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EPIDEMIOLOGY

# Is the high proportion of young age at breast cancer onset a unique feature of Asian breast cancer?

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## Abstract

**Purpose** Women with breast cancer in Asian and Western countries are similar in many respects, but there are also differences, such as in the age at onset and the proportion of breast cancer occurring at younger ages. There is controversy as to whether these differences are due to inter-racial genetic differences or to environmental or other factors.

**Methods** Using the Korean Breast Cancer Society's large breast cancer registry, we investigated the causes of Koreans' unique breast cancer characteristics by examining the changes in the incidence and proportion of young-onset breast cancer (YBC) in Korea over time. We analyzed data from 108,894 patients to compare characteristics between patients with YBC and non-YBC. For a subtype analysis, we analyzed data from 85,691 patients from 2000.

**Results** Among the 108,894 patients, 17,877 (15.5%) had YBC. The tumors associated with YBC showed aggressive clinicopathologic features. The incidence of breast cancer in Korea has increased over time, and while both YBC and non-YBC increased each year, the increase in non-YBC was more pronounced; thus, the proportion of YBC has decreased over time. By 2020, it appears that the ratio of YBC in Korea will be similar to that in Western countries. The increase in YBC was mainly due to an increase in the luminal A subtype. The incidence of other YBC subtypes did not change over time.

**Conclusions** Our data suggest that the current high proportion of YBC is probably not a unique feature of breast cancer in Asia but rather a transient phenomenon. Additionally, our results indirectly suggest that there were different causes for breast cancer in different age groups, suggesting the importance of using different approaches for different age groups to establish policies for preventing breast cancer.

**Keywords** Asia · Breast neoplasm · Incidence · Korea · Young adult

## Introduction

Breast cancer is the most commonly occurring cancer in Western women [1]. Although the incidence of breast cancer is higher in Western countries, changes in the incidence of

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and mortality from breast cancer have been the most dramatic in Asia [1–6]. Epidemiologic studies indicate that lifestyle factors related to Westernization are associated with increases in breast cancer incidence in Asian countries, which may be explained by a diet higher in animal fat, an increase in obesity, earlier menarche, and changing parity patterns [3, 4]. Comparisons of epidemiologic and clinical outcome data for breast cancer show important similarities between Asian and Western women; however, there are also clear differences, including the different peak age at onset and the proportion of young-onset breast cancer (YBC) [5, 6]. In Asia, the peak age at onset is in a woman's 40s, whereas in Western countries, it peaks in a woman's 60s [5, 7–10]. A high proportion of YBC is another unique characteristic of Asian breast cancer. The incidence of YBC is ~5% in the West [2, 11–13], compared to the much higher proportion in Asia, which is up to 20% [7, 9, 14]. Studies have reported racial differences related to breast cancer subtype. Several have reported a greater risk of triple-negative breast cancer (TNBC) in African-American women [9, 15–17] and of the human epidermal growth factor receptor 2 (HER2)-overexpressing type in Asian/Pacific Islanders compared with those in Caucasian women [18–20]. These differences may be due to genetic differences between Asian and Western breast cancer, or they may be due to environmental factors, or gene-by-environment interactions.

The purpose of this study was to investigate the causes of the unique characteristics of Korean breast cancer by examining the changes in the incidence of breast cancer and proportion of YBC in Korea over time. Additionally, we analyzed subtype changes to determine the changes in breast cancer characteristics in Korea from 2000. Finally, we sought to predict future trends for Korean breast cancer.

## Materials and methods

### Korean Breast Cancer Registry (KBCR)

The KBCR is a prospectively maintained, web-based database of the Korean Breast Cancer Society (KBCS) [2, 21, 22]. Nationwide, 102 general hospitals with at least 400 beds each, including 41 university hospitals and 61 surgical training hospitals, voluntarily participate in this registry. The KBCR includes essential registry items (the patient's unique Korean resident registration number, sex, age, the surgical method used, and cancer stage) and many other optional items, such as social data (place of residence, educational attainment, marital status, etc.), clinical data (body mass index [BMI], history of breastfeeding, menopause status, etc.), pathologic factors (estrogen receptor [ER] status, progesterone receptor [PR] status, HER2 status, subtype, histological grade, and lymphovascular invasion), and treatment (surgery, adjuvant therapy, etc.). The Korean Central Cancer Registry provides mortality data only, and the KBCR does not include information on tumor recurrence.

