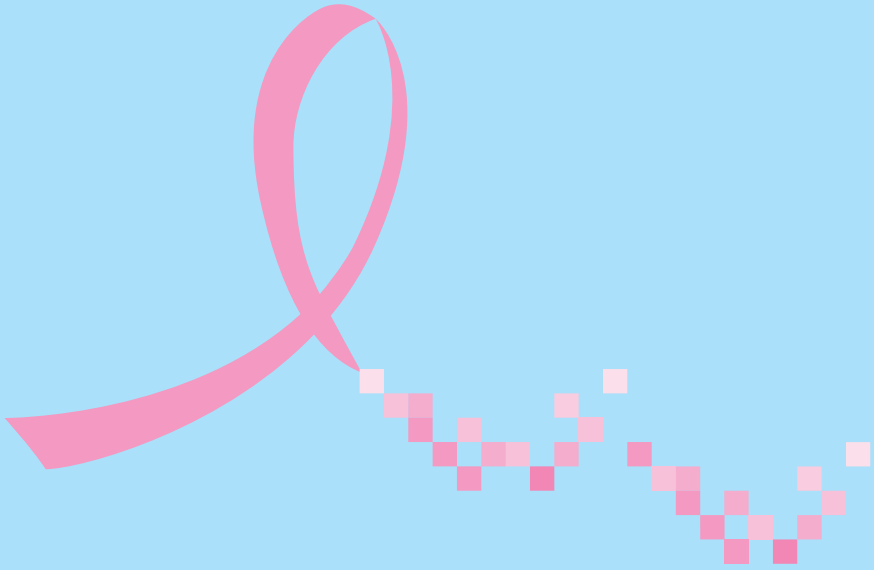

CHAPTER 2

DISEASE PATTERN, TREATMENT TREND AND CLINICAL OUTCOME OF BREAST CANCER IN HONG KONG

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I. Introduction

2.1 This chapter reviews the data collected from 20,138 breast cancer patients regarding their cancer's clinical presentation, cancer characteristics and treatment methods. The aim is to analyse the clinical management of breast cancer and identify the trends in disease and treatment in the local context in order to develop and improve the standard of care for breast cancer patients in Hong Kong.

KEY FINDINGS

The patients registered with the HKBCR, according to their year of cancer diagnosis, were divided into three cohorts (2006-2010, 2011-2015 and 2016-current). This report compares the cohorts to highlight the changes over the past decade in breast cancer status, diagnosis and management.

Clinical presentation

- The primary method of first cancer detection was still self-detection by chance among the patients in the 2016-current cohort (79.2%), even though the proportion had slightly decreased, compared to those in the previous two cohorts (82.4%-84.2%).
- A slight increase in mammography-detected cases was observed from 9.6% to 13.5% across the three cohorts.
- The proportion of stages 0-I cancer was higher among mammography-detected cases compared to self-detected cases (84.2%-85.4% vs. 38.0%-39.8%), while the proportion of stages III-IV cancer was lower (1.9%-3.4% vs. 17.8%-20.6%).
- After onset of symptoms (mainly, painless lumps), the majority (68.8%-72.0%) of patients who self-detected their cancer by chance sought their first medical consultation in three months. However, more patients were diagnosed with stage IV disease among those who sought medical consultation after 12 months (10.0%-11.5%) than those in less than one month (0.9%-2.0%).
- In each cohort, the most common cancer stage at diagnosis was stage II (34.0%-37.0%) followed by stage I (31.0%-31.2%) and stages III-IV (13.7%-16.8%). In addition, 12.4%-13.4% of the patients in the three cohorts were diagnosed with stage 0 (in situ) cancer.

Cancer characteristics

- The mean tumour size of invasive breast cancer in each patient cohort was 2.2 cm. The number of patients with no positive lymph nodes slightly increased to 60.6% in the 2016-current cohort. The most common type was invasive carcinoma of no specific type (86.8%-87.1%). Estrogen receptor (ER) positive or progesterone receptor (PR) positive cases increased (from 76.6% to 83.1% and 63.9% to 70.1%, respectively), while HER2 positive cases decreased (from 24.8% to 17.9%) based on the 2018 guideline. [42]
- The mean tumour size of in situ breast cancer was 2.0 cm in the 2006-2010 cohort, 2.1 cm in the 2011-2015 cohort, and 1.8 cm in the

2016-current cohort. Of the in situ cases where mammography was performed, 58.8%-63.5% showed microcalcification. Ductal cancer was the most common type of in situ breast cancer in each cohort (91.6%-93.4%). Similar to the trend observed in invasive cancer across the three cohorts, ER or PR positive cases increased (from 80.4% to 83.2% and 71.0% to 75.5%, respectively), whereas HER2 positive cases decreased (from 29.1% to 20.0%).

Treatment

- Of the patients in each cohort, 10.0%-17.8% received care at private medical service, 47.5%-54.1% received care at public medical service and 33.8%-38.0% received care at both private and public medical services.
- Surgery
  - The proportion of patients who underwent mastectomy dropped throughout the cohorts (from 65.9% to 58.1% in invasive cancer cases and 49.2% to 40.4% in in situ cancer cases). In contrast, more patients opted for breast-conserving surgery (from 32.5% to 39.2% in invasive cancer cases and 50.3% to 56.9% in in situ cases).
  - The percentage of the patients who underwent mastectomy was positively correlated with both increasing age and cancer stage in all three cohorts.
  - In the cohorts, nearly all (95.9%-97.2%) of the patients with invasive breast cancer underwent nodal surgery, while about two-thirds (60.3%-67.8%) of the patients with in situ cancer underwent nodal surgery. Among patients with negative clinical nodal status, the proportion of patients who had undergone sentinel node biopsy alone increased from 43.1% to 81.5% throughout the cohorts, whereas the use of axillary dissection alone decreased from 41.3% to 8.5%.
  - The use of axillary dissection without sentinel node biopsy was positively correlated with progressing cancer stage in each cohort.
- Radiotherapy
  - In the cohorts, 62.9%-63.9% of the patients had locoregional radiotherapy as part of their invasive cancer treatment. In the three cohorts, the majority (over 93%) of the patients who underwent breast-conserving surgery received radiotherapy, and the uptake increased with progressing cancer stage among patients who had undergone mastectomy.
- Chemotherapy
  - The proportion of patients with invasive cancer who underwent chemotherapy dropped from 70.8% to 58.3% throughout the three cohorts. Among them, the use of adjuvant chemotherapy decreased, while the use of neoadjuvant chemotherapy increased. In addition, the use of neoadjuvant chemotherapy in each cohort was positively correlated with progressing cancer stage from stage I to III.
  - In adjuvant setting, first generation chemotherapy regimens used by all biological subtypes decreased, while the use of HER2 regimen increased in luminal B (HER2 positive) and HER2 positive breast cancer throughout the cohorts.
  - In each cohort, the use of third generation chemotherapy regimens in adjuvant setting was positively correlated with progressing cancer stage.
- Endocrine therapy
  - In the three cohorts, 67.7%-68.8% of the patients were treated with endocrine therapy. While 14.8%-16.6% of patients with in situ

breast cancer received endocrine therapy, over 70% of patients with invasive breast cancer received endocrine therapy.

- Targeted therapy
  - In the cohorts, 10.1%-16.3% of the patients received targeted therapy, in which anti-HER2 drugs accounted for the majority. The use of anti-HER2 targeted therapy increased from 38.4% to 74.7% throughout the three cohorts.
  - In each cohort, the use of anti-HER2 targeted therapy was much lower for patients with stage I disease, and the proportions of patients with stage II or above having anti-HER2 targeted therapy were roughly the same for the 2011-2015 and 2016-current cohorts.
- Multimodality treatment
  - Combinations of treatment modalities are usually used to treat breast cancer effectively. In the three cohorts, the number of treatment modalities increased with increasing cancer stage.
- Complementary and alternative therapies
  - In the cohorts, 22.8%-41.6% of the patients sought complementary and alternative therapies as part of their treatment. Among them, 64.1%-67.9% used traditional Chinese medicines.

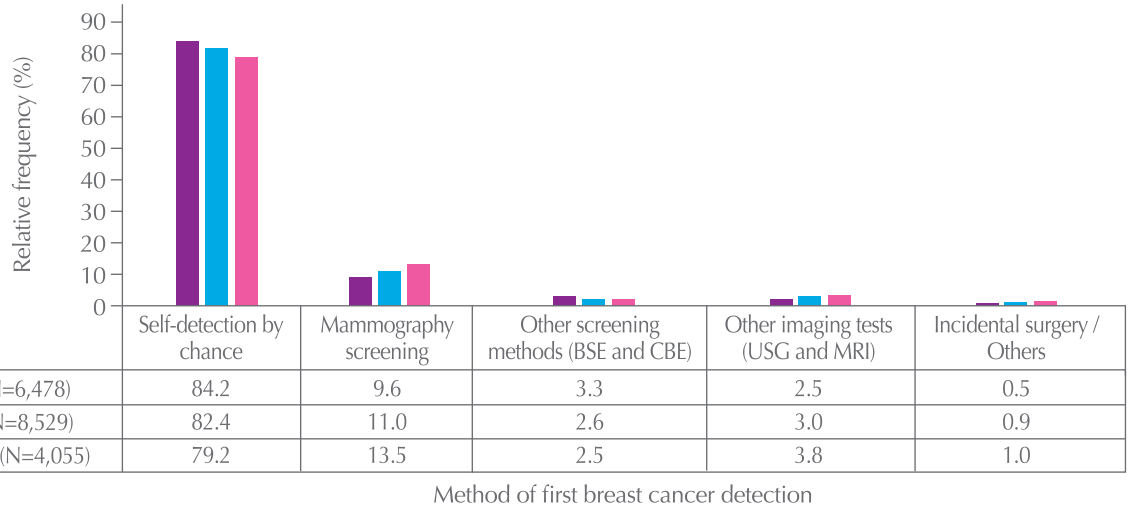
Patient status

- Combining the three cohorts, a total of 18,155 patients were studied to examine the survival aspects of the patients. The mean and median follow-up period were 4.7 and 4.1 years respectively.
- Of the patients who have been followed up, 1.8% experienced only locoregional recurrence, 2.4% experienced only distant recurrence, and 1.7% experienced both locoregional and distant recurrence.
- The common sites for locoregional recurrence were chest wall (32.2%) and breast (31.7%), while the top four organs involved in distant recurrence were bone (55.7%), lung (45.3%), liver (37.7%) and brain (18.8%).

II. Clinical presentation

2.2 The primary method of first breast cancer detection in the patient cohorts was self-detection by chance (79.2%-84.2%) (Figure 2.1). Detection through healthcare service-assisted screening methods, including clinical breast examination (CBE), mammography screening (MMG), and ultrasound screening (USG) constituted a small proportion (15.4%-19.8%). Compared to Western countries, the uptake of MMG, in particular, was low (9.6%-13.5%) in each cohort. A study in the United States, for instance, found that 43% of the breast cancer cases were detected through MMG.[43]

Figure 2.1: Methods of first breast cancer detection in the patient cohorts (N=19,062)



	Self-detection by chance	Mammography screening	Other screening methods (BSE and CBE)	Other imaging tests (USG and MRI)	Incidental surgery / Others
2006-2010 (N=6,478)	84.2	9.6	3.3	2.5	0.5
2011-2015 (N=8,529)	82.4	11.0	2.6	3.0	0.9
2016-current (N=4,055)	79.2	13.5	2.5	3.8	1.0

BSE: breast self-examination; CBE: clinical breast examination; USG: breast ultrasound screening; MRI: magnetic resonance imaging

2.3 In terms of the types of medical service received, the proportion of patients who self-detected their breast cancer by chance was higher among public medical service users (83.4%-85.6%) or mixed public/private medical service users (78.5%-86.7%) than among private medical service users (65.1%-72.8%). In contrast, the proportion of the patients who first detected their breast cancer through MMG was higher among private medical service users (14.0%-23.5%) than among public medical service users (9.8%-12.0%) or mixed public/private medical service users (7.0%-13.8%) (Table 2.1).

Table 2.1: Methods of first breast cancer detection by type of medical service users (N=19,062)

	Type of medical service users % for 2006-2010, % for 2011-2015, % for 2016-current								
	Public			Private			Mixed public / private		
Self-detection by chance	85.6	83.4	84.8	72.8	72.2	65.1	86.7	83.8	78.5
Mammography screening	9.8	12.0	9.8	15.7	14.0	23.5	7.0	8.7	13.8
Other screening methods (BSE and CBE)	2.8	2.2	2.9	4.2	2.8	1.4	3.6	3.1	2.5
Other imaging tests (USG and MRI)	1.3	1.5	1.5	6.6	9.3	8.5	2.3	3.6	4.5
Incidental surgery / Others	0.6	0.9	1.0	0.7	1.7	1.5	0.4	0.8	0.8

Total number of patients in each group:

Public: 3,078 (for 2006-2010), 4,584 (for 2011-2015), 1,965 (for 2016-current)

Private: 937 (for 2006-2010), 864 (for 2011-2015), 716 (for 2016-current)

Mixed public / private: 2,463 (for 2006-2010), 3,081 (for 2011-2015), 1,374 (for 2016-current)

BSE: breast self-examination; CBE: clinical breast examination; USG: breast ultrasound screening; MRI: magnetic resonance imaging

2.4 Studies have shown that MMG is effective in detecting early cancer when there are neither signs nor symptoms that can be observed by patients or medical professionals.[44] While self-detection could only pick up 7.9%-9.3% in situ breast cancer, MMG could detect 37.2%-45.4% in the patient cohorts (Table 2.2). Table 2.3 also shows that MMG detected a much higher proportion of early stage cancer cases, i.e. 84.2%-85.4%, than advanced stage cancer cases.

