

Chronological changes in risk exposures, detection and treatment pattern for breast cancer patients in Hong Kong over a 12-year period

Editor's message

This issue intends to complement the “Hong Kong Breast Cancer Registry Report No. 11” on the chronological changes in breast cancer detection and management among local breast cancer patients. Our findings suggested that while there were substantial changes in breast cancer treatment pattern over the years, unhealthy lifestyles related to breast cancer and lack of regular breast screening habits still remained as important health issues in Hong Kong. Our study aims to provide insights into breast cancer management to encourage more research and discussion conducive to policy change in synch with our mission to mitigate the threat and sequelae of breast cancer.

Introduction

The number of breast cancer (BC) cases has been rising steadily in Hong Kong, making it the most common cancer among local women over the last two decades.¹ Studying BC patients' risk exposures over time may help explore the potential key factors that might have contributed to the increased incidence of BC in Hong Kong. Multimodality treatment, i.e. combination of treatments including surgery, radiotherapy, chemotherapy, endocrine therapy, and anti-HER2 targeted therapy, is usually used for treating BC effectively. Over the past years, substantial advances have been made in medical technologies and new drug discoveries which have led to longer survival and better quality of life for BC survivors. Also, improved understanding of the biologic heterogeneity of BC has allowed the development of targeted therapy and individualised approach to treatment. Hence, the treatment pattern for local BC patients may have changed substantially over time. The objective of this study is to examine the changes in the risk exposures and treatment pattern among local BC patients over time.

Methodology

Records on 18,666 female patients who were diagnosed with invasive BC in 2006-2017 were retrieved from the Hong Kong Breast Cancer Registry (HKBCR). Among these patients, 228 who were diagnosed or received any BC treatment outside Hong Kong were excluded. Hence, a total of 18,438 patients registered in the HKBCR were included in this study. According to their year of cancer diagnosis, patients were divided into four cohorts (2006-2008, 2009-2011, 2012-2014, and 2015-2017) to examine the changes in the risk exposures, cancer detection and treatment pattern over time. Chi square test with pairwise comparisons between the four groups was used to test for the difference in categorical variables (e.g. the proportion of patients using chemotherapy). A p-value of less than 0.05 was considered statistically significant. Bonferroni adjustment was applied to correct for multiple comparisons.

Results and Discussion

The median age at diagnosis for patients in the 2015-2017 cohort was 54.2, which was found to be higher than those for the other three cohorts (2006-2008: 49.5; 2009-2011: 51.6; 2012-2014: 52.9) ($p < 0.05$) (data not shown).

A. Risk exposure

More patients in the 2015-2017 cohort, when compared to that in the 2006-2008 cohort, had no breastfeeding (66.5% vs. 63.4%; $p < 0.05$), were overweight/obese (39.7% vs. 36.1%; $p < 0.05$), had no childbirth/first live birth after age 35 (28.8% vs. 21.3%; $p < 0.05$), had family history of BC (16.2% vs. 13.3%; $p < 0.05$), or had habits of drinking alcohol (6.2% vs. 4.0%; $p < 0.05$) (Table 1). On the other hand, less patients in the 2015-2017 (2.5%) cohort used hormone replacement therapy prior to cancer diagnosis, compared to 4.3% for that in the 2006-2008 cohort ($p < 0.05$). The results suggested that the efforts of promoting a healthy lifestyle as a means of preventing BC in the past years was inadequate or not effective and must be further reinforced in the community. It is worth noting that some of these risk factors, for example exercise, are modifiable. The reasons for having inadequate exercise or other modifiable risk factors might be due to the fact that women are not aware of these modifiable risk factors, or there is no incentive to change their behaviours, or that life in Hong Kong is too busy to give time to exercise etc. Yet, since these factors are modifiable, it is worthwhile to actively promote them for breast cancer prevention among women in Hong Kong.