### Definitions of YBC and incidence

There are various definitions for YBC. We defined it as an onset of breast cancer occurring in a woman under 40 years of age. The incidence of breast cancer in this study was defined as the number of new cases occurring per 100 Korean women per year. Among them, patients with missing data related to stage and subgroup were excluded from analysis. Because cancer cases with missing data were excluded from the analysis, it should be considered that our study reports an incidence of breast cancer that is different from the overall incidence of breast cancer reported in national data.

### Intrinsic subtype classification by immunohistochemistry

A molecular subtype classification was performed based on immunohistochemical surrogates for ER, PR, and HER2 status. Breast cancer subtype definitions were as follows: Luminal A (ER or PR+, HER2−), luminal B (ER or PR+/HER2+), HER2-enriched (ER−/PR−/HER2+), and TNBC (ER−/PR−/HER2−).

### Data selection and cleaning (Fig. 1)

Approval was granted by the Institutional Review Board of Samsung Medical Center (IRB File No. 2015-10-189). To protect personal information, patient records and information were anonymized and de-identified by the KBCS.

For analysis, we excluded patients with incomplete data, such as those with unknown surgical methods and pathologic stage, and data before 1990 were not included because of questionable reliability. After this exclusion, we included data from 108,894 patients. This group was used to compare YBC and non-YBC to determine the characteristics of YBC (Table 1), breast cancer incidence change over time (Fig. 2) and the prediction of proportion change of in Korea (Fig. 4). To see subtype (Fig. 3) changes over time, we analyzed 85,691 patients who were able to obtain reliable data for hormone receptor and HER2 status and the Korean female population from 2000 to 2013.

### Statistical analysis

Comparisons of clinicopathologic characteristics between groups were performed using chi-squared and Fisher's exact tests for categorical variables. Three hypotheses to explain the differences in the frequencies and proportions

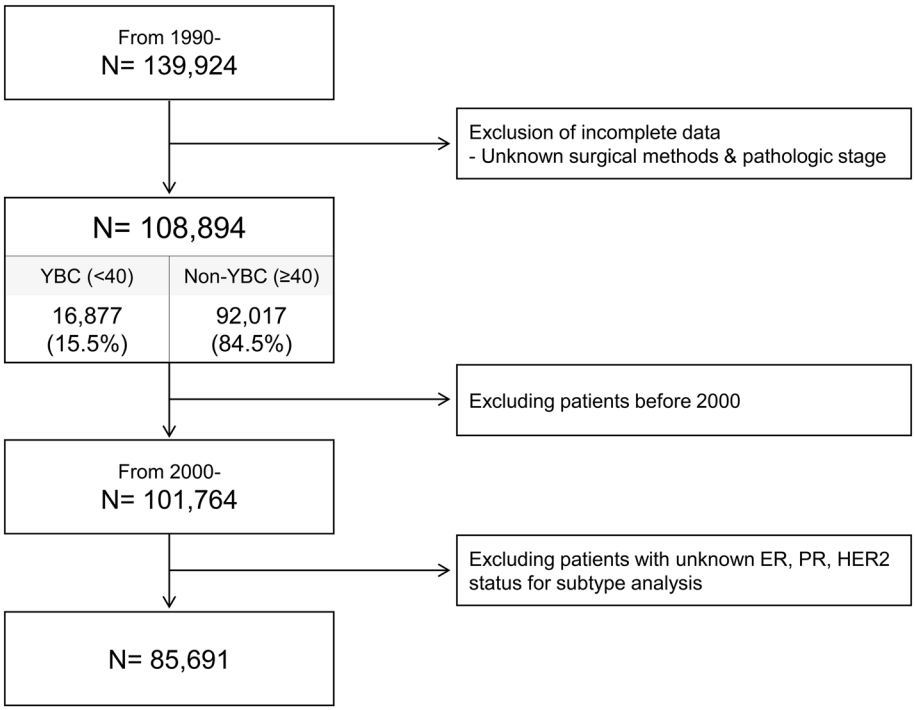


**Fig. 1** Patient selection

between each age group and subtype groups, for the increasing incidence over time, and for the interaction effect between groups and time period (2000–2013) with respect to incidence were tested using a multiple linear regression analysis. Bonferroni corrections were performed for multiple comparison tests. We fit a linear regression line using the proportion of YBC data points between 2008 and 2013 and predicted the YBC incidence after 2014. All analyses were performed using SAS 9·4 (SAS Institute, Cary, NC, USA).