Table 2.2: Methods of first breast cancer detection by type of cancer (N=18,922)

	Type of cancer % for 2006-2010, % for 2011-2015, % for 2016-current					
	Invasive			In situ		
Self-detection by chance	90.7	92.1	91.2	9.3	7.9	8.8
Mammography screening	54.6	57.5	62.8	45.4	42.5	37.2
Other screening methods (BSE and CBE)	84.8	84.1	86.0	15.2	15.9	14.0
Other imaging tests (USG and MRI)	74.4	72.4	68.6	25.6	27.6	31.4
Incidental surgery / Others	87.9	75.3	73.8	12.1	24.7	26.2

Total number of patients in each group:
Self-detection by chance: 5,420 (for 2006-2010), 6,972 (for 2011-2015), 3,187 (for 2016-current)
Mammography screening: 619 (for 2006-2010), 931 (for 2011-2015), 546 (for 2016-current)
Other screening methods (BSE and CBE): 210 (for 2006-2010), 214 (for 2011-2015), 100 (for 2016-current)
Other imaging tests (USG and MRI): 160 (for 2006-2010), 254 (for 2011-2015), 153 (for 2016-current)
Incidental surgery / Others: 33 (for 2006-2010), 81 (for 2011-2015), 42 (for 2016-current)

BSE: breast self-examination; CBE: clinical breast examination; USG: brest ultrasound screening; MRI: magnetic resonance imaging

Table 2.3: Methods of first breast cancer detection by cancer stage (N=18,298)

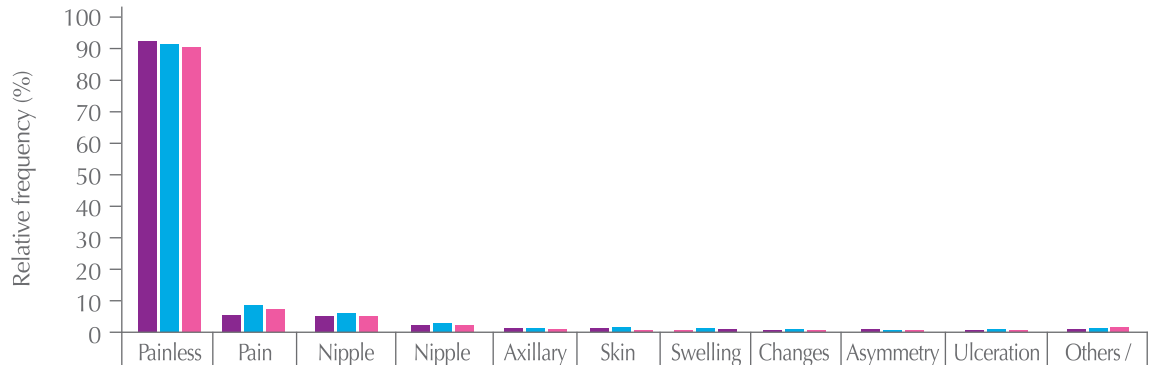
	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current																	
	0			I			IIA			IIB			III			IV		
Self-detection by chance	9.4	7.9	9.1	30.2	30.1	30.7	28.1	26.4	27.7	14.1	15.0	14.8	15.9	17.3	14.9	2.3	3.3	2.9
Mammography screening	45.4	42.9	36.4	38.8	41.3	49.0	10.5	10.7	10.2	1.9	2.1	2.5	3.2	2.3	1.7	0.2	0.8	0.2
Other screening methods (BSE and CBE)	15.5	16.5	14.7	39.1	43.2	38.9	24.2	23.3	18.9	9.2	10.7	9.5	10.6	4.4	16.8	1.4	1.9	1.1
Other imaging tests (USG and MRI)	25.6	27.5	32.0	53.1	44.6	50.0	14.4	17.1	14.0	3.8	4.0	1.3	1.9	5.2	2.0	1.2	1.6	0.7
Incidental surgery / Others	12.1	26.7	24.4	24.2	41.3	39.0	33.3	16.0	19.5	12.1	5.3	4.9	12.1	8.0	9.8	6.1	2.7	2.4

Total number of patients in each group:
Self-detection by chance: 5,322 (for 2006-2010), 6,727 (for 2011-2015), 2,968 (for 2016-current)
Mammography screening: 619 (for 2006-2010), 917 (for 2011-2015), 527 (for 2016-current)
Other screening methods (BSE and CBE): 207 (for 2006-2010), 206 (for 2011-2015), 95 (for 2016-current)
Other imaging tests (USG and MRI): 160 (for 2006-2010), 251 (for 2011-2015), 150 (for 2016-current)
Incidental surgery / Others: 33 (for 2006-2010), 75 (for 2011-2015), 41 (for 2016-current)

BSE: breast self-examination; CBE: clinical breast examination; USG: breast ultrasound screening; MRI: magnetic resonance imaging

2.5 Most (90.4%-92.3%) patients who self-detected their cancer by chance found a painless lump on their breast(s). Pain is usually not a symptom of breast cancer; only 5.6%-8.1% of the patients felt pain in their breast(s) at initial presentation. Some patients (7.8%-9.6%) experienced changes in nipple (such as nipple discharge, nipple retraction, redness, scaliness or thickening of nipple) (Figure 2.2).

Figure 2.2: Major presenting symptoms of self-detected breast cancer in the patient cohorts (N=15,692)



	Painless lump	Pain	Nipple discharge	Nipple retraction	Axillary node	Skin change	Swelling	Changes in nipple	Asymmetry	Ulceration	Others / not known
2006-2010 (N=5,452)	92.3	5.6	5.3	2.3	1.0	1.0	0.2	0.4	0.4	0.2	0.8
2011-2015 (N=7,030)	91.4	8.1	6.2	2.9	1.0	1.2	0.8	0.5	0.3	0.5	1.3
2016-current (N=3,210)	90.4	7.3	5.3	2.2	0.9	0.4	0.5	0.3	0.3	0.2	1.5

A. Time interval between the onset of symptoms and first medical consultation

2.6 Longer delay in seeking medical consultation is associated with higher probability of local cancer spread or distant metastasis and poorer prognosis.[45] After the onset of symptoms, more than one-third (35.4%-40.2%) of the patients who self-detected their cancers by chance sought first medical consultation in less than one month (Table 2.4). More than one quarter (28.0%-31.3%) waited more than three months before seeking first medical consultation.

2.7 Among self-detected patients, the proportion of the patients who sought first medical consultation in less than one month was higher among private medical service users (41.1%-46.8%) than among public medical service users (27.6%-32.5%) (Table 2.5).

Table 2.4: Time interval between onset of symptoms and first medical consultation for patients who self-detected their cancer (N=4,255)

	2006-2010 (N=1,621) %	2011-2015 (N=1,687) %	2016-current (N=947) %
Less than 1 month	40.2	35.4	35.6
1-3 months	28.6	33.6	36.4
4-12 months	20.4	22.9	20.6
More than 12 months	10.9	8.1	7.4

Table 2.5: Time interval between onset of symptoms and first medical consultation for patients who self-detected their cancer by type of medical service users (N=4,255)

	Type of medical service users % for 2006-2010, % for 2011-2015, % for 2016-current								
	Public			Private			Mixed public / private		
Less than 1 month	32.5	29.4	27.6	46.0	41.1	46.8	42.7	45.4	43.6
1-3 months	26.0	33.6	38.5	27.3	32.9	32.9	31.5	33.7	34.8
4-12 months	27.8	26.6	24.9	17.8	17.7	17.1	16.1	17.4	14.9
More than 12 months	13.7	10.4	9.1	9.0	8.2	3.2	9.7	3.4	6.7

Total number of patients in each group:
Public: 539 (for 2006-2010), 1,007 (for 2011-2015), 507 (for 2016-current)
Private: 422 (for 2006-2010), 158 (for 2011-2015), 158 (for 2016-current)
Mixed public / private : 660 (for 2006-2010), 522 (for 2011-2015), 282 (for 2016-current)

2.8 A much higher proportion (10.0%-11.5%) of the patients who sought first medical consultation after 12 months of symptom onset was diagnosed with stage IV disease than those who sought first medical consultation in less than one month (0.9%-2.0%) (Table 2.6).

Table 2.6: Cancer stage at diagnosis among self-detected patients by time interval between onset of symptoms and first medical consultation (N=3,734)

	Time interval between onset of symptoms and first medical consultation % for 2006-2010, % for 2011-2015, % for 2016-current											
	Less than 1 month			1-3 months			4-12 months			More than 12 months		
Stage I	38.6	33.4	38.0	33.7	29.3	32.7	30.6	22.8	33.5	22.3	30.0	28.3
Stage IIA	34.1	33.4	32.3	34.6	29.9	31.6	28.5	33.5	31.1	23.7	20.0	36.7
Stage IIB	13.3	15.6	16.5	14.4	17.5	20.2	17.4	19.6	13.4	20.9	13.3	13.3
Stage III	12.5	16.7	11.1	15.9	19.3	12.5	19.8	18.7	17.1	21.6	26.7	11.7
Stage IV	1.5	0.9	2.0	1.5	4.1	3.0	3.8	5.3	4.9	11.5	10.0	10.0

Total number of patients in each group:
Less than 1 month: 586 (for 2006-2010), 527 (for 2011-2015), 297 (for 2016-current)
1-3 months: 410 (for 2006-2010), 509 (for 2011-2015), 297 (for 2016-current)
4-12 months: 288 (for 2006-2010), 337 (for 2011-2015), 164 (for 2016-current)
More than 12 months: 139 (for 2006-2010), 120 (for 2011-2015), 60 (for 2016-current)

III. Cancer characteristics

2.9 Breast cancer can occur in one (unilateral) or both (bilateral) breasts. The majority (2006-2010: 95.4%; 2011-2015: 94.7%; 2016-current: 94.6%) of the patients had unilateral breast cancer, while a small proportion (2006-2010: 2.2%; 2011-2015: 2.7%; 2016-current: 2.6%) had synchronous bilateral breast cancer at first diagnosis (Table 2.7).

Table 2.7: Number of patients and breast cancer cases in the patient cohorts (N=20,138)

	No. of patients	No. of cases	Time interval for metachronous cases, median (range) (years)
2006-2010			
Unilateral	**6,431**	**6,431**	**—**
Bilateral (synchronous)	**151**	**302**	**—**
All bilateral (metachronous) cases	**158**	**202**	**5.6 (0.5 – 34.5)**
Bilateral (metachronous)	*44*	*88*	*2.4 (0.7 – 3.8)*
- Initial diagnosis happened within 2006-2010			
Bilateral (metachronous)	*114*	*114*	*7.8 (0.5 – 34.5)*
- Initial diagnosis happened before 2006			
2011-2015			
Unilateral	**8,235**	**8,235**	**—**
Bilateral (synchronous)	**238**	**476**	**—**
All bilateral (metachronous) cases	**226**	**260**	**7.0 (0.5 – 36.1)**
Bilateral (metachronous)	*34*	*68*	*2.2 (0.8 – 4.4)*
- Initial diagnosis happened within 2011-2015			
Bilateral (metachronous)	*92*	*92*	*5.4 (0.5 – 8.8)*
- Initial diagnosis happened within 2006-2010			
Bilateral (metachronous)	*100*	*100*	*12.0 (5.4 – 36.1)*
- Initial diagnosis happened before 2006			
2016-current			
Unilateral	**3,891**	**3,891**	**—**
Bilateral (synchronous)	**109**	**218**	**—**
All bilateral (metachronous) cases	**114**	**123**	**9.0 (0.5 – 21.1)**
Bilateral (metachronous)	*9*	*18*	*1.5 (0.5 – 2.7)*
- Initial diagnosis happened within 2016-current			
Bilateral (metachronous)	*28*	*28*	*5.0 (1.4 – 8.3)*
- Initial diagnosis happened within 2011-2015			
Bilateral (metachronous)	*57*	*57*	*9.9 (5.5 – 15.0)*
- Initial diagnosis happened within 2006-2010			
Bilateral (metachronous)	*20*	*20*	*15.6 (11.0 – 21.1)*
- Initial diagnosis happened before 2006			

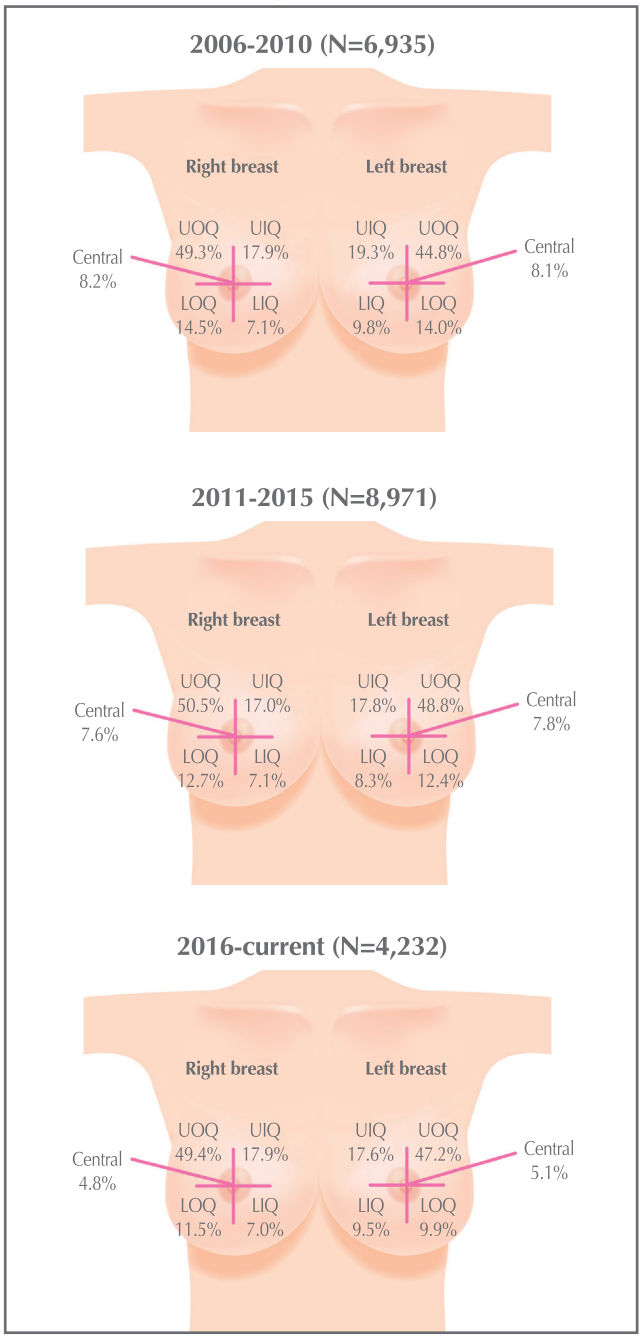
2.10 As regards the locations of malignant breast tumour, about half of the breast cancer cases in either the left or the right breast (44.8%-48.8% and 49.3%-50.5% respectively) were detected in the upper outer quadrant (Figure 2.3).

A. Diagnostic tests for breast cancer

2.11 There are two types of breast cancer diagnostic tests: imaging tests and biopsies. Imaging tests include diagnostic MMG, USG and magnetic resonance imaging (MRI). Diagnostic MMG is the main procedure for breast cancer diagnosis, and USG is used to distinguish a solid mass, which may be cancer, from a fluid-filled cyst, which is usually not cancer. Breast MRI is usually performed on women who have been diagnosed with breast cancer to check the extent of their disease.

2.12 For cancer diagnosis, MMG was used on 83.4%-88.2% of the patients, and USG on 76.8%-85.9%, while MRI was used on only 6.0%-12.8% of the patients (Table 2.8). Results of imaging tests are classified into categories using the Breast Imaging Reporting and Data System (BIRADS). BIRADS 4 or 5 are suspected breast cancer and should be checked by further surgical tests such as biopsies.