B. Breast screening habits prior to cancer diagnosis

For each cohort, about three-fifths of the patients conducted breast self-examination (BSE) prior to cancer diagnosis (Table 2), which did not show significant changes over time. Although the proportions of patients who underwent clinical breast examination (CBE) decreased significantly ($p < 0.05$), the proportions of patients who had ever undertaken mammogram (MMG) or breast ultrasound screening (USG) increased over time. However, our data showed that the proportions who regularly conducted or underwent these examinations decreased significantly over time (Table 2). Previous studies found that women did not go for regular breast screening because they forgot to do it or perceived themselves healthy (data not published). Therefore, another key message that should also be emphasised during breast health promotion is the importance of having regular screening to detect cancer early.

C. Cancer detection and staging

The primary method of first BC detection in the cohorts was self-detection by chance (81.4%-86.1%). The proportion of patients who were detected by MMG slightly increased ($p < 0.05$). After the onset of symptoms, one-third (28.2%-32.6%) of the patients in each cohort who self-detected their cancers by chance waited more than three

Table 1: Ten factors associated with breast cancer in each patient cohort (N=17,762)

	2006-2008 (N=3,464) %	2009-2011 (N=4,808) %	2012-2014 (N=5,196) %	2015-2017 (N=4,294) %	Changes over the study period
Lack of exercise (<3 hrs / week)	76.3 ^a	77.4 ^{a,b}	79.0 ^b	76.9 ^{a,b}	No change
No breastfeeding	63.4 ^a	67.0 ^b	67.2 ^b	66.5 ^b	Increase
Being overweight / obese	36.1 ^a	38.5 ^{a,b}	39.2 ^b	39.7 ^b	Increase
High level of stress (>50% of time)	36.3 ^a	37.5 ^a	36.8 ^a	37.3 ^a	No change
No childbirth / first live birth after age 35	21.3 ^a	27.2 ^b	28.6 ^a	28.8 ^b	Increase
Family history of breast cancer	13.3 ^a	14.7 ^{a,b}	14.6 ^{a,b}	16.2 ^b	Increase
Diet rich in meat / dairy products	13.5 ^{a,b}	15.1 ^b	14.6 ^{a,b}	13.1 ^a	No change
Early menarche (<12 years old)	12.8 ^a	14.4 ^a	14.5 ^a	14.2 ^a	No change
Habit of drinking alcohol	4.0 ^a	5.2 ^{a,b}	4.9 ^a	6.2 ^b	Increase
Use of hormone replacement therapy	4.3 ^a	4.8 ^a	3.2 ^b	2.5 ^b	Decrease

The values with different superscript letters in a row are significantly different (p<0.05)

Table 2: Breast screening habits prior to cancer diagnosis in each patient cohort

	2006-2008 %	2009-2011 %	2012-2014 %	2015-2017 %	Changes over the study period
Breast self-examination (N=3,377)					
Ever	58.2 ^a	59.5 ^a	60.3 ^a	60.6 ^a	No change
<i>monthly, within ever</i>	39.2 ^a	39.2 ^a	31.0 ^b	30.6 ^b	Decrease
Clinical breast examination (N=3,387)					
Ever	52.4 ^a	51.9 ^{a,b}	48.7 ^c	49.1 ^{b,c}	Decrease
<i>regular*, within ever</i>	76.5 ^a	75.1 ^a	68.8 ^b	64.2 ^c	Decrease
Mammography screening # (N=2,947)					
Ever	30.8 ^a	30.2 ^a	30.5 ^a	35.5 ^b	Increase
<i>regular*, within ever</i>	66.9 ^a	64.2 ^a	62.3 ^a	55.8 ^b	Decrease
Ultrasound screening # (N=2,837)					
Ever	25.5 ^a	26.1 ^a	26.5 ^a	33.2 ^b	Increase
<i>regular*, within ever</i>	63.1 ^a	62.8 ^a	62.3 ^a	56.6 ^b	Decrease

