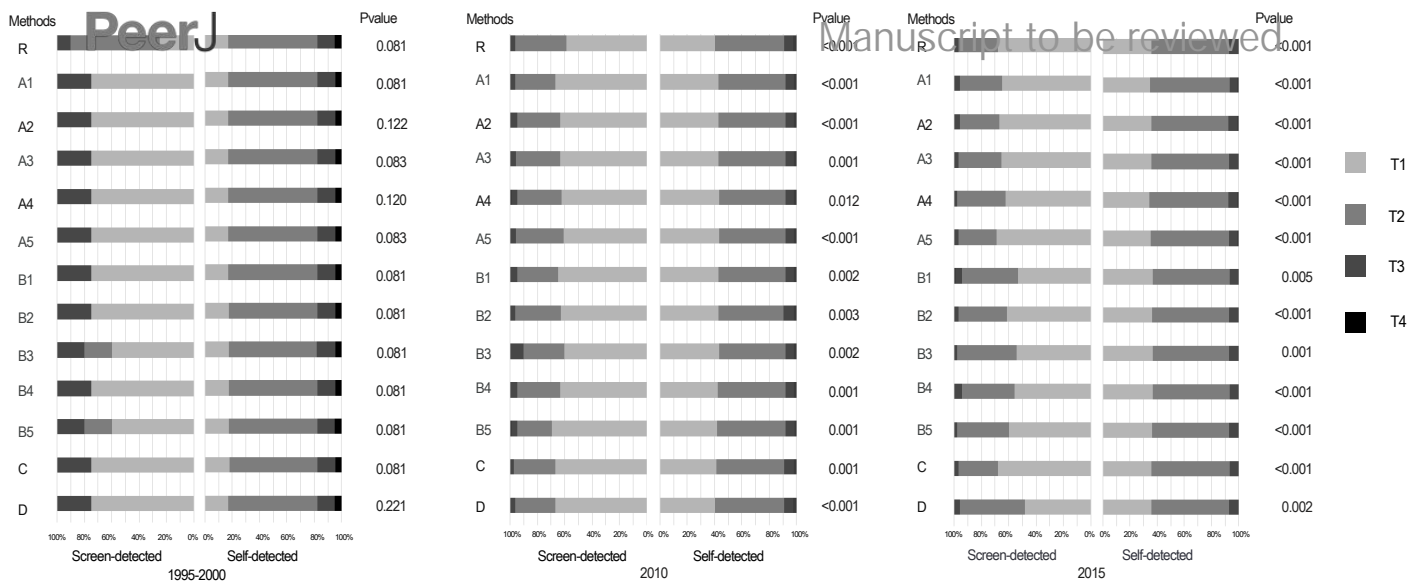
Methods | Pvalue | Methods | Pvalue | Methods | Pvalue

a

R — 0.081 | R — <0.001 | R — <0.001
A1 — 0.081 | A1 — <0.001 | A1 — <0.001
A2 — 0.122 | A2 — <0.001 | A2 — <0.001
A3 — 0.083 | A3 — 0.001 | A3 — <0.001
A4 — 0.120 | A4 — 0.012 | A4 — <0.001
A5 — 0.083 | A5 — <0.001 | A5 — <0.001
B1 — 0.081 | B1 — 0.002 | B1 — 0.005
B2 — 0.081 | B2 — 0.003 | B2 — <0.001
B3 — 0.081 | B3 — 0.002 | B3 — 0.001
B4 — 0.081 | B4 — 0.001 | B4 — <0.001
B5 — 0.081 | B5 — 0.001 | B5 — <0.001
C — 0.081 | C — 0.001 | C — <0.001
D — 0.221 | D — <0.001 | D — 0.002

Screen-detected Self-detected 1995-2000 | Screen-detected Self-detected 2010 | Screen-detected Self-detected 2015

Legend: T1, T2, T3, T4

b

R — 0.745 | R — 0.014 | R — 0.276
A1 — 0.747 | A1 — <0.001 | A1 — 0.175
A2 — 0.996 | A2 — 0.004 | A2 — 0.420
A3 — 0.742 | A3 — 0.009 | A3 — 0.562
A4 — 0.955 | A4 — 0.019 | A4 — 0.129
A5 — 0.759 | A5 — <0.001 | A5 — 0.315
B1 — 0.751 | B1 — 0.109 | B1 — 0.887
B2 — 0.751 | B2 — 0.220 | B2 — 0.992
B3 — 0.751 | B3 — 0.011 | B3 — 0.354
B4 — 0.751 | B4 — 0.031 | B4 — 0.316
B5 — 0.751 | B5 — 0.014 | B5 — 0.156
C — 0.752 | C — 0.024 | C — 0.394
D — 0.285 | D — 0.004 | D — 0.029

Screen-detected Self-detected 1995-2000 | Screen-detected Self-detected 2010 | Screen-detected Self-detected 2015

Legend: N0, N1, N2, N3

c

R — 0.074 | R — 0.017 | R — 0.491
A1 — 0.072 | A1 — 0.005 | A1 — 0.992
A2 — 0.349 | A2 — 0.051 | A2 — 0.205
A3 — 0.074 | A3 — 0.000 | A3 — 0.854
A4 — 0.092 | A4 — 0.001 | A4 — 0.517
A5 — 0.071 | A5 — 0.001 | A5 — 0.846
B1 — 0.073 | B1 — 0.058 | B1 — 0.426
B2 — 0.073 | B2 — 0.010 | B2 — 0.799
B3 — 0.073 | B3 — 0.060 | B3 — 0.304
B4 — 0.073 | B4 — 0.059 | B4 — 0.435
B5 — 0.073 | B5 — 0.098 | B5 — 0.594
C — 0.073 | C — 0.026 | C — 0.617
D — 0.280 | D — 0.012 | D — 0.150

Screen-detected Self-detected 1995-2000 | Screen-detected Self-detected 2010 | Screen-detected Self-detected 2015

Legend: H1, H2, H3

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).