Figure 2.3: Locations of malignant tumour on breasts within the patient cohorts (N=20,138)



UOQ: upper outer quadrant UIQ: upper inner quadrant
LOQ: lower outer quadrant LIQ: lower inner quadrant
Note: figures included multicentric cancers

Table 2.8: Sensitivity and diagnostic results of breast imaging tests (N=20,138)

	2006-2010 (N=6,935) %	2011-2015 (N=8,971) %	2016-current (N=4,232) %
Mammography			
Proportion of patients using the test	83.4	86.0	88.2
Overall sensitivity*	79.2	85.8	90.5
BIRADS category			
Diagnostic / malignant (BIRADS 5)	28.4	35.2	29.9
Suspicious abnormality (BIRADS 4)	50.8	50.6	60.6
Probably benign (BIRADS 3)	7.4	4.1	3.1
Benign (BIRADS 2)	5.2	3.2	3.1
Normal (BIRADS 1)	7.9	6.0	2.7
Incomplete (BIRADS 0)	0.3	0.9	0.6
Breast ultrasound			
Proportion of patients using the test	76.8	81.0	85.9
Overall sensitivity*	88.4	92.8	95.0
BIRADS category			
Diagnostic / malignant (BIRADS 5)	35.4	39.0	31.7
Suspicious abnormality (BIRADS 4)	52.9	53.8	63.4
Probably benign (BIRADS 3)	6.8	4.6	3.2
Benign (BIRADS 2)	2.2	1.2	1.3
Normal (BIRADS 1)	2.6	1.4	0.4
Incomplete (BIRADS 0)	0.1	0.1	0.0
MRI			
Proportion of patients using the test	6.0	11.8	12.8
Overall sensitivity*	95.4	97.3	98.0
BIRADS category			
Diagnostic / malignant (BIRADS 5)	70.0	83.0	83.0
Suspicious abnormality (BIRADS 4)	25.4	14.4	15.0
Probably benign (BIRADS 3)	1.9	1.2	1.3
Benign (BIRADS 2)	1.5	0.4	0.4
Normal (BIRADS 1)	1.2	0.9	0.4
Incomplete (BIRADS 0)	0.0	0.1	0.0

MRI: magnetic resonance imaging; BIRADS: Breast Imaging Reporting and Data System
*Sensitivity: number of true positives (BIRADS 4-5) divided by total number of patients who had the test

2.13 Opacity was observed in 58.3%-71.8% of the patients in the three cohorts with BIRADS 4 or 5 mammograms, while microcalcification was observed in 43.1%-50.3% (Table 2.9). The mammographic density of a woman's breasts affects the sensitivity of mammography. Heterogeneously dense breast may obscure small masses, while extremely dense breast lowers the sensitivity of mammography. In the three patient cohorts, more than two-thirds (67.1%-72.5%) had heterogeneously dense breasts, while a small proportion (5.3%-9.4%) had extremely dense breasts (Figure 2.4). Mammographic density of a woman's breasts declines with increasing age. The proportion of patients with extremely dense breast decreases significantly from 10.5%-30.0% among patients aged between 20 and 29 to 0.9%-4.1% among patients aged 70 and above (Table 2.10).

Table 2.9: Mammographic findings of patients diagnosed through mammography (N=14,582)

	2006-2010 (N=4,585) %	2011-2015 (N=6,618) %	2016-current (N=3,379) %
Opacity	58.3	67.0	71.8
Microcalcification	50.3	50.2	43.1
Architectural distortion	13.2	15.0	13.1
Asymmetric density	10.3	7.4	4.4
Unclassified	5.8	5.6	7.4

Note: the total percentages may exceed 100 as multiple mammographic abnormalities may be found.

Figure 2.4: Mammographic density of breasts of patients diagnosed through mammogram (N=10,037)

	Fatty	Scattered density	Heterogeneous density	Extreme density
2006-2010 (N=3,299)	19.5	8.1	67.1	5.3
2011-2015 (N=4,728)	13.6	9.1	70.0	7.3
2016-current (N=2,010)	6.7	11.3	72.5	9.4

Mammographic breast density

Table 2.10: Mammographic density of breasts of patients diagnosed through mammogram by age group (N=9,864)

	Age group % for 2006-2010, % for 2011-2015, % for 2016-current																	
	20-29			30-39			40-49			50-59			60-69			≥70		
Fatty	10.5	5.0	0.0	7.5	5.5	0.7	10.7	7.7	3.8	21.0	12.3	4.6	32.0	20.2	10.0	47.3	31.3	17.6
Scattered density	5.3	0.0	10.0	4.3	3.4	5.8	6.4	5.5	7.8	9.2	9.6	10.3	10.4	12.2	15.8	9.9	17.9	18.2
Heterogeneous density	73.7	75.0	60.0	79.4	76.7	73.4	75.4	76.5	71.5	65.4	71.6	77.6	54.9	63.7	70.9	41.9	48.9	60.0
Extreme density	10.5	20.0	30.0	8.9	14.4	20.1	7.5	10.2	16.8	4.3	6.5	7.5	2.8	3.9	3.4	0.9	2.0	4.1

Total number of patients in each group:

20-29: 19 (for 2006-2010), 20 (for 2011-2015), 10 (for 2016-current)
30-39: 281 (for 2006-2010), 326 (for 2011-2015), 139 (for 2016-current)
40-49: 1,127 (for 2006-2010), 1,356 (for 2011-2015), 499 (for 2016-current)
50-59: 1,108 (for 2006-2010), 1,619 (for 2011-2015), 653 (for 2016-current)
60-69: 472 (for 2006-2010), 984 (for 2011-2015), 501 (for 2016-current)
≥70: 222 (for 2006-2010), 358 (for 2011-2015), 170 (for 2016-current)

2.14 Biopsies (samplings of breast cells or tissues for examination) for breast cancer diagnosis include fine needle aspiration (FNA), core needle biopsy (CNB) and excisional biopsy. As a standard of care, biopsies are for confirming before surgery if a breast lesion is malignant. FNA and CNB are less invasive sampling methods and used more often, but sometimes an excisional biopsy, which removes a relatively larger portion of breast tissue, is necessary. FNA and/or CNB were performed in the majority (2006-2010: 82.9%; 2011-2015: 86.7%; 2016-current: 89.2%) of the patients in the three cohorts and among them, 10.0%-36.6% (2006-2010: 36.6%; 2011-2015: 18.9%; 2016-current: 10.0%) received only FNA, 43.3%-68.3% (2006-2010: 43.3%; 2011-2015: 56.9%; 2016-current: 68.3%) received only CNB, while 20.1%-24.3% (2006-2010: 20.1%; 2011-2015: 24.3%; 2016-current: 21.7%) received both FNA and CNB. In addition, 4.9%-13.7% of the patients had excisional biopsy. Excisional biopsy had the highest overall sensitivity of 100%, followed by CNB (98.8%-99.7%) and FNA (90.2%-92.5%) (Table 2.11).

Table 2.11: Sensitivity and diagnostic results of breast tissue biopsies (N=20,138)

	2006-2010 (N=6,935) %	2011-2015 (N=8,971) %	2016-current (N=4,232) %
Fine needle aspiration			
Proportion of patients using the test	47.0	37.4	28.3
Overall sensitivity*	90.5	90.2	92.5
Class			
Diagnostic / malignant (Class V)	60.0	65.5	69.5
Suspicious (Class IV)	18.8	13.1	13.2
Atypical (Class III)	11.7	11.6	9.8
Benign (Class II)	4.8	3.4	2.3
Scanty benign (Class I)	3.3	4.6	4.7
Incomplete (Class 0)	1.4	1.8	0.6
Core needle biopsy			
Proportion of patients using the test	52.5	70.3	80.3
Overall sensitivity*	98.8	98.8	99.7
Class			
Diagnostic / malignant (Class V)	94.6	95.9	96.9
Suspicious (Class IV)	2.5	1.2	1.8
Atypical (Class III)	1.7	1.8	1.0
Benign (Class II)	0.7	0.9	0.2
Scanty benign (Class I)	0.5	0.2	0.1
Incomplete (Class 0)	0.0	0.0	0.0
Excisional biopsy			
Proportion of patients using the test	13.7	9.0	4.9
Overall sensitivity*	100.0	100.0	100.0
Class			
Diagnostic / malignant (Class V)	100.0	100.0	100.0
Suspicious (Class IV)	–	–	–
Atypical (Class III)	–	–	–
Benign (Class II)	–	–	–
Scanty benign (Class I)	–	–	–
Incomplete (Class 0)	–	–	–

FNA: fine needle aspiration; CNB: core needle biopsy
*Sensitivity: number of true positives (Class III-V) divided by total number of patients who had the test

B. Methods of cancer staging

2.15 Cancer staging is the process of finding out the extent of the disease in the body pre-operatively after diagnosis of breast cancer. Cancer staging is essential for patients with clinically node positive or locally advanced disease. Patients who only had chest x-ray are considered not having adequate workup for cancer stage to be determined.

2.16 The proportions of patients with invasive breast cancer who did not have any cancer staging as part of their diagnosis and treatment ranged from 36.6% to 53.4% across the three cohorts (2006-2010: 36.6%; 2011-2015: 53.4%; 2016-current: 53.2%). Among those patients who had cancer staging as part of their treatment, a combination of chest x-ray and ultrasound of abdomen (55.5%) was the most common method used for the 2006-2010 cohort, while positron emission tomography scan (PET scan) was the most common method used for the 2011-2015 (59.3%) and 2016-current (71.4%) cohorts (Table 2.12).

2.17 According to the National Comprehensive Cancer Network (NCCN) guidelines, PET scan is not recommended for patients with early breast cancer, including stage I, stage II, or operable stage III breast cancer, to determine the extent of disease.[46] This might be due to its low sensitivity and fairly low specificity in staging of the axillary lymph nodes and poor detection of metastases in patients with apparent early-stage disease. However, among those patients who had cancer staging, 13.2%-43.6% of stage I and 27.0%-69.8% of stage IIA patients had PET scan to determine the extent of their disease (Table 2.13).

Table 2.12: Method of cancer staging among invasive breast cancer patients (N=8,020)

	2006-2010 (N=3,124) %	2011-2015 (N=3,288) %	2016-current (N=1,608) %
Positron emission tomography scan (PET scan)	34.4	59.3	71.4
Chest x-ray and ultrasound abdomen	55.5	31.9	18.6
Computed tomography (CT) of body parts*	4.2	7.9	8.4
Bone scan	3.6	3.0	1.9
Magnetic resonance imaging (MRI) of whole body	0.7	0.6	1.2
Others (e.g. bone x-ray)	4.8	6.6	6.7
Not known	11.5	1.1	0.7

*Body parts included thorax, abdomen, pelvis, brain, or whole body
Note: the total percentages may exceed 100 as multiple methods of cancer staging may be used.

Table 2.13: Use of PET scan among patients who had cancer staging by cancer stage (N=8,020)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current					
	I	IIA	IIB	III	IV	Unstaged
PET scan used	13.2 25.6 43.6	27.0 47.7 69.8	39.6 70.2 80.6	63.3 83.2 88.5	82.8 90.4 81.2	67.9 80.9 94.2

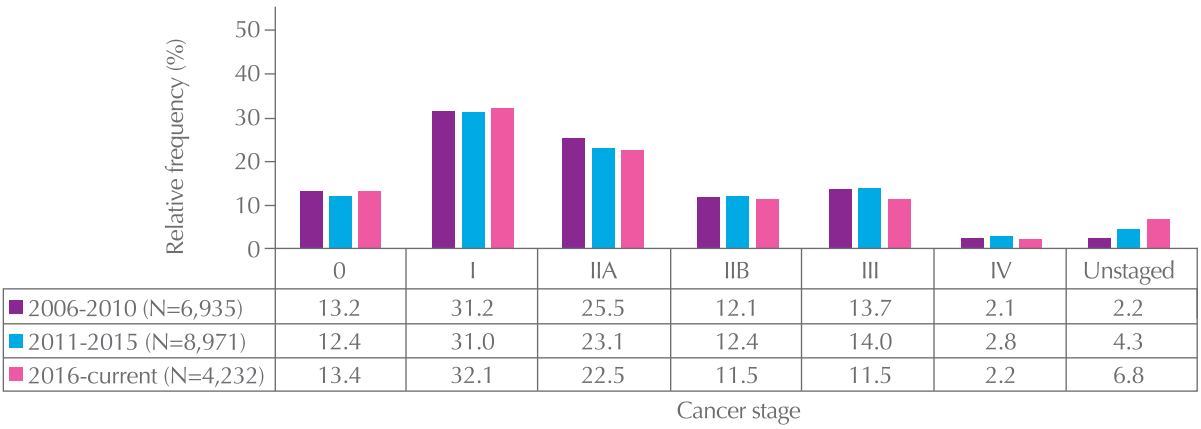
Total number of patients in each group:

I:	1,045 (for 2006-2010), 820 (for 2011-2015), 413 (for 2016-current)	III:	615 (for 2006-2010), 859 (for 2011-2015), 347 (for 2016-current)
IIA:	823 (for 2006-2010), 745 (for 2011-2015), 384 (for 2016-current)	IV:	128 (for 2006-2010), 240 (for 2011-2015), 85 (for 2016-current)
IIB:	457 (for 2006-2010), 493 (for 2011-2015), 242 (for 2016-current)	Unstaged:	56 (for 2006-2010), 131 (for 2011-2015), 137 (for 2016-current)

2.18 The American Joint Committee on Cancer (AJCC) Anatomic Breast Cancer Staging (8th edition)[47] is used for determining cancer staging in the patient cohorts. There are two stage groups according to this system: anatomic and prognostic stage groups. The anatomic stage group assigns a cancer stage based on the anatomic information on the tumour (T), regional nodes (N), and distant metastases (M) categories. The prognostic stage group, in conjunction with the aforementioned anatomic information (i.e. TNM categories), also takes into account other factors, including the tumour grade, biomarkers [human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), progesterone receptor (PR)] expression and genomic assays in assigning a stage.

2.19 Although prognostic stage group was recommended for patient care and was used for reporting of all cancer patients in the United States starting from 2018, it was not adopted in this report. The reason was that patients in the cohorts were mostly diagnosed in 2006 to 2017 and the treatment offered to patients in the cohort was based on the prevailing anatomic stage group. It is noted that there is only minimal difference in the TNM anatomic staging between the 7th and 8th edition. The most common cancer stage at diagnosis was stage II (34.0%-37.6%) followed by stages III-IV (13.7%-16.8%). In addition, 12.4%-13.4% of the patients were diagnosed with in situ cancer (stage 0) (Figure 2.5).