* "regular" is defined as having the breast screening test every 1-3 years

included patients aged 40 or above only

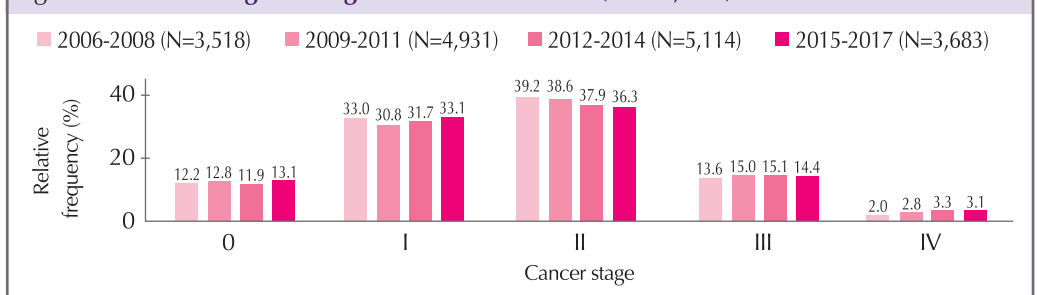
The values with different superscript letters in a row are significantly different (p<0.05)

months before seeking first medical consultation. The most common cancer stage at diagnosis in each cohort was stage II followed by stage I (Figure 1). The rise in MMG detected cancer is likely related to the increase in prevalent screen in women who undertook MMG occasionally.

D. Cancer characteristics

Over the study period, the proportions of patients having estrogen receptor (ER) positive or progesterone receptor (PR) positive disease increased, while proportions of patients having human epidermal growth factor receptor 2 (HER2) positive disease decreased (data not shown). The proportions of patients with HR-HER2+ and TND were roughly the same over the study period (Figure 2). The reason for the increased proportions of ER or PR positive cancer might be due to the fact that in 2010, the American Society of Clinical Oncology has lowered the immunohistochemical cut-off for determining ER positivity from the previous value of 10% to 1% of stained cells.² Another possible reason for this is that more elderly patients, who are known to be more likely to have ER or PR positive

Figure 1: Cancer stage at diagnosis in each cohort (N=17,246)

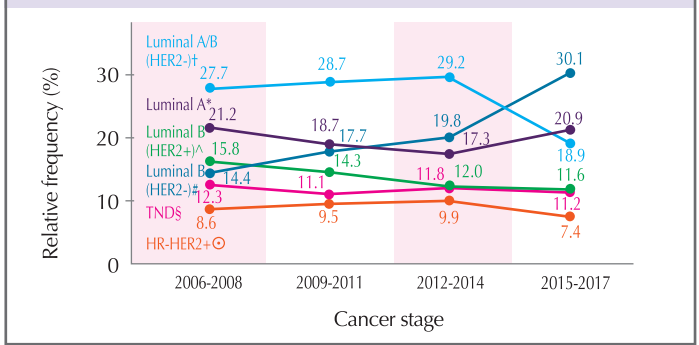


cancer,³ constituted to a higher proportion in the more recently diagnosed cohort. Furthermore, the wider adoption of the Allred system in which a lower threshold for ER or PR positivity is used compared to the H score system is also likely contributing to the increase in ER or PR positive tumours. Furthermore, to improve the efficiency and accuracy of HER2 screening, recommendations for HER2 testing in BC was first released in 2007⁴ by the American Society of Clinical Oncology and the College of American Pathologists and was further updated in 2013.⁵ Hence, the changing in the accuracy of the HER2 test may have contributed to the decrease of HER2 positive cases over the study period.