## Results

### Characteristics of YBC in Korea (Table 1)

Of a total 108,894 patients, 16,877 (15.5%) had YBC. A comparison of the data for patients with YBC and non-YBC is shown in Table 1. The median age for patients to be diagnosed with YBC was 36 years (range, 14–39). Patients with YBC were significantly more likely to be unmarried, nulliparous, well educated, treated with total mastectomy, and breast reconstruction. The tumors associated with YBC showed aggressive clinicopathologic features, including higher nuclear grade, positive lymphovascular invasion, advanced pathologic stage, ER and PR negativity, negative HER2 expression, and a high proportion of TNBC.

### Breast cancer development over time (Fig. 2)

The overall number of cases and incidence of both total breast cancer and non-YBC increased over time ($p < 0.0001$). Compared to non-YBC and breast cancer overall, the number of cases and incidence of YBC increased relatively slowly ($p = 0.0176$ for the number of cases and $p = 0.0012$ for the incidence according to the regression analysis and corrected with Bonferroni's method). In terms of proportion, the proportion of YBC neared 30% in the 1990s. This high proportion of YBC decreased annually. By the 2010s, the proportion of YBC had decreased to about 10%.

### Breast cancer development by subtype for each age subgroup (Fig. 3)

We sought to determine the number of cases and the change in incidence over time by cancer subtype for each age group. In the YBC group, both the frequency ($p < 0.0001$) and incidence ($p = 0.0002$) of the luminal A subtype significantly increased over time. However, the frequency of the luminal B subtype ($p = 0.2688$), HER2 subtype ($p = 0.796$), and TNBC ($p = 1.0000$) did not increase over time. With respect to incidence, the luminal B subtype ($p = 0.5864$), HER2 subtype ($p = 1.0000$), and TNBC ($p = 1.0000$) also showed a stable incidence. Compared to the other subtypes, then, the increase in the luminal A subtype was statistically significant ($p < 0.0001$). For the non-YBC group, the frequency and incidence of all subtypes significantly increased over

**Table 1** Characteristic comparison between young age onset breast cancer (YBC) and other breast cancers ($N = 108,894$)

| | Analyzed total patients (%) | YBC (< 40) ($N = 16,877$ (15.5%)) | Others (≥ 40) ($N = 92,017$ (84.5%)) | $p$ value |
|---|---|---|---|---|
| Age (median (range)) | | 36 (14–39) | 50 (40–99) | |
| Marital status | 80,082 (73.5) | | | < 0.0001 |
| Single | 4729 | 2294 (18.0) | 2435 (3.6) | |
| Married | 75,353 | 10,433 (82.0) | 64,920 (96.4) | |
| Parity | 72,489 (66.6) | | | < 0.0001 |
| Nulliparous | 1956 | 597 (6.0) | 1359 (2.2) | |
| Parous | 70,533 | 9385 (94.0) | 61,147 (97.8) | |
| Lactation experience | 69,202 (63.5) | | | < 0.0001 |
| Yes | 48,540 | 5435 (11.2) | 43,105 (88.8) | |
| No | 20,662 | 5445 (26.4) | 15,217 (73.6) | |
| Education | 57,690 (53.0) | | | < 0.0001 |
| More than college | 16,257 | 4845 (52.5) | 11,412 (23.6) | |
| Less than college | 41,433 | 4388 (47.5) | 37,045 (76.4) | |
| Breast surgery | 108,894 (100) | | | 0.014 |
| TM | 52,990 | 8359 (49.5) | 44,631 (48.5) | |
| BCS | 55,904 | 8518 (50.5) | 47,386 (51.5) | |
| Reconstruction | 90,079 (82.7) | | | < 0.0001 |
| Yes | | 2324 (17.0) | 6088 (8.0) | |
| No | | 11,378 (83.0) | 70,289 (92.0) | |
| Tumor location | 101,696 (93.4) | | | 0.139 |
| Right breast | 49,750 | 7837 (49.5) | 41,913 (48.8) | |
| Left breast | 51,946 | 8008 (50.5) | 43,938 (51.2) | |
| Multiplicity | 92,620 (85.1) | | | < 0.0001 |
| Single | 82,034 | 12,451 (86.3) | 69,583 (89.0) | |
| Two | 7107 | 1245 (8.6) | 5862 (7.5) | |
| More than 3 | 3479 | 733 (5.1) | 2746 (3.5) | |
| Histologic grade | 86,643 (81.0) | | | < 0.0001 |
| Low | 14,651 | 1569 (11.8) | 13,082 (17.8) | |
| Intermediate | 40,253 | 5878 (44.3) | 34,375 (46.9) | |
| High | 31,739 | 5829 (43.9) | 25,910 (35.3) | |
| Histopathology | 106,882 (98.2) | | | < 0.0001 |
| In situ | 11,098 | 1552 (9.4) | 9546 (10.6) | |
| IDC | 91,870 | 14,604 (88.2) | 77,266 (85.5) | |
| ILC | 2919 | 238 (1.4) | 2681 (3.0) | |
| Mucinous carcinoma | 147 | 17 (0.1) | 130 (0.1) | |
| Others | 848 | 144 (0.9) | 704 (0.8) | |
| Presence of LVI | 85,523 (78.5) | | | < 0.0001 |
| Yes | 58,884 | 4693 (37.3) | 21,946 (30.1) | |
| No | 26,639 | 7887 (62.7) | 20,997 (69.9) | |
| Hormone receptor | 108,894 (100) | | | < 0.0001 |
| Negative | 31,979 | 5561 (33.0) | 26,418 (28.7) | |
| Positive | 76,915 | 11,316 (67.0) | 65,599 (71.3) | |
| HER2 | 87,105 (80.0) | | | < 0.0001 |
| Negative | 65,562 | 9924 (76.5) | 55,638 (75.1) | |
| Positive | 21,543 | 3057 (23.5) | 18,486 (24.9) | |
| Subtype | 87,105 (80.0) | | | < 0.0001 |
| Luminal A | 50,251 | 6832 (52.6) | 43,419 (58.6) | |
| Luminal B | 10,772 | 1694 (13.0) | 9078 (12.2) | |
| HER2 enriched | 10,771 | 1363 (10.5) | 9408 (12.7) | |
| TNBC | 15,311 | 3092 (23.8) | 12,219 (16.5) | |