Figure 2.5: Cancer stage at diagnosis (N=20,138)



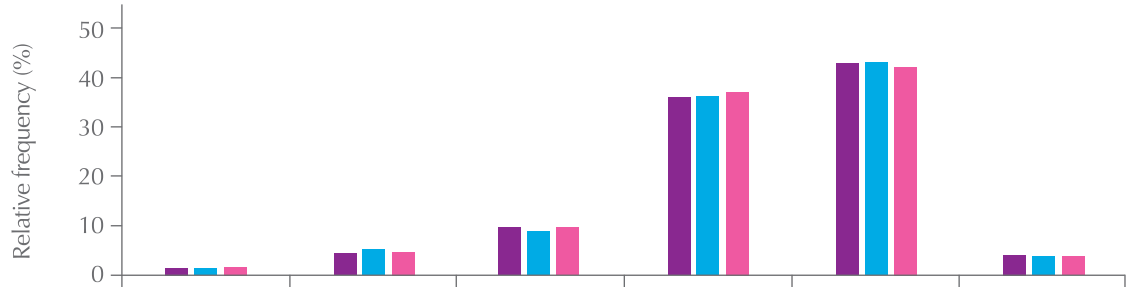
	0	I	IIA	IIB	III	IV	Unstaged
2006-2010 (N=6,935)	13.2	31.2	25.5	12.1	13.7	2.1	2.2
2011-2015 (N=8,971)	12.4	31.0	23.1	12.4	14.0	2.8	4.3
2016-current (N=4,232)	13.4	32.1	22.5	11.5	11.5	2.2	6.8

2.20 Of the 20,138 breast cancer cases analysed, data from 19,630 cases with available pathology data were used for subsequent analyses on cancer characteristics. A total of 16,996 (2006-2010: 86.5%; 2011-2015: 87.0%; 2016-current: 85.8%) patients were diagnosed with invasive cancer, while 2,617 (2006-2010: 13.4%; 2011-2015: 12.9%; 2016-current: 14.1%) patients were diagnosed with in situ cancer. In addition, 17 (2006-2010: 0.1%; 2011-2015: 0.1%; 2016-current: 0.1%) cases were diagnosed with occult primary breast cancer.

C. Characteristics of invasive breast cancer

2.21 The mean size of tumours of invasive breast cancer in each patient cohort was 2.2 cm (range: 0.01 to 27.0 cm; standard deviation: ±1.4 cm). Tumours of one cm or less in size were found in 15.7%-16.2% of the patients, while tumours of sizes 1.01 to 2.00 cm and 2.01 to 5.00 cm were respectively found in about 36.7%-37.6% and 42.6%-43.8% of the patients in all the three cohorts (Figure 2.6). Only a small proportion (3.6%-3.9%) of patients had tumours of sizes exceeding five cm. In all the patient cohorts, screen-detected tumours were significantly smaller than those self-detected by chance (2006-2010: mean: 1.3±1.0 cm vs. 2.3±1.4 cm; $p<0.001$; 2011-2015: mean: 1.2±0.9 cm vs. 2.3±1.4 cm; $p<0.001$; 2016-current: mean: 1.3±0.9 cm vs. 2.3±1.5 cm; $p<0.001$).

Figure 2.6: Distribution of tumour size (cm) of invasive breast cancer (N=14,561)

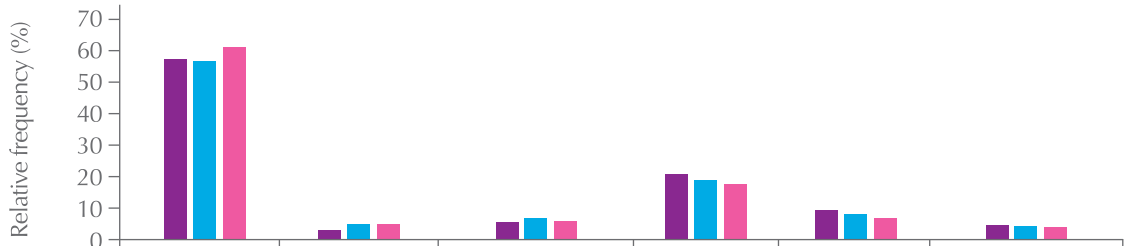


	≤ 0.10	0.11-0.50	0.51-1.00	1.01-2.00	2.01-5.00	> 5.00
2006-2010 (N=5,345)	1.6	4.4	9.7	36.8	43.7	3.9
2011-2015 (N=6,383)	1.5	5.5	8.8	36.7	43.8	3.7
2016-current (N=2,833)	1.7	4.7	9.8	37.6	42.6	3.6

Tumour size (cm)

2.22 Lymph node status is one of the factors used for determining breast cancer stage. Multiple affected lymph nodes signify a higher disease stage. Of the patients with invasive breast cancer, 56.3%-60.6% had no positive axillary lymph nodes, 3.1%-4.9% had isolated tumour cells (metastasis size ≤ 0.2 mm or a cluster of fewer than 200 tumour cells), 5.9%-7.2% had micrometastasis (metastasis size > 0.2 mm to ≤ 2 mm), while 28.4%-34.5% had at least one positive axillary lymph node with metastasis size larger than two mm (Figure 2.7).

Figure 2.7: Number of positive axillary lymph nodes among patients with invasive breast cancer (N=16,134)



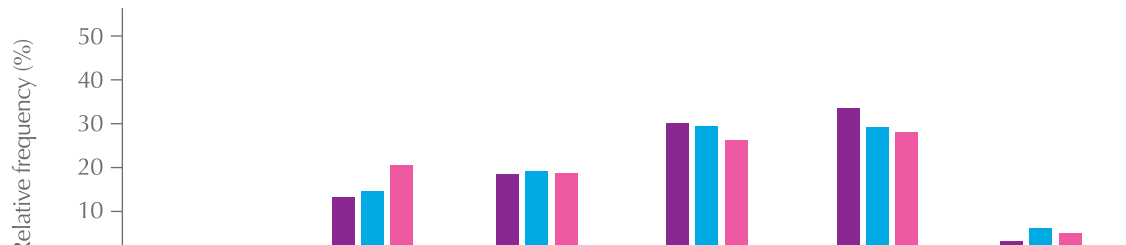
	0+ve nodes	Isolated tumour cell	Micrometastasis (0.2-2.0mm)	1-3+ve nodes	4-9+ve nodes	10 or above +ve nodes
2006-2010 (N=5,690)	56.5	3.1	5.9	20.3	9.4	4.8
2011-2015 (N=7,221)	56.3	4.7	7.2	18.8	8.5	4.4
2016-current (N=3,223)	60.6	4.9	6.1	17.7	6.9	3.8

Axillary nodal status

D. Characteristics of in situ breast cancer

2.23 The mean size of tumours of in situ breast cancer was 2.0 cm in the 2006-2010 cohort (range: 0.02 to 10.4 cm; standard deviation: ±1.5 cm), 2.1 cm in the 2011-2015 cohort (range: 0.05 to 25.0 cm; standard deviation: ±1.9 cm), and 1.8 cm in the 2016-current cohort (range: 0.04 to 8.5 cm; standard deviation: ±1.5 cm). Tumours of one cm or less in size were found in 32.5%-41.2% of the patients while tumours of 2.01 to 5.00 cm in size were found in 27.9%-33.6% of the patients (Figure 2.8). A small proportion (3.4%-6.6%) of the patients had in situ tumours larger than five cm. Of the in situ breast cancer cases where MMG was performed, around three-fifths (2006-2010: 61.7%; 2011-2015: 63.5%; 2016-current: 58.8%) showed microcalcification.

Figure 2.8: Distribution of tumour size (cm) of in situ breast cancer (N=2,159)



	≤0.10	0.11-0.50	0.51-1.00	1.01-2.00	2.01-5.00	>5.00
2006-2010 (N=797)	0.9	13.3	18.3	30.5	33.6	3.4
2011-2015 (N=896)	1.2	14.5	19.0	29.5	29.2	6.6
2016-current (N=466)	2.1	20.4	18.7	26.4	27.9	4.5

Tumour size (cm)

IV. Histological and biological characteristics

2.24 Breast cancer is a heterogeneous group of tumours, consisting of different histologic subtypes with diverse microscopic appearances. The histological data of breast carcinomas provide valuable prognostic information. They complement other independent parameters including size, grade, nodal status, hormonal receptor status and HER2 oncogene status to help predict the likelihood of recurrence and response to treatment.

A. Invasive breast cancer

2.25 As far as histological characteristics, grading, multifocality and multicentricity of invasive breast cancer in the patient cohorts are concerned, the majority (86.8%-87.1%) was invasive carcinoma of no specific type (Table 2.14), and about one-third (29.6%-33.7%) of the invasive tumours are of grade 3 (Table 2.15).

Table 2.14: Histological type of invasive breast cancer (N=16,996)

	2006-2010 (N=5,883) %	2011-2015 (N=7,620) %	2016-current (N=3,493) %
Invasive carcinoma of no specific type	86.8	87.1	86.9
Lobular	3.6	3.4	4.4
Mucinous (colloid)	3.8	3.3	3.0
Papillary	0.9	1.2	1.2
Tubular	0.8	0.7	0.5
Carcinoma with medullary features	0.6	0.6	0.3
Micropapillary	0.4	0.5	0.6
Mixed ductal and lobular	0.5	0.4	0.6
Borderline / malignant phyllodes	0.4	0.5	0.5
Metaplastic carcinoma	0.3	0.4	0.3
Carcinoma with neuroendocrine features	0.2	0.3	0.1
Carcinoma with apocrine features	0.2	0.2	0.3
Adenoid cystic carcinoma	0.0	0.2	0.1
Cribriform carcinoma	0.1	<0.1	0.1
Tubulo-lobular	<0.1	0.1	0.1
Sarcoma	0.0	<0.1	<0.1
Inflammatory	<0.1	<0.1	<0.1
Paget's disease of nipple	<0.1	<0.1	0.0
Lipid rich carcinoma	<0.1	<0.1	0.0
Squamous cell	<0.1	<0.1	0.0
Secretory carcinoma	<0.1	0.0	0.0
Acinic cell carcinoma	0.0	<0.1	0.0
Others	0.1	0.3	0.2
Not known	1.2	0.9	0.8

Table 2.15: Grading, multifocality and multicentricity of invasive breast cancer (N=16,996)

	2006-2010 (N=5,883) %	2011-2015 (N=7,620) %	2016-current (N=3,493) %
Grade			
Grade 1	16.5	16.0	18.0
Grade 2	39.0	40.3	38.2
Grade 3	33.7	31.1	29.6
Not known	10.8	12.6	14.2
Lymphovascular invasion	**28.5**	**24.7**	**22.0**
Multifocality	**9.7**	**8.7**	**10.1**
Number of foci			
2	53.1	55.1	58.4
3-4	18.6	15.9	18.7
5 or more	12.3	7.4	7.9
Not known	16.1	21.6	15.0
Multicentricity	**2.7**	**2.6**	**2.4**
Number of quadrants			
2	85.3	85.8	81.9
3	7.1	5.1	2.4
4	5.1	1.0	2.4
Not known	2.6	8.1	13.3

2.26 Of the patients with invasive breast cancer, almost all (2006-2010: 97.6%; 2011-2015: 97.5%; 2016-current: 97.0%) were tested for ER or PR status. Among them, more than three-quarters (2006-2010: 79.5%; 2011-2015: 78.7%; 2016-current: 83.8%) were either ER or PR positive. Using immunohistochemistry (IHC), score 3 is considered as c-erbB2/HER2 positive and score 0 or 1 is considered as negative. As for score 2 (equivocal), it is also considered as HER2 positive, if the results are positive in the in situ hybridization (ISH) test. Based on the 2018 guideline,[42] most of the cases classified as equivocal previously (i.e. cases with low HER2 copy number, or low HER2:CEP17 ratio) are now classified as negative. In the three cohorts, less than one-quarter (17.9%-24.8%) of the invasive breast cancer cases were c-erbB2/HER2 positive. The biological characteristics of invasive breast cancer in the three patient cohorts are shown in Table 2.16.

Table 2.16: Biological characteristics of invasive breast cancer (N=16,996)

	2006-2010 (N=5,883) %	2011-2015 (N=7,620) %	2016-current (N=3,493) %
Estrogen receptor (ER) [% had the test]	**[97.6]**	**[97.4]**	**[97.0]**
Positive	76.6	77.9	83.1
Negative	23.4	22.1	16.9
Progesterone receptor (PR) [% had the test]	**[97.3]**	**[97.2]**	**[96.7]**
Positive	63.9	65.1	70.1
Negative	36.1	34.9	29.9
c-erbB2 / HER2 [% had the test]	**[96.7]**	**[96.7]**	**[94.1]**
Positive (IHC Score 3)	23.8	18.6	15.2
Equivocal (IHC Score 2) ISH positive	1.0	3.2	2.7
Equivocal (IHC Score 2) ISH equivocal	0.2	1.3	1.6
Equivocal (IHC Score 2) ISH negative	10.4	22.1	16.2
Equivocal (IHC Score 2) ISH not done	14.5	10.6	9.1
Negative (IHC Score 0/1)	50.0	44.2	55.2
Ki-67 index [% had the test]	**[53.3]**	**[55.8]**	**[72.7]**
<14%	41.0	34.2	31.5
≥14%	59.0	65.8	68.5

HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization

2.27 Breast cancer is well known to be a heterogeneous disease and can be further classified into several biological subtypes[48] by immunohistochemical staining of several biological markers (Table 2.16). While amplification or over-expression of HER2 oncogene is associated with the development of certain types of breast cancer, further prognostic and predictive information can be obtained by assessing these biological markers together, rather than separately. The surrogate definitions of these intrinsic biological subtypes and their relative frequencies by cancer stage in the three patient cohorts are shown in Table 2.17.