E. Cancer Treatment

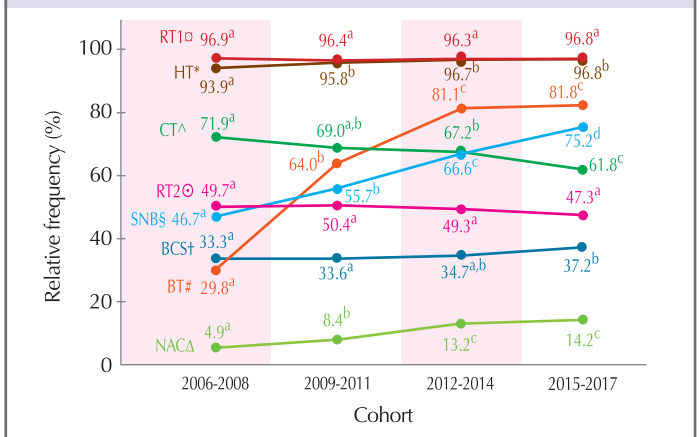
- Surgery** – One-third (33.3%) of the patients in the 2006-2008 cohort underwent breast-conserving surgery (BCS), and the proportion increased to 37.2% in the 2015-2017 cohort ($p < 0.05$) (Figure 3). When the type of surgery was further analysed by cancer stage, significant increase in the proportion of BCS was observed for patients with stage I disease (from 46.0% in the 2006-2008 cohort to 51.8% in the 2015-2017 cohort) ($p < 0.05$). For nodal surgery, the proportions of patients receiving sentinel node biopsy (SNB) increased from 46.7% in the 2006-2008 cohort to 75.2% in the 2015-2017 cohort ($p < 0.05$). The significant increases in SNB use were observed for patients of all cancer stages (I-IV), all age groups (<40, 40-69, and 70+), and both negative and positive clinical nodal status. BCS and SNB reduce the complexity of BC surgery and its complication, as well as increase the quality of life on women. Our study showed that patients with early-stage disease benefited more from these important surgical advancements over the study period which further supported the importance of early BC detection.
- Radiotherapy** – The proportions of patients receiving radiotherapy, regardless of the type of surgery they received, did not show significant changes over time (Figure 3). However, when it was further analysed by cancer stage, significant decreases were observed for patients with mastectomies who were diagnosed with stage I (from 13.0% in the 2006-2008 cohort to 8.8% in the 2015-2017 cohort) ($p < 0.05$) or IIA disease (from 40.0% in the 2006-2008 cohort to 32.2% in the 2015-2017 cohort) ($p < 0.05$) (data not shown). In contrast, three-quarters (76.2%) of patients with mastectomies who were diagnosed with stage IIB disease in the 2006-2008 cohort received radiotherapy and the proportion was slightly increased to 82.8% in the 2015-2017 cohort ($p < 0.05$) (data not shown). A meta-analysis⁶ was conducted to evaluate the use of radiotherapy after mastectomy and axillary dissection and the results showed that radiotherapy reduced both recurrence and breast cancer mortality in women with one to three positive lymph nodes but no survival advantage was observed for patients with negative nodes. The paper was published in 2014 which may likely explain the observed changes in the use of radiotherapy for certain subgroups of patients over the study period.
- Chemotherapy** – Over the study period, the proportion of patients receiving chemotherapy (all settings) decreased significantly ($p < 0.05$) (Figure 3). When it was further analysed by cancer stage and biological subtype, significant decreases were only observed

Figure 2: Biological subtypes of invasive breast cancer in each cohort (N=14,358)



HR: hormonal receptor; HER2: human epidermal growth factor receptor 2
 * Luminal A: ER and/or PR+, HER2-, and low Ki-67 index (<14%)
 ‡ Luminal B (HER2-): ER and/or PR+, HER2-, and high Ki-67 index (≥14%)
 † Luminal A/B (HER2-): ER and/or PR+, HER2-, and Ki-67 index not known
 ‡ Luminal B (HER2+): ER and/or PR+, HER2+, and any Ki-67 index
 ⊙ HR-HER2+: ER and PR-, HER2+, and any Ki-67 index
 § TND (Triple negative disease): ER and PR-, HER2-, and any Ki-67 index