**Table 1** (continued)

| | Analyzed total patients (%) | YBC (< 40) (*N* = 16,877 (15.5%)) | Others (≥ 40) (*N* = 92,017 (84.5%)) | *p* value |
|---|---|---|---|---|
| Stage | 108,894 (100) | | | < 0.0001 |
| In situ | 10,902 | 1528 (9.1) | 9374 (10.2) | |
| I | 39,826 | 5214 (30.9) | 34,615(37.6) | |
| II | 42,762 | 7320 (43.4) | 35,442 (38.5) | |
| III | 14,200 | 2601 (15.4) | 11,599 (12.6) | |
| IV | 1204 | 214 (1.3) | 990 (1.1) | |
| Adjuvant chemotherapy | 97,973 (90.0) | | | < 0.0001 |
| Yes | 66,677 | 11,770 (77.4) | 54,907 (66.3) | |
| No | 31,296 | 3436 (22.6) | 27,860 (33.7) | |
| Adjuvant radiotherapy | 94,544 (86.8) | | | < 0.0001 |
| Yes | 57,746 | 9270 (63.4) | 48,476 (60.7) | |
| No | 36,798 | 5354 (36.6) | 31,444 (39.3) | |
| Adjuvant hormonal therapy | 92,292 (84.8) | | | < 0.0001 |
| Yes | 63,909 | 8990 (63.7) | 54,919 (70.3) | |
| No | 28,383 | 5132 (36.3) | 23,251 (29.7) | |

*BCS* breast conserving surgery, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *LVI* lymphovascular invasion, *TM* total mastectomy, *TNBC* triple-negative breast cancer

time. Among all subtypes, the luminal A subtype increased most quickly. Estimates of the frequency of the luminal A, luminal B, HER2, and TNBC subtypes were 360.24, 56.74, 59.56, and 53.67, respectively. Estimates of the incidence for the luminal A, luminal B, HER2, and TNBC subtypes were 0.0014, 0.0002, 0.0002, and 0.0002, respectively. The rate of increase for the luminal A subtype was almost 5 times that for other subtypes ($p < 0.0001$).

### Prediction of the future change in the proportion of YBC in Korea (Fig. 4)

The proportion of breast cancer developing in women under the age of 40 years in the developed world has been reported to be only 4–7% of all breast cancer patients [11–13]. Our KBCR data showed a higher proportion of YBC (15.5%). However, we also observed a steeper increase in the rate of increase in non-YBC compared to that for YBC, and as a result, the relative proportion of YBC is expected to decrease over time. As shown in Fig. 4, the proportion of YBC has decreased annually, and if this trend continues, in 2020, we predict that the relative proportion of YBC will be similar to that reported for Western countries (Fig. 4).

## Discussion

Our large study based on national data clearly demonstrated changing trends in the incidence of YBC and non-YBC over time in Korea. The increase in the incidence of Korean breast cancer was caused primarily by the increase of non-YBC, and not by an even increase in the incidence of all types of breast cancer. The increase of the luminal A subtype breast cancer was the main contributor to the increase in the incidence of all breast cancer over time, while the increase of non-luminal A subtype was only clear in the non-YBC (Fig. 3).