Table 2.17: Biological subtypes of invasive tumours by cancer stage (N=15,853)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current														
	I			IIA			IIB			III			IV		
Luminal A	27.6	26.0	34.4	17.0	16.0	19.9	18.4	12.0	13.8	11.6	10.5	12.6	7.3	9.0	6.0
Luminal B (HER2 negative)	14.1	18.0	32.5	18.1	22.1	36.5	19.9	22.8	40.9	20.9	22.8	31.5	17.7	20.1	39.8
Luminal A/B (HER2 negative)	27.6	28.6	12.4	25.7	25.9	14.8	25.8	29.6	18.5	24.3	26.6	20.0	27.1	26.5	21.7
Luminal B (HER2 positive)	13.4	9.7	8.1	15.6	11.3	12.1	15.6	13.0	9.7	20.4	17.4	13.3	27.1	18.5	14.5
HER2 positive	7.7	7.9	5.5	8.8	10.1	6.2	9.4	8.7	5.6	11.9	11.9	11.0	13.5	16.4	8.4
TNBC	9.5	9.8	7.1	14.7	14.4	10.4	10.9	13.8	11.5	10.9	10.9	11.5	7.3	9.5	9.6

Total number of patients in each group:

I: 2,078 (for 2006-2010), 2,682 (for 2011-2015), 1,254 (for 2016-current)
IIA: 1,709 (for 2006-2010), 2,010 (for 2011-2015), 881 (for 2016-current)
IIB: 819 (for 2006-2010), 1,073 (for 2011-2015), 443 (for 2016-current)
III: 907 (for 2006-2010), 1,185 (for 2011-2015), 444 (for 2016-current)
IV: 96 (for 2006-2010), 189 (for 2011-2015), 83 (for 2016-current)

Luminal A: ER and/or PR+, HER2-, and low Ki-67 index (<14%)
Luminal B (HER2 negative): ER and/or PR+, HER2-, and high Ki-67 index (≥14%)
Luminal A/B (HER2 negative): ER and/or PR+, HER2-, and Ki-67 index not known
Luminal B (HER2 positive): ER and/or PR+, HER2+, and any Ki-67 index
HER2 positive: ER and PR-, HER2+, and any Ki-67 index
TNBC (Triple Negative Breast Cancer): ER and PR-, HER2-, and any Ki-67 index

2.28 In the past, chemotherapy is often given to breast cancer patients with positive hormone-receptor. However, it has been shown that the vast majority of these patients with early-stage breast cancer do not benefit from adjuvant chemotherapy and could be burdened by the short- and long-term side effects caused. There is, therefore, a change of paradigm in early breast cancer management in recent practice, i.e. considering proven chemotherapy benefit instead of assuming chemotherapy benefit. Oncotype DX Breast Recurrence Score test can classify patients into groups based on the genomic assay that is predictive of chemotherapy benefit.[49] In the three cohorts, most of the tested patients were found with a low or moderate risk of recurrence of breast cancer (2006-2010: 87.9%; 2011-2015: 87.6%; 2016-current: 83.5%).

B. In situ breast cancer

2.29 Ductal cancer was found to be the most common type of in situ breast cancer in each cohort (91.6%-93.4%). Table 2.18 shows the histological characteristics, grading, multifocality and multicentricity of in situ breast cancer in the three patient cohorts.

Table 2.18: Histological type, grading, multifocality and multicentricity of in situ breast cancer (N=2,617)

	2006-2010 (N=915) %	2011-2015 (N=1,128) %	2016-current (N=574) %
Histological type			
Ductal	93.4	91.6	92.2
Mixed	2.5	2.4	1.0
Papillary	1.4	1.7	1.6
Intracystic papillary	0.9	0.6	0.2
Encapsulated papillary	0.0	0.6	1.0
Apocrine	0.1	0.4	0.3
Neuroendocrine	0.1	0.3	0.0
Cribriform	0.0	0.0	0.3
Micropapillary	0.1	0.0	0.0
Others	0.4	0.7	0.5
Not known	1.0	1.7	2.8
Necrosis	**39.1**	**30.4**	**28.9**
Nuclear grade			
Low	24.9	25.0	28.9
Intermediate	32.8	31.9	35.2
High	38.0	36.7	29.4
Not known	4.3	6.4	6.4
Multifocality	**12.2**	**11.3**	**10.8**
Number of foci			
2	50.9	39.1	61.3
3	6.2	8.6	8.1
4 or more	5.4	3.9	1.6
Not known	37.5	48.4	29.0
Multicentricity	**2.3**	**2.3**	**1.4**
Number of quadrants			
2	81.0	84.6	87.5
3	4.8	7.7	0.0
Not known	14.3	7.7	12.5

2.30 Of the patients with in situ breast cancer, one-half to three-quarters (2006-2010: 74.8%; 2011-2015: 70.4%; 2016-current: 57.1%) were tested for ER or PR status. Among them, the majority (2006-2010: 82.5%; 2011-2015: 81.6%; 2016-current: 83.5%) were either ER or PR positive. In addition, 20.0%-29.1% of in situ breast cancer patients were HER2 positive in the three cohorts. Table 2.19 shows the biological characteristics of in situ breast cancer in the three patient cohorts.

Table 2.19: Biological characteristics of in situ breast cancer (N=2,617)

	2006-2010 (N=915) %	2011-2015 (N=1,128) %	2016-current (N=574) %
Estrogen receptor (ER) [% had the test]	**[74.8]**	**[70.3]**	**[57.1]**
Positive	80.4	81.3	83.2
Negative	19.6	18.7	16.8
Progesterone receptor (PR) [% had the test]	**[73.9]**	**[68.5]**	**[55.4]**
Positive	71.0	71.9	75.5
Negative	29.0	28.1	24.5
c-erbB2 / HER2 [% had the test]	**[70.4]**	**[61.9]**	**[50.5]**
Positive (IHC Score 3)	28.9	24.8	20.0
Equivocal (IHC Score 2) ISH positive	0.2	0.1	0.0
Equivocal (IHC Score 2) ISH equivocal	0.0	0.0	0.0
Equivocal (IHC Score 2) ISH negative	1.6	1.6	0.7
Equivocal (IHC Score 2) ISH not done	28.0	37.8	30.3
Negative (IHC Score 0/1)	41.5	35.7	49.0
Ki-67 index [% had the test]	**[45.6]**	**[38.1]**	**[47.0]**
<14%	71.2	60.2	55.6
≥14%	28.8	39.8	44.4

HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization

V. Treatment methods

2.31 Of the patients, less than one-fifth (2006-2010: 14.5%; 2011-2015: 10.0%; 2016-current: 17.8%) received care at private medical service, about half (2006-2010: 47.5%; 2011-2015: 54.1%; 2016-current: 48.4%) received care at public medical services, and one-third (2006-2010: 38.0%; 2011-2015: 35.8%; 2016-current: 33.8%) received care at both private and public medical services. Patients with invasive cancer were usually given multimodality treatments, which could include surgery, chemotherapy, anti-HER2 targeted therapy, endocrine therapy and radiotherapy. In contrast, patients with in situ cancer required less aggressive treatments including surgery, endocrine therapy, and radiotherapy. Chemotherapy and anti-HER2 targeted therapy were generally not required for patients with in situ cancer. These treatments, except surgery, could be applied in adjuvant (after surgery), neoadjuvant (before surgery) or palliative (for metastatic disease) settings according to the stage of disease at diagnosis.

A. Surgical treatment

2.32 Surgery is an important consideration in the effective treatment of both in situ and invasive breast cancer. With the continuing developments in breast cancer treatment, surgery is less disfiguring nowadays. Options for local treatment include breast-conserving surgery or total mastectomy. Breast-conserving surgery followed by radiotherapy gives equivalent survival rates compared with mastectomy. Women who have a mastectomy may decide to have breast reconstruction, either at the same time or at a later stage.

2.33 Nodal surgery is usually performed together with breast surgery to ascertain the extent of disease. Lymph node surgery includes sentinel lymph node biopsy (SNB) or axillary dissection (AD). For patients with negative clinical nodal status, SNB can be conducted before AD to determine whether any lymph node is affected. This is to prevent lymphoedema which may occur when a large number of lymph nodes are removed by surgery.

2.34 In the cohorts, about half (2006-2010: 54.0%; 2011-2015: 47.5%; 2016-current: 54.1%) of the patients had surgery at private medical facilities, while half (2006-2010: 46.0%; 2011-2015: 52.5%; 2016-current: 45.9%) had surgery at public medical facilities.

2.35 For patients with invasive breast cancer, the majority (97.8%-98.6%) underwent surgery as part of their treatment. Of the patients with invasive cancer, more than half (58.1%-65.9%) had mastectomy, while about one-third (32.5%-39.2%) had breast-conserving surgery. Among the patients who had mastectomy, 11.4%-13.8% had either immediate or delayed reconstruction. The most common type of reconstruction was TRAM flap (68.0%-71.4%) (Table 2.20). Nearly all (95.9%-97.2%) the patients with invasive breast cancer received nodal surgery and among them, 22.6%-50.7% required AD alone, and 33.1%-62.9% required SNB alone.

2.36 For patients with in situ breast cancer, almost all (98.2%-99.5%) underwent surgery (Table 2.21). Half (50.3%-56.9%) had breast-conserving surgery, while about a quarter (19.8%-22.8%) had reconstruction after mastectomy. In addition, about one-third (32.2%-39.7%) did not receive nodal surgery, and among those who received nodal surgery, the majority (76.4%-97.5%) had SNB only and 1.4%-19.5% had AD without SNB.

Table 2.20: Use of surgery for patients with invasive cancer

	2006-2010 %	2011-2015 %	2016-current %
Type of surgery (N=17,334)	**(N=5,967)**	**(N=7,755)**	**(N=3,612)**
No surgery	1.4	1.9	1.9
Breast-conserving surgery	32.5	33.2	39.2
Mastectomy	65.9	64.5	58.1
Nodal surgery only	0.1	0.1	0.4
Type of surgery not known	0.1	0.2	0.1
Not known if surgery done	0.1	0.2	0.3
Type of mastectomy (N=11,031)	**(N=3,932)**	**(N=5,000)**	**(N=2,099)**
Total mastectomy	94.2	94.5	92.3
Skin sparing	4.9	3.6	2.6
Areolar sparing	0.2	0.2	0.0
Nipple sparing	0.5	1.5	4.8
Type not known	0.2	0.2	0.3
Type of reconstruction (N=1,347)	**(N=488)**	**(N=569)**	**(N=290)**
TRAM flap	68.0	69.2	71.4
Implant	14.1	17.4	18.6
LD flap	9.0	7.7	5.5
LD flap & implant	7.4	3.0	3.1
Type not known	1.4	2.6	1.4
Type of nodal surgery (N=16,753)	**(N=5,801)**	**(N=7,489)**	**(N=3,463)**
Sentinel node biopsy alone	33.1	47.6	62.9
Sentinel node biopsy followed by axillary dissection	15.8	17.4	14.1
Axillary dissection alone	50.7	33.6	22.6
Type not known	0.5	1.5	0.4

Table 2.21: Use of surgery for patients with in situ cancer

	2006-2010 %	2011-2015 %	2016-current %
Type of surgery (N=2,650)	**(N=923)**	**(N=1,135)**	**(N=592)**
No surgery	0.5	0.8	1.9
Breast-conserving surgery	50.3	50.6	56.9
Mastectomy	49.2	48.3	40.4
Nodal surgery only	0.0	0.0	0.2
Type of surgery not known	0.0	0.4	0.7
Not known if surgery done	0.0	0.0	0.0
Type of mastectomy (N=1,241)	**(N=454)**	**(N=548)**	**(N=239)**
Total mastectomy	87.2	86.7	85.8
Skin sparing	11.5	8.8	5.0
Areolar sparing	0.2	0.5	0.0
Nipple sparing	0.9	4.0	8.8
Type not known	0.2	0.0	0.4
Type of reconstruction (N=267)	**(N=90)**	**(N=125)**	**(N=52)**
TRAM flap	66.7	61.6	53.8
Implant	22.2	29.6	38.5
LD flap	4.4	5.6	5.8
LD flap & implant	6.7	2.4	0.0
Type not known	0.0	0.8	1.9
Type of nodal surgery (N=1,735)	**(N=609)**	**(N=769)**	**(N=357)**
Sentinel node biopsy alone	76.4	90.5	97.5
Sentinel node biopsy followed by axillary dissection	3.6	1.8	1.1
Axillary dissection alone	19.5	6.1	1.4
Type not known	0.5	1.6	0.0

2.37 The percentage of patients who underwent mastectomy was positively correlated with increasing age, while the percentage of patients who underwent mastectomy with reconstruction was negatively correlated with increasing age (Table 2.22).

2.38 For the patients with tumours larger than 0.5 cm in size, the percentage of patients who had breast-conserving surgery was negatively correlated with increasing tumour size (Table 2.23).

Table 2.22: Type of breast surgery by age group (N=19,320)

	Age group % for 2006-2010, % for 2011-2015, % for 2016-current																							
	<20			20-29			30-39			40-49			50-59			60-69			70-79			≥80		
Breast-conserving surgery	—	0.0	—	44.2	56.5	70.0	47.3	46.8	52.1	41.3	44.4	49.5	31.7	36.2	46.4	26.4	25.5	34.6	12.6	18.4	19.9	14.5	10.5	13.1
Mastectomy	—	0.0	—	32.7	10.9	16.7	34.0	31.9	27.0	47.1	43.2	34.1	62.7	58.7	47.3	71.9	72.5	64.1	87.1	81.4	79.3	85.5	89.5	86.9
Mastectomy + Reconstruction	—	100.0	—	23.1	32.6	13.3	18.6	21.3	20.9	11.6	12.3	16.3	5.5	5.1	6.3	1.7	2.0	1.4	0.3	0.2	0.7	0.0	0.0	0.0

Total number of patients in each group:

<20: 0 (for 2006-2010), 1 (for 2011-2015), 0 (for 2016-current)
20-29: 52 (for 2006-2010), 46 (for 2011-2015), 30 (for 2016-current)
30-39: 676 (for 2006-2010), 677 (for 2011-2015), 263 (for 2016-current)
40-49: 2,505 (for 2006-2010), 2,583 (for 2011-2015), 1,078 (for 2016-current)
50-59: 2,171 (for 2006-2010), 2,929 (for 2011-2015), 1,298 (for 2016-current)
60-69: 879 (for 2006-2010), 1,768 (for 2011-2015), 1,013 (for 2016-current)
70-79: 326 (for 2006-2010), 526 (for 2011-2015), 276 (for 2016-current)
≥80: 76 (for 2006-2010), 86 (for 2011-2015), 61 (for 2016-current)

Table 2.23: Type of breast surgery by invasive tumour size (cm) (N=15,405)

	Invasive tumour size (cm) % for 2006-2010, % for 2011-2015, % for 2016-current																	
	≤0.10			0.11-0.50			0.51-1.00			1.01-2.00			2.01-5.00			>5.00		
Breast-conserving surgery	31.1	38.4	36.8	32.4	38.0	45.3	46.0	44.1	61.2	43.5	45.9	52.6	25.5	25.6	29.5	4.6	5.6	6.5
Mastectomy	46.7	53.6	50.9	56.0	51.0	37.3	48.2	48.2	32.4	50.8	49.4	42.1	65.8	66.9	62.4	75.8	77.8	67.3
Mastectomy + Reconstruction	22.2	8.0	12.3	11.6	11.0	17.4	5.8	7.8	6.5	5.8	4.7	5.4	8.7	7.5	8.1	19.6	16.5	26.2

Total number of patients in each group:

≤0.10 cm: 90 (for 2006-2010), 112 (for 2011-2015), 57 (for 2016-current)
0.11-0.50 cm: 259 (for 2006-2010), 408 (for 2011-2015), 161 (for 2016-current)
0.51-1.00 cm: 531 (for 2006-2010), 631 (for 2011-2015), 309 (for 2016-current)
1.01-2.00 cm: 2,013 (for 2006-2010), 2,446 (for 2011-2015), 1,120 (for 2016-current)
2.01-5.00 cm: 2,433 (for 2006-2010), 2,960 (for 2011-2015), 1,244 (for 2016-current)
>5.00 cm: 240 (for 2006-2010), 284 (for 2011-2015), 107 (for 2016-current)

Table 2.24: Type of breast surgery by cancer stage (N=19,044)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current														
	0			I			II			III			IV		
Breast-conserving surgery	50.6	51.4	58.1	46.2	47.0	54.8	30.6	31.6	36.0	12.3	14.5	16.2	7.0	7.5	17.5
Mastectomy	39.6	37.6	33.5	47.3	47.1	38.8	61.3	61.5	55.7	76.4	74.6	72.6	82.6	79.9	73.0
Mastectomy + Reconstruction	9.8	11.0	8.4	6.5	5.8	6.4	8.1	6.9	8.3	11.3	10.9	11.2	10.5	12.6	9.5

Total number of patients in each group:

0: 915 (for 2006-2010), 1,108 (for 2011-2015), 558 (for 2016-current)
I: 2,159 (for 2006-2010), 2,779 (for 2011-2015), 1,354 (for 2016-current)
II: 2,598 (for 2006-2010), 3,165 (for 2011-2015), 1,427 (for 2016-current)
III: 945 (for 2006-2010), 1,238 (for 2011-2015), 475 (for 2016-current)
IV: 86 (for 2006-2010), 174 (for 2011-2015), 63 (for 2016-current)

2.39 The proportion of patients who received breast-conserving surgery was negatively correlated with increasing cancer stage. Mastectomy with reconstruction did not show any correlation with increasing cancer stage (Table 2.24).