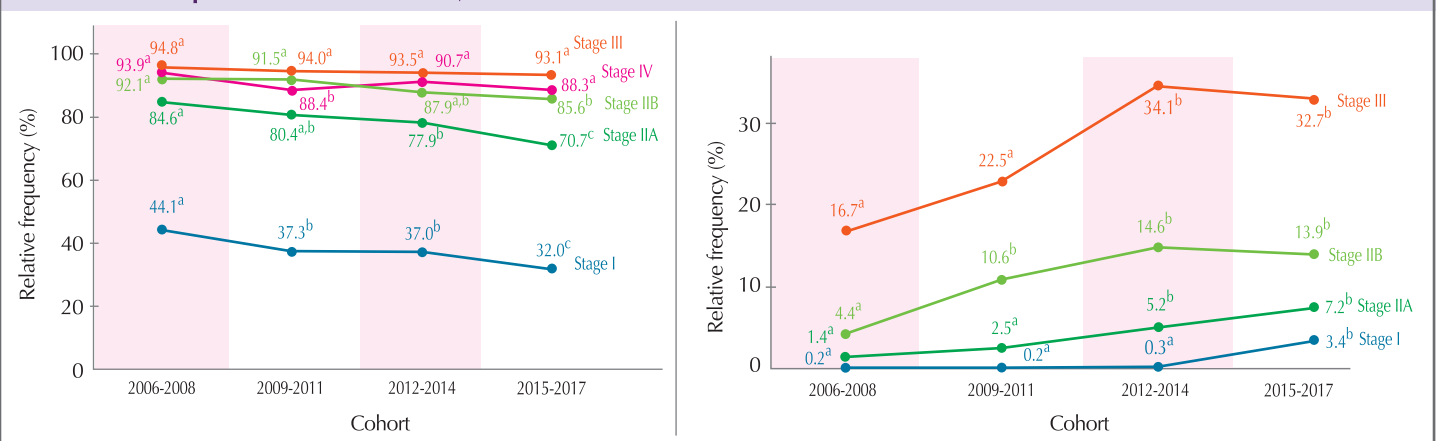
Figure 3: Changes in the treatment pattern for breast cancer patients in Hong Kong over time



The values with different superscript letters in a line are significantly different ($p < 0.05$)
 * anti-HER2 targeted therapy; HT: endocrine therapy; CT: chemotherapy; NAC: neoadjuvant chemotherapy;
 RT: radiotherapy; BCS: breast conserving surgery; SNB: sentinel node biopsy
 # among HER2 positive patients (N=3,165); * among hormonal receptor positive patients (N=11,278);
 ^ included all settings of chemotherapy (N=14,160); Δ among stage I-III patients who received CT (N=9,502);
 ⊙ among patients who received BCS (N=4,908); ⊙ among patient who received mastectomy (N=9,095);
 † among patients who received breast surgery (N=14,793); § among patients who received nodal surgery (N=14,784)

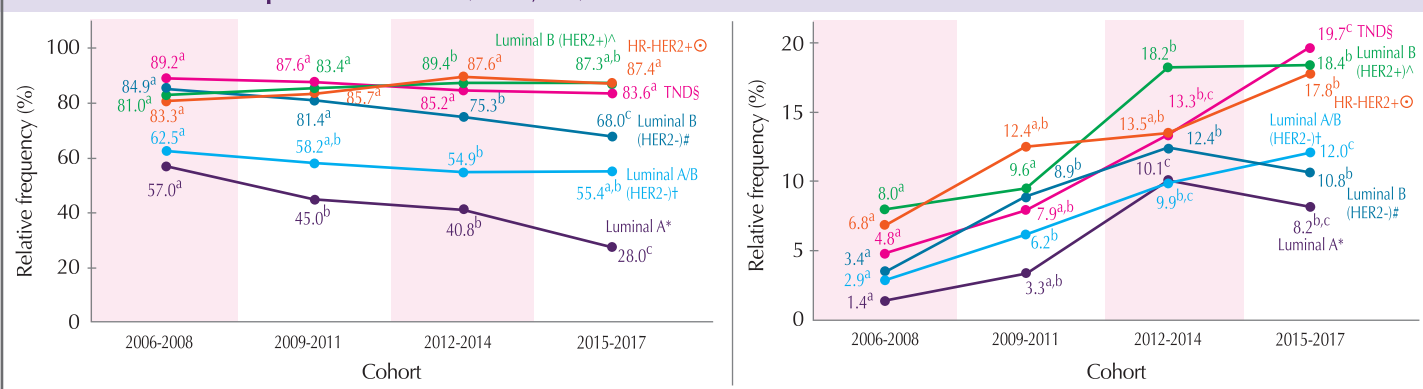
among patients with early stage (stages I-IIB) (Figure 4), luminal A, or luminal B (HER2 negative) disease (Figure 5). Advance in medical knowledge and techniques over the past years have found that all cancer tumours that are smaller than 0.5 cm and ER positive cancer tumours smaller than one cm have good prognosis with endocrine