YBC is considered to be different from breast cancer in older women. Generally, YBC is characterized by a more aggressive phenotype [2, 12, 23–31]. Numerous publications describe that YBC is associated with a higher nuclear grade [12, 23, 25–29, 32, 33], vascular invasion [26, 28, 29], node involvement [2, 12, 24, 25, 27, 33], negative hormone receptor status [2, 12, 23–29, 33], and higher HER2 expression [29, 30]. In this study, we also observed aggressive features in Korean YBC.

Additionally, although there are opposing reports [25, 28], several studies have also shown that younger age itself was an independent prognostic factor [2, 32–34], and that YBC displayed a higher rate of local recurrence [13, 33, 35] and poor prognosis even after aggressive adjuvant treatment [2, 12, 25, 32, 33, 36, 37]. Therefore, recent studies have demonstrated that extensive anti-hormonal therapies noticeably improved outcomes for young women with hormone receptor-positive breast cancer [6, 38, 39]. Because of these unique characteristics and relationship with BRCA mutations, YBC has been recognized as a unique biologic entity.

Compared to that in under-developed and developing countries, the cumulative risk of YBC is higher in developed countries [40]. However, the proportion of YBC among all breast cancer occurrences is very high in undeveloped countries [9, 41–45]. The proportion of breast cancer occurring in women under the age of 40 years is generally about 5% of all breast cancer patients