2.40 A higher proportion (44.3%-52.1%) of patients who had surgery at private medical facilities underwent breast-conserving surgery than those who had surgery at public medical facilities (25.8%-32.4%) (Table 2.25).

Table 2.25: Type of breast surgery by type of medical service (N=18,937)

	Type of medical service users % for 2006-2010, % for 2011-2015, % for 2016-current					
	Public			Private		
Breast-conserving surgery	25.8	28.1	32.4	44.3	45.5	52.1
Mastectomy	66.3	65.2	62.5	46.5	45.2	36.6
Mastectomy + Reconstruction	7.9	6.6	5.1	9.2	9.3	11.3

Total number of patients in each group:
Public: 3,029 (for 2006-2010), 4,416 (for 2011-2015), 1,803 (for 2016-current)
Private: 3,557 (for 2006-2010), 3,997 (for 2011-2015), 2,135 (for 2016-current)

2.41 SNB without AD was more commonly performed on patients with negative clinical nodal status (43.1%-81.5%) than those with positive clinical nodal status (9.0%-22.0%). On the other hand, AD without SNB was more commonly performed on the patients with positive clinical nodal status (56.5%-80.7%) than those with negative clinical nodal status (8.5%-41.3%). Table 2.26 shows the type of nodal surgery received by patients with positive or negative clinical nodal status in the three patient cohorts.

2.42 The use of AD alone was positively correlated with progressing cancer stage in each cohort. In each cohort, the use of AD after SNB increased from stage I to II patients, but decreased for stage III or IV patients. This is because most of the patients with stage III or IV disease received AD as their first nodal surgery (Table 2.27).

Table 2.26: Type of nodal surgery by clinical nodal status (N=18,388)

	Clinical nodal status % for 2006-2010, % for 2011-2015, % for 2016-current					
	Positive			Negative		
SNB alone	9.0	19.0	22.0	43.1	63.0	81.5
SNB followed by AD	10.4	14.5	21.5	15.5	16.6	10.0
AD alone	80.7	66.5	56.5	41.3	20.3	8.5

Total number of patients in each group:
Positive: 1,082 (for 2006-2010), 1,988 (for 2011-2015), 976 (for 2016-current)
Negative: 5,317 (for 2006-2010), 6,179 (for 2011-2015), 2,846 (for 2016-current)

SNB: sentinel node biopsy; AD: axillary dissection

Table 2.27: Type of nodal surgery for invasive cancer by cancer stage (N=16,194)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current														
	I			IIA			IIB			III			IV		
SNB alone	60.7	82.0	92.4	33.4	52.4	72.9	3.2	12.8	25.9	1.0	3.8	8.9	2.3	8.6	21.3
SNB followed by AD	7.1	6.5	2.6	19.2	19.1	14.4	33.6	39.7	42.2	15.3	22.0	21.3	4.7	9.3	4.9
AD alone	32.2	11.5	5.0	47.4	28.5	12.7	63.1	47.5	31.9	83.8	74.1	69.8	93.0	82.1	73.8

Total number of patients in each group:
I: 2,129 (for 2006-2010), 2,736 (for 2011-2015), 1,349 (for 2016-current)
IIA: 1,732 (for 2006-2010), 2,025 (for 2011-2015), 937 (for 2016-current)
IIB: 833 (for 2006-2010), 1,082 (for 2011-2015), 467 (for 2016-current)
III: 931 (for 2006-2010), 1,203 (for 2011-2015), 461 (for 2016-current)
IV: 86 (for 2006-2010), 162 (for 2011-2015), 61 (for 2016-current)

SNB: sentinel node biopsy; AD: axillary dissection

2.43 About half (55.3%-59.9%) of the patients with node positive invasive cancer had tumours of 2.01 to 5.00 cm in size, while a small proportion (6.4%-7.0%) had tumours larger than five cm. In the patient cohorts, more patients with node negative invasive cancer (61.9%-64.3%) had tumours of two cm or less, compared to patients with node positive invasive cancer (33.0%-37.9%) (Table 2.28).

2.44 Of the patients in the cohorts, 92.2%-98.0% who underwent only SNB had no positive lymph node, while 29.9%-49.4% who underwent only AD and 9.5%-18.1% who underwent AD after SNB had no positive lymph node (Table 2.29).

Table 2.28: Distribution of tumour size (cm) in invasive cancer with negative or positive nodal status (N=14,231)

	Nodal status % for 2006-2010, % for 2011-2015, % for 2016-current					
	Positive			Negative		
≤0.10 cm	0.5	0.3	0.3	2.3	2.2	2.3
0.11-0.50 cm	1.2	1.4	0.2	6.4	8.0	7.0
0.51-1.00 cm	4.3	3.9	2.7	13.0	11.9	13.5
1.01-2.00 cm	31.9	29.7	29.8	40.2	41.4	41.5
2.01-5.00 cm	55.3	58.3	59.9	36.4	35.1	33.8
>5.00 cm	6.8	6.4	7.0	1.7	1.5	1.8

Total number of patients in each group:
Positive: 2,077 (for 2006-2010), 2,384 (for 2011-2015), 918 (for 2016-current)
Negative: 3,175 (for 2006-2010), 3,860 (for 2011-2015), 1,817 (for 2016-current)

Table 2.29: Number of positive nodes by type of nodal surgery (N=17,911)

	Type of nodal surgery % for 2006-2010, % for 2011-2015 % for 2016-current								
	SNB alone			SNB followed by AD			AD alone		
0 +ve nodes	98.0	94.6	92.2	18.1	14.3	9.5	49.4	39.2	29.9
1-3 +ve nodes	1.9	5.1	7.0	67.5	67.1	72.5	27.8	32.6	37.0
4-9 +ve nodes	0.1	0.3	0.6	11.7	14.2	11.9	14.2	17.4	20.6
10 or above +ve nodes	0.0	0.1	0.2	2.7	4.4	6.1	8.6	10.8	12.4

Total number of patients in each group:

SNB alone: 2,364 (for 2006-2010), 4,194 (for 2011-2015), 2,416 (for 2016-current)

SNB followed by AD: 916 (for 2006-2010), 1,278 (for 2011-2015), 472 (for 2016-current)

AD alone: 3,021 (for 2006-2010), 2,502 (for 2011-2015), 748 (for 2016-current)

SNB: sentinel node biopsy; AD: axillary dissection

B. Radiotherapy

2.45 Radiotherapy is a treatment to kill cancer cells using ionizing radiation. It is capable of inflicting damage on the DNA structure, and thus induces cell death and causes cell division failure. Radiotherapy can be administered in two settings: firstly, locoregional radiotherapy where the breast or chest wall, with or without regional lymph nodes, are irradiated with curative intent; and secondly palliative radiotherapy (e.g. to bone) is used to reduce symptoms that can be pain, pressure symptoms, airway obstruction, bleeding and secretion from metastases.

i. Locoregional radiotherapy

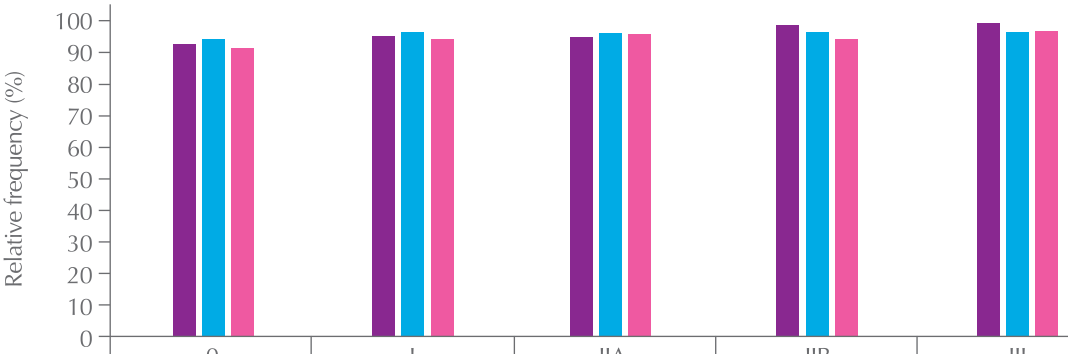
2.46 Locoregional radiotherapy to the breast following breast-conserving surgery is an integral part of breast-conserving therapy in order to achieve an outcome equivalent to mastectomy. This applies to all patients with invasive breast cancer and most patients with in situ cancer. Following mastectomy, some patients whose tumour is locally advanced, or with cancer cells found in the lymphatic or blood vessels also need radiotherapy.

2.47 In the patient cohorts, two-thirds (2006-2010: 62.9%; 2011-2015: 63.1%; 2016-current: 63.9%) of the patients had locoregional radiotherapy as part of their treatment, with almost all (2006-2010: 99.9%; 2011-2015: 99.7%; 2016-current: 99.6%) being adjuvant. More than four-fifths (2006-2010: 86.8%; 2011-2015: 89.2%; 2016-current: 81.9%) of the patients were treated with radiotherapy at public medical facilities, while the remainder (2006-2010: 13.2%; 2011-2015: 10.8%; 2016-current: 18.1%) had radiotherapy at private medical facilities.

2.48 The proportions of the invasive breast cancer patients who had undergone either breast-conserving surgery or mastectomy and received locoregional radiotherapy as part of their treatment by different cancer stages in the three patient cohorts are shown in Figures 2.9 and 2.10 respectively. The majority (over 93%) of the invasive breast cancer patients in the three cohorts who underwent breast-conserving surgery also received locoregional radiotherapy (Figure 2.9). On the other hand, the proportion of invasive breast cancer patients who underwent mastectomy and also received locoregional radiotherapy increased significantly with progressing cancer stage (Figure 2.10).

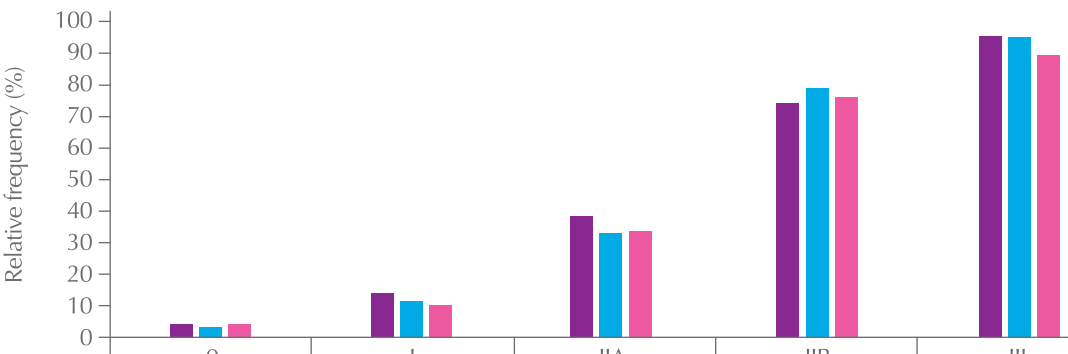
2.49 Of the patients with in situ cancer who had breast-conserving surgery, over 91% of them received locoregional radiotherapy afterwards (Figure 2.9), while less than 5% of the patients with in situ cancer who had mastectomy underwent radiotherapy (Figure 2.10).

Figure 2.9: Use of locoregional radiotherapy among patients who underwent breast-conserving surgery by cancer stage (N=7,087)



	0	I	IIA	IIB	III
2006-2010 (N=2,373)	92.4	95.2	94.6	98.4	99.1
2011-2015 (N=3,057)	94.2	96.5	95.7	96.0	97.2
2016-current (N=1,657)	91.4	93.9	95.0	93.3	97.4

Figure 2.10: Use of locoregional radiotherapy among patients who underwent mastectomy by cancer stage (N=11,634)



	0	I	IIA	IIB	III
2006-2010 (N=4,244)	4.6	14.2	38.4	74.7	95.7
2011-2015 (N=5,233)	3.3	11.8	32.7	79.1	95.1
2016-current (N=2,157)	4.3	10.0	33.5	76.7	89.4

2.50 Radiotherapy for breast cancer involves localised irradiation of regions such as breast/chest wall, with or without regional nodes. Table 2.30 shows the irradiated regions of adjuvant locoregional radiotherapy among those patients who received radiotherapy by the type of surgery they underwent.

Table 2.30: Coverage of regional lymph nodes by adjuvant locoregional radiotherapy (N=7,355)

	2006-2010 %	2011-2015 %	2016-current %
Breast-conserving surgery	**(N=1,553)**	**(N=1,663)**	**(N=738)**
Breast alone	84.7	83.3	90.7
Breast and regional lymph nodes	15.3	16.7	9.3
Mastectomy	**(N=1,472)**	**(N=1,442)**	**(N=487)**
Chest wall alone	27.9	23.5	24.2
Chest wall and regional lymph nodes	72.1	76.5	75.8

ii. Palliative radiotherapy

2.51 Palliative radiotherapy for breast cancer is used for reducing symptoms which can be pain, pressure symptoms, airway obstruction, bleeding and secretion from metastases.