Figure 4: Changes in the use of chemotherapy (all settings) (left) and neoadjuvant chemotherapy (right) by cancer stage for breast cancer patients over time (N=14,425)



The values with different superscript letters in a line are significantly different ($p < 0.05$)

Figure 5: Changes in the use of chemotherapy (all settings) (left) and neoadjuvant chemotherapy (right) by biological subtypes for breast cancer patients over time (N=14,017)



The values with different superscript letters in a line are significantly different ($p < 0.05$)
^{*}Luminal A: ER and/or PR+, HER2-, and low Ki-67 index (<14%)
[†]Luminal A/B (HER2 -ve): ER and/or PR+, HER2-, and Ki-67 index not know
[‡]Luminal B (HER2 -ve): ER and/or PR+, HER2-, and high Ki-67 index ($\geq 14\%$)
[^]Luminal B (HER2 +ve): ER and/or PR+, HER2+, and any Ki-67 index
[⊕]HR-HER2 +ve: ER and PR-, HER2+, and any Ki-67 index
[§]TND (Triple negative disease): ER and PR-, HER2-, and any Ki-67 index

therapy alone, suggesting chemotherapy is not usually required. To further guide clinical decision-making, especially for early-stage disease, genomic profiling assays of the tumours were developed to identify patients with low chances of recurrence that the absolute benefit of chemotherapy may not justify the risk of toxicities.⁷ These developments might have contributed to the observed decreased use of chemotherapy (all settings) in certain subgroups of patients over the study period.

Despite of the observed decrease in the use of chemotherapy (all settings), the proportions of patients receiving neoadjuvant chemotherapy (NAC) increased significantly from 4.9% to 14.2% over the study period ($p < 0.05$) (Figure 3). When it was further analysed by cancer stage and biological subtype, significant increases were observed for patients with stages I to III (Figure 4) and all biological subtypes (Figure 5). NAC was found effective in downsizing tumour, facilitating BCS to be performed for patients in whom mastectomy would otherwise be indicated. Therefore, as expected, NAC was more and more commonly deployed over the study period. The use of NAC for patients with luminal A or luminal B (HER2 negative) subtype, though not statistically significant, decreased after the 2012-2014 cohort. This might be probably due to the findings that these two subtypes are less likely to receive benefits from chemotherapy.

- Anti-HER2 targeted therapy – Substantial increase was observed in the use of anti-HER2 targeted therapy, of which the proportion increased from 29.8% in the 2006-2008 cohort to 81.8% in the 2015-2017 cohort ($p < 0.05$) (Figure 3). When it was further analysed by cancer stage, significant increases were observed for all cancer stages ($p < 0.05$) (data not shown). Trastuzumab was approved to be the first anti-HER2 targeted therapy for metastatic BC in 1998 and was then approved as an adjuvant treatment for patients with HER2 positive node-positive and node-negative BC in 2006⁸ and 2008⁹ respectively. This explains why there was a sharp increase in the use of anti-HER2 targeted therapy over the study period.
- Endocrine therapy – The proportion of patients receiving endocrine therapy was slightly increased over the study period ($p < 0.05$).

Conclusion

Our results indicated that while there were substantial changes in cancer treatment to improve patients' quality of life, no significant improvement, however, could be observed in patients' breast screening habits over the years. Screening helps detect cancer early and early detection saves lives.

These findings further highlighted the importance of increasing breast awareness and regular screening habits among women in Hong Kong. Future studies will be conducted to look at the change in survival for these BC patients over time.

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