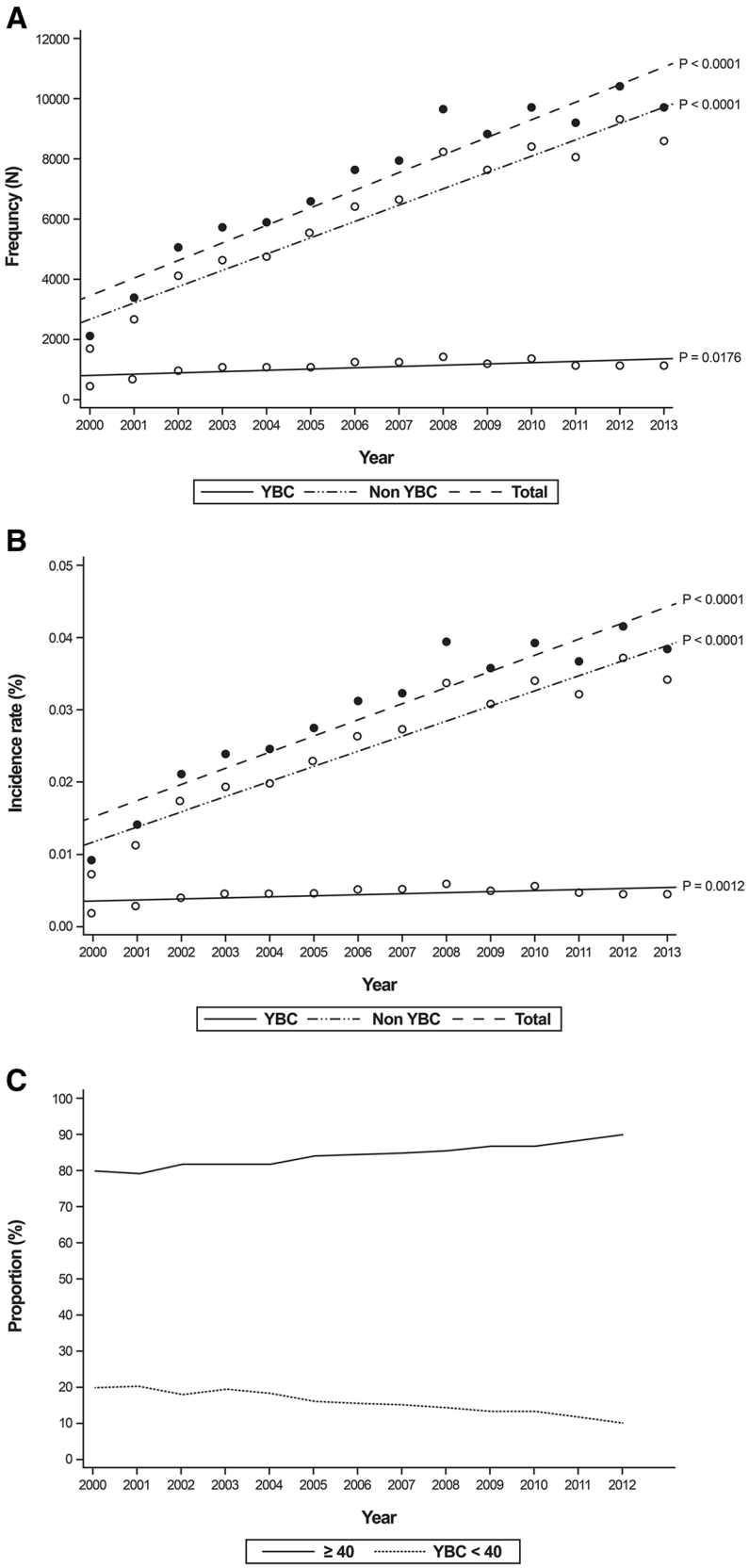


**Fig. 2** Breast cancer development over time, **a** frequency change over time in each group, **b** incidence rate change over time in each group and **c** proportion change over time in each group

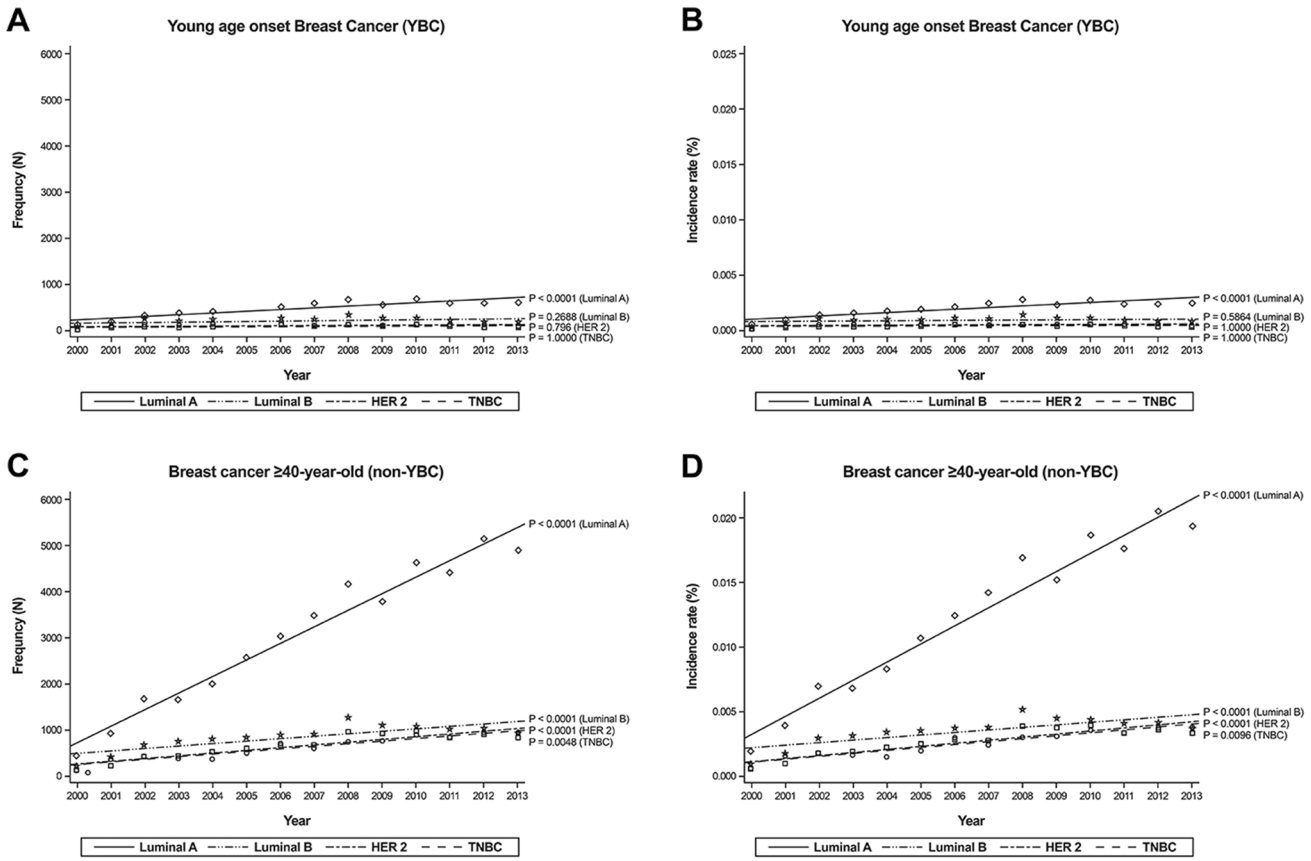


**Fig. 3** Breast cancer development by subtype in each age subgroup, **a** frequency change over time by subtype in young age onset breast cancer, **b** incidence rate change over time by subtype in young age onset breast cancer, **c** frequency change over time by subtype in more than 40-year-old breast cancer patients and **d** incidence rate change over time by subtype in more than 40-year-old breast cancer patients