2.52 Among the patients with metastatic breast cancer, about three-fifths (2006-2010: 57.6%; 2011-2015: 60.9%; 2016-current: 63.8%) underwent palliative radiotherapy to various sites.

C. Chemotherapy

2.53 Chemotherapy is a form of systemic treatment using one or more cytotoxic drugs to kill or control cancer cell growth. The drugs destroy breast cancer cells by interfering with their ability to grow and divide. Chemotherapy is generally not required for patients with in situ tumour. Chemotherapy regimens are classified into three generations[50] and the number of cycles actually delivered within any regimen may vary, depending on patient factors such as bone marrow reserve and severity of side effects.

2.54 A total of 11,509 (2006-2010: 70.8%; 2011-2015: 66.8%; 2016-current: 58.3%) patients with invasive cancer in the cohorts underwent chemotherapy. Of these patients, the majority (2006-2010: 90.0%; 2011-2015: 81.1%; 2016-current: 75.8%) had adjuvant chemotherapy, less than one-fifth (2006-2010: 6.9%; 2011-2015: 14.3%; 2016-current: 20.0%) had neoadjuvant chemotherapy, and a small proportion (2006-2010: 3.1%; 2011-2015: 4.7%; 2016-current: 4.2%) had palliative chemotherapy. The majority (2006-2010: 85.9%; 2011-2015: 87.1%; 2016-current: 83.9%) of the patients received chemotherapy in public medical facilities, and the remainder (2006-2010: 14.1%; 2011-2015: 12.9%; 2016-current: 16.1%) in private medical facilities.

2.55 In each patient cohort, the use of curative intent chemotherapy was positively correlated to progressing cancer stage from stage I to III. In contrast, the majority (73.4%-88.1%) of the patients with stage IV cancers underwent palliative chemotherapy (Table 2.31).

2.56 In general, for all cancer stages, the use of chemotherapy among the patients aged 70 or above was much lower than that among patients aged below 70. Table 2.32 shows the percentage of the patients in the three cohorts who received chemotherapy in the same age group and cancer stage.

Table 2.31: Chemotherapy treatment by cancer stage (N=16,713)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current														
	I			IIA			IIB			III			IV		
Yes, neoadjvuant	0.1	0.5	0.6	1.6	4.3	5.9	6.1	13.7	13.0	19.0	32.4	34.2	–	–	–
Yes, adjuvant	42.7	36.5	29.3	81.1	73.1	59.0	85.1	75.6	68.1	75.3	61.3	57.8	–	–	–
Yes, palliative	–	–	–	–	–	–	–	–	–	–	–	–	87.5	88.1	73.4
Not done	57.2	63.0	70.1	17.2	22.6	35.1	8.8	10.7	18.9	5.7	6.3	8.0	12.5	11.9	26.6

Total number of patients in each group:

I: 2,161(for 2006-2010), 2,781 (for 2011-2015), 1,360 (for 2016-current)
IIA: 1,766 (for 2006-2010), 2,069 (for 2011-2015), 954 (for 2016-current)
IIB: 840 (for 2006-2010), 1,110 (for 2011-2015), 486 (for 2016-current)
III: 951 (for 2006-2010), 1,258 (for 2011-2015), 486 (for 2016-current)
IV: 144 (for 2006-2010), 253 (for 2011-2015), 94 (for 2016-current)

Table 2.32: Use of chemotherapy by age group and cancer stage at diagnosis (N=16,418)

	Cancer stage, % of patients in the same age group and cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current														
	I			IIA			IIB			III			IV		
20-29	76.5	50.0	41.7	92.9	80.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	0.0
30-39	62.0	55.9	45.2	90.6	91.4	88.3	100.0	97.7	93.9	100.0	99.1	97.3	100.0	84.2	37.5
40-49	49.5	44.4	31.8	93.7	85.8	74.2	97.3	95.7	91.5	98.9	98.0	98.4	98.0	95.0	88.9
50-59	42.3	38.8	35.3	90.8	85.4	76.3	96.5	95.9	87.6	97.0	98.4	96.7	94.1	87.6	84.4
60-69	25.5	29.1	23.7	70.4	72.5	56.4	87.0	92.6	80.2	96.4	93.9	91.8	87.5	87.2	64.7
≥70	2.4	3.2	12.8	9.0	10.8	16.3	11.6	16.7	29.4	37.5	39.5	38.7	26.7	50.0	44.4

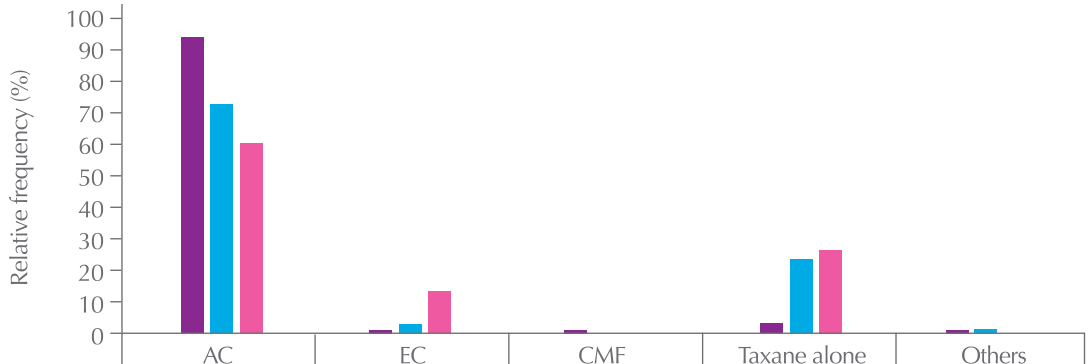
Total number of patients in each group:

I & 20-29: 17 (for 2006-2010), 12 (for 2011-2015), 12 (for 2016-current)
I & 30-39: 221 (for 2006-2010), 195 (for 2011-2015), 84 (for 2016-current)
I & 40-49: 814 (for 2006-2010), 847 (for 2011-2015), 362 (for 2016-current)
I & 50-59: 672 (for 2006-2010), 912 (for 2011-2015), 416 (for 2016-current)
I & 60-69: 263 (for 2006-2010), 556 (for 2011-2015), 334 (for 2016-current)
I & ≥70: 126 (for 2006-2010), 217 (for 2011-2015), 117 (for 2016-current)
IIA & 20-29: 14 (for 2006-2010), 10 (for 2011-2015), 6 (for 2016-current)
IIA & 30-39: 192 (for 2006-2010), 162 (for 2011-2015), 60 (for 2016-current)
IIA & 40-49: 590 (for 2006-2010), 557 (for 2011-2015), 233 (for 2016-current)
IIA & 50-59: 566 (for 2006-2010), 690 (for 2011-2015), 287 (for 2016-current)
IIA & 60-69: 233 (for 2006-2010), 477 (for 2011-2015), 250 (for 2016-current)
IIA & ≥70: 134 (for 2006-2010), 148 (for 2011-2015), 92 (for 2016-current)
IIB & 20-29: 10 (for 2006-2010), 6 (for 2011-2015), 1 (for 2016-current)
IIB & 30-39: 81 (for 2006-2010), 88 (for 2011-2015), 33 (for 2016-current)
IIB & 40-49: 294 (for 2006-2010), 328 (for 2011-2015), 118 (for 2016-current)
IIB & 50-59: 283 (for 2006-2010), 364 (for 2011-2015), 161 (for 2016-current)
IIB & 60-69: 115 (for 2006-2010), 229 (for 2011-2015), 116 (for 2016-current)
IIB & ≥70: 43 (for 2006-2010), 78 (for 2011-2015), 51 (for 2016-current)
III & 20-29: 6 (for 2006-2010), 6 (for 2011-2015), 1 (for 2016-current)
III & 30-39: 71 (for 2006-2010), 116 (for 2011-2015), 37 (for 2016-current)
III & 40-49: 364 (for 2006-2010), 352 (for 2011-2015), 124 (for 2016-current)
III & 50-59: 303 (for 2006-2010), 446 (for 2011-2015), 152 (for 2016-current)
III & 60-69: 138 (for 2006-2010), 246 (for 2011-2015), 134 (for 2016-current)
III & ≥70: 56 (for 2006-2010), 76 (for 2011-2015), 31 (for 2016-current)
IV & 20-29: 1 (for 2006-2010), 2 (for 2011-2015), 0 (for 2016-current)
IV & 30-39: 7 (for 2006-2010), 19 (for 2011-2015), 8 (for 2016-current)
IV & 40-49: 50 (for 2006-2010), 80 (for 2011-2015), 27 (for 2016-current)
IV & 50-59: 51 (for 2006-2010), 97 (for 2011-2015), 32 (for 2016-current)
IV & 60-69: 16 (for 2006-2010), 39 (for 2011-2015), 17 (for 2016-current)
IV & ≥70: 15 (for 2006-2010), 12 (for 2011-2015), 9 (for 2016-current)

i. Neoadjuvant chemotherapy

2.57 Of the patients who underwent chemotherapy in each cohort, less than one-fifth (2006-2010: 6.9%; 2011-2015: 14.3%; 2016-current: 20.0%) of patients received it as neoadjuvant treatment. The use of neoadjuvant chemotherapy increased substantially with progressing cancer stage (Table 2.31). Figures 2.11, 2.12 and 2.13 show the use of chemotherapy regimens of the three generations in neoadjuvant setting among patients in the three cohorts. The use of HER2 regimens is shown in Figure 2.14. The types of chemotherapy regimens used by patients with different biological subtype in the three cohorts are shown in Figure 2.15.

Figure 2.11: Type of first generation chemotherapy regimens (non-HER2) used in neoadjuvant setting (N=162)

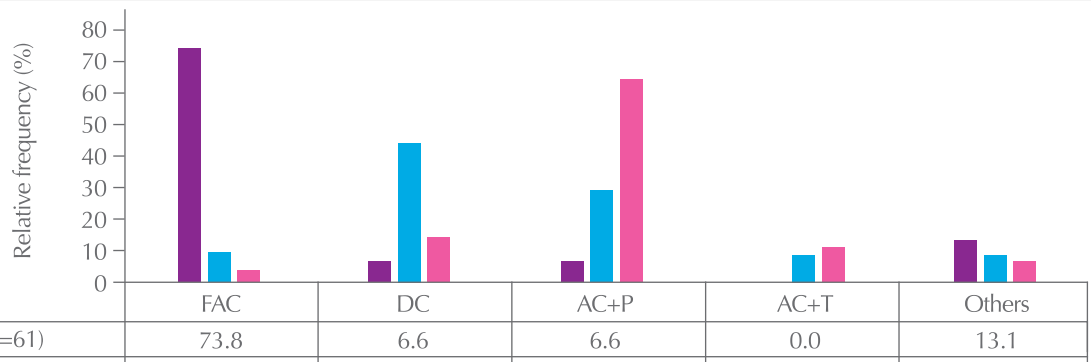


	AC	EC	CMF	Taxane alone	Others
2006-2010 (N=78)	93.6	1.3	1.3	2.6	1.3
2011-2015 (N=69)	72.5	2.9	0.0	23.2	1.4
2016-current (N=15)	60.0	13.3	0.0	26.7	0.0

1st generation regimens

A: Adriamycin/Doxorubicin; E: Epirubicin; C: Cyclophosphamide; M: Methotrexate; F: 5FU; Taxane: Docetaxel or Paclitaxel

Figure 2.12: Type of second generation chemotherapy regimens (non-HER2) used in neoadjuvant setting (N=145)

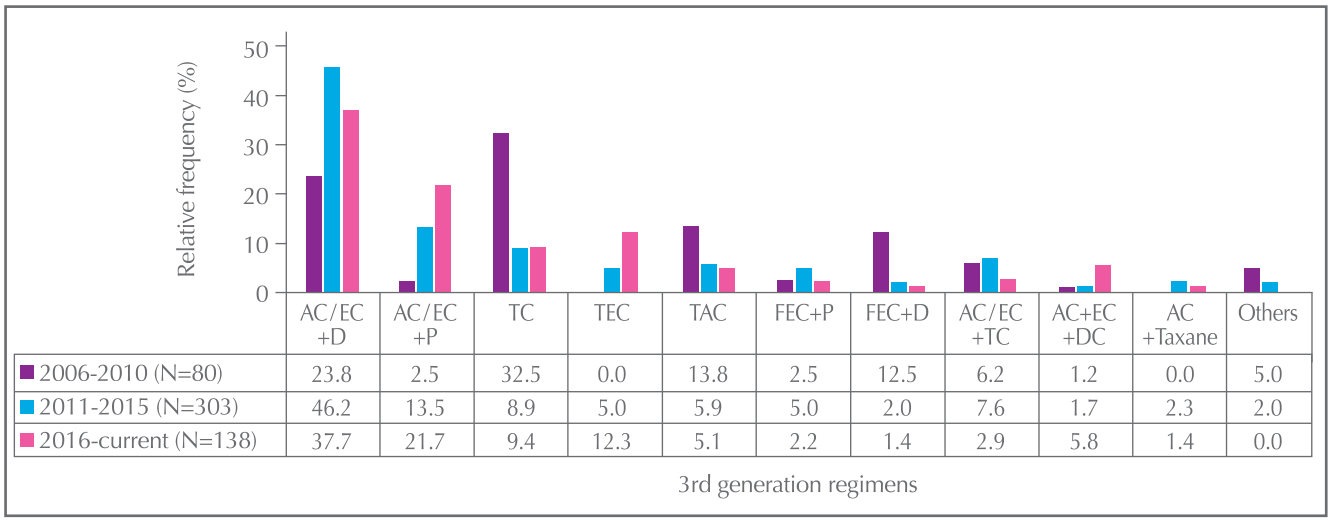


	FAC	DC	AC+P	AC+T	Others
2006-2010 (N=61)	73.8	6.6	6.6	0.0	13.1
2011-2015 (N=56)	8.9	44.6	28.6	8.9	8.9
2016-current (N=28)	3.6	14.3	64.3	10.7	7.1