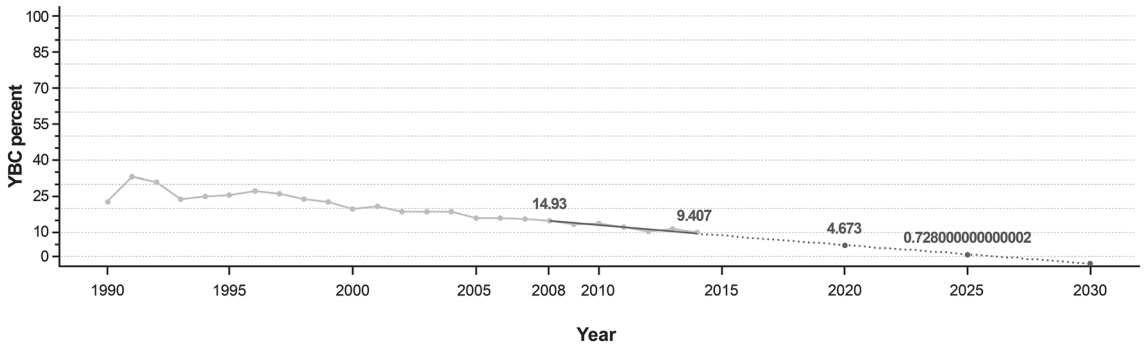


**Fig. 4** Prediction of proportion change of young age onset breast cancer in Korea

in the developed world [11–13]. Anders et al. reported that approximately 7% of women with breast cancer are diagnosed before the age 40 years, based on data from the US Surveillance, Epidemiology and End Results (SEER) study [11, 12]. In the UK, the proportion of YBC was reported to be approximately 4% of all women with breast cancer between 2012 and 2014 [12]. However, our KBCR data showed a higher proportion of YBC, about 15%. Several authors also reported a higher proportion of YBC in Asian countries, up to 20% [7, 9, 14]. Brinton et al. have also shown differences in the rates of YBC between races in the same country. They reported that Caucasians had a higher incidence of breast cancer than African-Americans did after the age of 40 years, but the reverse trend was true among younger women [13]. Because of the high proportion of YBC, the peak age at breast cancer onset is very

young in non-Caucasian countries [5, 7]. The peak age at breast cancer onset is between 40 and 50 years in Asia, while it is between 60 and 70 years in Western countries [5, 7–10]. This is a striking difference between Asian and Western countries.

In addition to differences in the median age at diagnosis for breast cancer and the proportion of YBC, a distinction in the patterns for breast cancer subtypes has also been observed among various populations [9, 15–20]. Some authors reported a greater risk of TNBC among African-American women [9, 15–17] and of the HER2-overexpressing subtype among Asians/Pacific Islanders than among Caucasian women [18–20].

Many breast cancer experts have questioned the causes of these differences among populations. These differences could result from genetic differences in breast cancer incidence between Asians and Caucasians, or they could be due to environmental reasons or combined reasons. Our study for changes in breast cancer development over time may provide an indirect answer to the different incidence of breast cancer among races. Over the last several decades, the incidence of breast cancer onset at an older age has dramatically increased in Korea. However, the increase in YBC over time was smaller than that for non-YBC and the increase of YBC was mainly confined to the luminal A subtype, as the incidence of the non-luminal A subtype in YBC remained stable. Although it is diversified due to globalization, Koreans are relatively less ethnically changed over time. Within this same genetic pool, the increase in specific breast cancer group, such as non-YBC and luminal A subgroup, indicates that these groups were particularly affected by environmental changes over time. On the contrary, the YBC (particularly the non-luminal A subtype) which the incidence rate that has changed little over time can be caused by unchanging factors such as genetic factors. Our results are consistent with the previous studies showing that changes in Westernized lifestyle result (e.g., higher animal fat consumption and increased BMI) and reproductive behaviors (e.g., later age at first birth, nulliparity and fewer children birth) are risk factors for postmenopausal breast cancer and luminal A subtype [4, 46, 47]. The incidence of breast cancer has very quickly increased among women worldwide, and the most widely accepted reason for this global increase is the Westernization of the developing world [4]. In addition to these environmental factors, screening mammography program for women aged 40 years or over could explain the increasing of non-YBC and luminal A subtype breast cancer. In Korea, free screening mammography services were available for the all National Health Insurance beneficiaries in 2002–2003 and from then, the screening program utilization rate has steadily increased [48, 49]. Several studies reported that the luminal A subtype was more frequent among screen-detected breast cancers [50–52].

Based on these reasons, the development of YBCs, which are thought to be highly genetically affected, did not change significantly over time. Conversely, non-YBCs, which are highly environmentally affected, increased rapidly with time. This result, on the other hand, means that the high proportion of YBC in Asian countries is not a unique phenomenon in Asians, but rather a transient phenomenon during Westernizing process. Additionally, it may reflect the original proportion of human breast cancer development before civilization. A report from Western countries also indicated that the overall rate of breast cancer in young women was stable [53].

Although the incidence of breast cancer in Korea is increasing, the relative proportion of YBC decreased annually. If this trend continues, by 2020, we can expect that the proportion of YBC will be similar to that in Western countries (Fig. 4). This inversely implies that the incidence of breast cancer in Korea will continue to increase until at least 2020. A recent report from Japan also indicated that the peak age at breast cancer onset had increased and was similar to that in Western countries [54].

The major concern of this study is selection bias. While this KBCR could provide more information, such as stage and subtype, than nation-wide cancer registry, we could not be sure that this registry represents the whole breast cancer feature in Korea. To overcome this weakness, we compared the data between the KBCR ad nation-wide cancer registry [3]. From 2000 to 2013, The proportion of YBC for each data set is 14.8% (15,086/101,764) from KBCR, and 15.7% (25,487/137,354) from nation-wide cancer registry [3], respectively, giving 95% confidence interval of the difference of these two proportion, (−1.11%, −0.55%). This result provides equivalence of the two YBC proportions with equivalence margin 2%. Based on the comparison analysis, our KBCR can be said to represent Korean breast cancer to some extent. However, for the analysis of each subgroup, because there were numerous unavailable data and missing essential data (e.g., immunohistochemistry results for subtype classification), there still remains a problem of selection bias. The results of this study should therefore be interpreted with caution because of this limitation. Although there were some limitations of this study, this study was conducted with the largest data set in Korea, including stage and molecular subtype data, which are important factors for examining tumor character. In addition to this, to our knowledge, this is the first report to show the serial changes in the incidence of YBC over a long period. Although the genetic characteristics of Koreans could not said to represent Asians, we can say that our study more accurately shows the characteristics and changing trend of breast cancer in Asians more than in Western studies.

This report suggests an answer for the relatively high development of YBC and breast cancer development for

each age group in Asia. This finding also implies that it is necessary to adopt different approaches for different age groups to establish policies for preventing breast cancer. Since YBC is mainly caused by factors that do not change with time, such as genetic factors. We can not control the occurrence of YBC until now; however, in the case of non-YBCs that were influenced by several environmental factors, we can try to reduce the occurrence by modifying environmental factors. This study could contribute to the development of an optimal clinical trial protocol and aid in directing future strategies for reducing the burden of breast cancer for Asian women and, potentially, worldwide.

## Conclusion

In this study, we found that the overall number and incidence of breast cancer cases in Korea definitely increased over time. Both YBC and non-YBC increased each year, but the increase in non-YBC was more pronounced. The increase in YBC was mainly due to an increase in the luminal A subtype. Other subtypes in YBC were not changed over time. The increase in non-YBC compared to YBC is much clearer, and as a result, the relative proportion of YBC was shown to decrease over time. Our data suggested that the current high proportion of YBC may be not a unique feature of breast cancer in Asia but rather a transient phenomenon.

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**Author contributions** SKL, SJN, and SWK conceived and designed the study; the HGM, EKK, JYK, JW, SL, SSK, KBCS constructed the data; SKL and SJN analyzed the data; SKL, SJN, SWK, JHY, and JEL contributed reagents, materials, and/or analysis tools; SKL wrote the manuscript; and JHY, JEL, and the KBCS made other contributions.

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**Data availability** Korean breast cancer registry (KBCR) which was used for this study is available with the permission of KBCS (the Korean Breast Cancer Society). I'll provide the information on where data supporting the results reported in this article can be found including, where applicable, hyperlinks to publicly archived datasets analyzed or generated during the study.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interests.

**Ethical approval** Approval was granted by the Institutional Review Board of Samsung Medical Center (IRB File No. 2015-10-189). This study was performed in accordance with the Declaration of Helsinki.

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