2nd generation regimens

DC: Docetaxel+Cyclophosphamide; P: Paclitaxel; T: Taxane

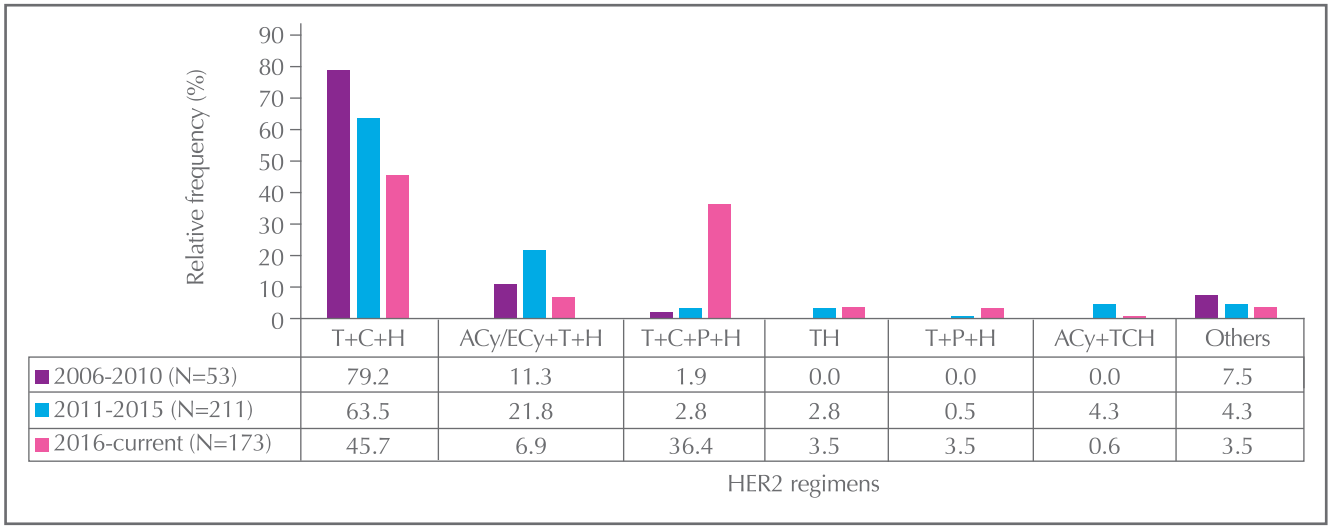
Figure 2.13: Type of third generation chemotherapy regimens (non-HER2) used in neoadjuvant setting (N=521)



	AC/EC +D	AC/EC +P	TC	TEC	TAC	FEC+P	FEC+D	AC/EC +TC	AC+EC +DC	AC +Taxane	Others
2006-2010 (N=80)	23.8	2.5	32.5	0.0	13.8	2.5	12.5	6.2	1.2	0.0	5.0
2011-2015 (N=303)	46.2	13.5	8.9	5.0	5.9	5.0	2.0	7.6	1.7	2.3	2.0
2016-current (N=138)	37.7	21.7	9.4	12.3	5.1	2.2	1.4	2.9	5.8	1.4	0.0

D: Docetaxel; P: Paclitaxel; TC: Paclitaxel+Carboplatin; DC: Docetaxel+Cyclophosphamide

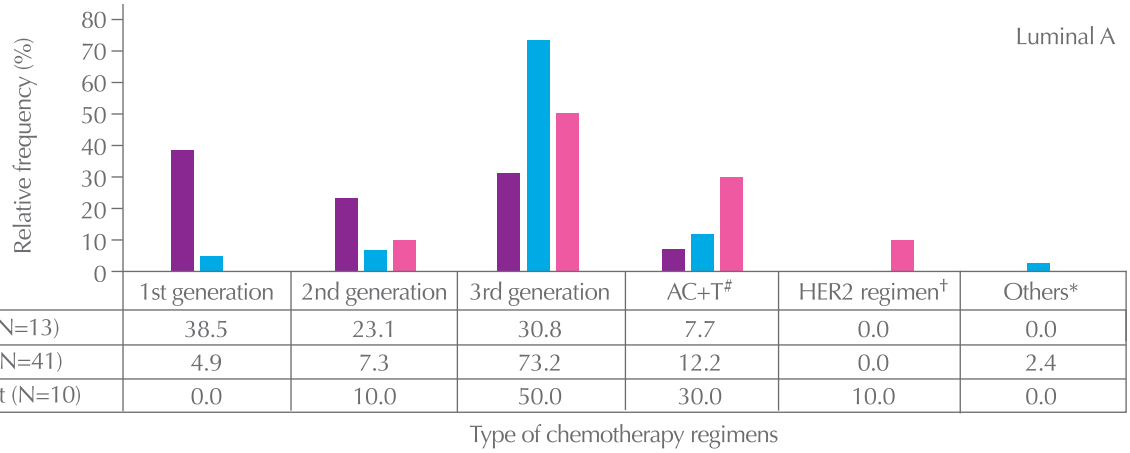
Figure 2.14: Type of HER2 regimens used in neoadjuvant setting (N=437)



	T+C+H	ACy/ECy+T+H	T+C+P+H	TH	T+P+H	ACy+TCH	Others
2006-2010 (N=53)	79.2	11.3	1.9	0.0	0.0	0.0	7.5
2011-2015 (N=211)	63.5	21.8	2.8	2.8	0.5	4.3	4.3
2016-current (N=173)	45.7	6.9	36.4	3.5	3.5	0.6	3.5

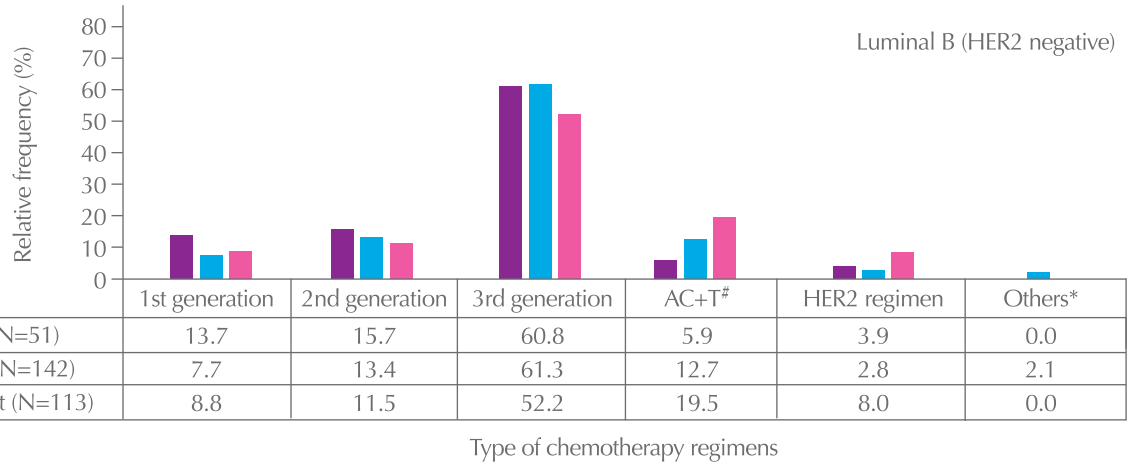
A: Anthracycline; C: Carboplatin; T: Taxane; H: Trastuzumab; P: Pertuzumab; Cy: Cyclophosphamide

Figure 2.15: Type of chemotherapy regimens used by biological subtype in neoadjuvant setting (N=1,208)



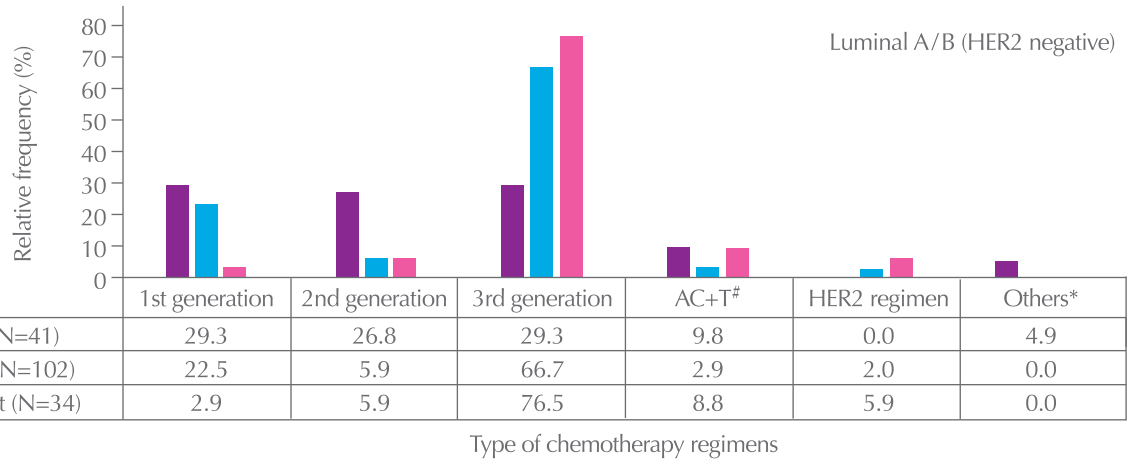
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen†	Others*
2006-2010 (N=13)	38.5	23.1	30.8	7.7	0.0	0.0
2011-2015 (N=41)	4.9	7.3	73.2	12.2	0.0	2.4
2016-current (N=10)	0.0	10.0	50.0	30.0	10.0	0.0

Type of chemotherapy regimens



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=51)	13.7	15.7	60.8	5.9	3.9	0.0
2011-2015 (N=142)	7.7	13.4	61.3	12.7	2.8	2.1
2016-current (N=113)	8.8	11.5	52.2	19.5	8.0	0.0

Type of chemotherapy regimens

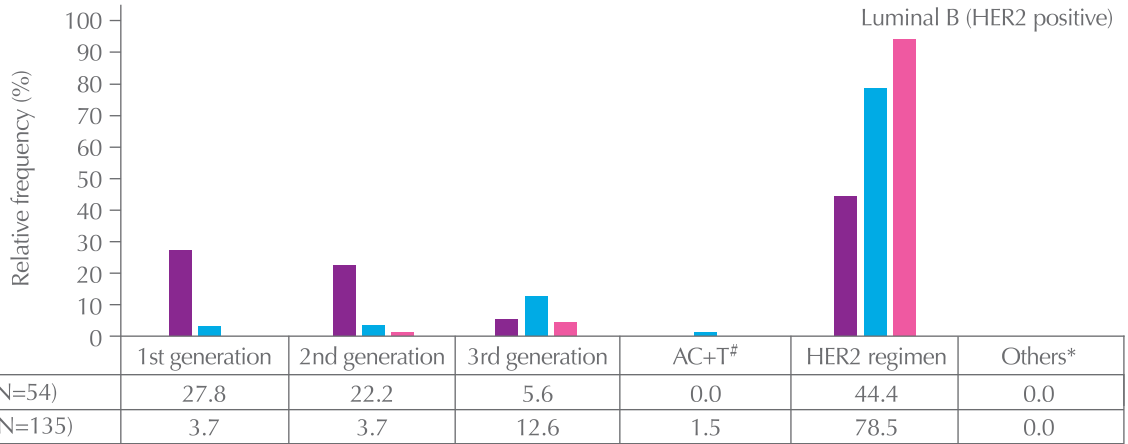


	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=41)	29.3	26.8	29.3	9.8	0.0	4.9
2011-2015 (N=102)	22.5	5.9	66.7	2.9	2.0	0.0
2016-current (N=34)	2.9	5.9	76.5	8.8	5.9	0.0

Type of chemotherapy regimens

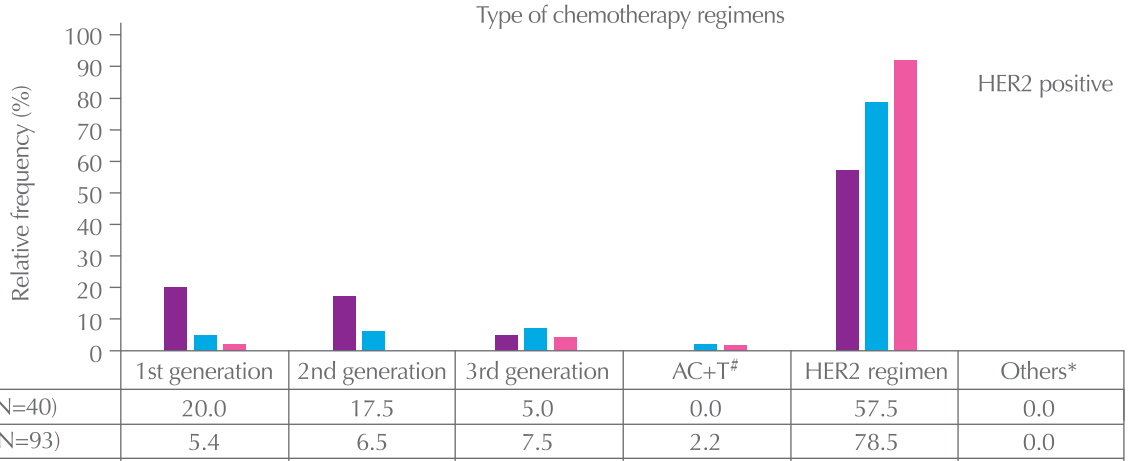
#AC+T: uncertain 2nd / 3rd generation due to uncertain week intervals
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine
†One patient with luminal A cancer used HER2 regimen as she had luminal B (HER2 positive) cancer on another side of breasts at the same time

Figure 2.15: Type of chemotherapy regimens used by biological subtype in neoadjuvant setting (N=1,208) (cont'd)



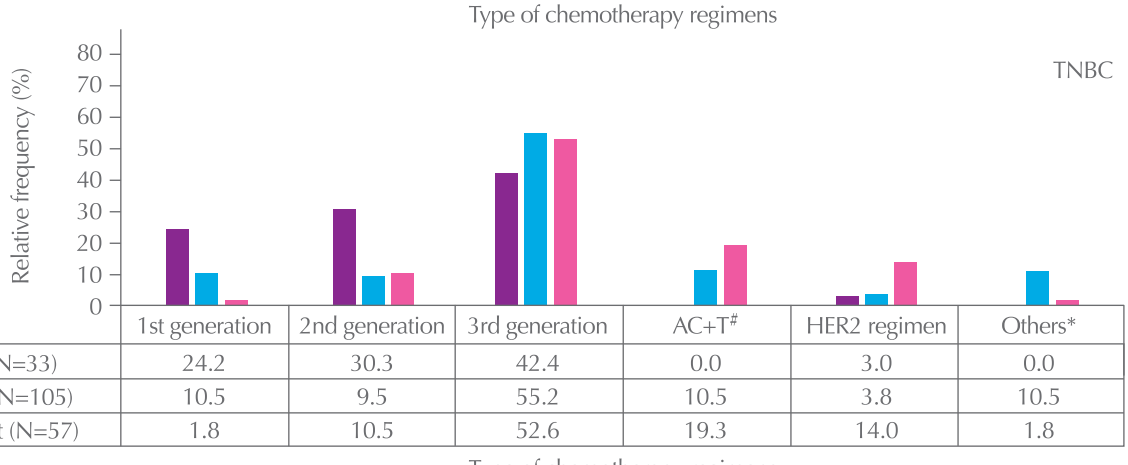
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=54)	27.8	22.2	5.6	0.0	44.4	0.0
2011-2015 (N=135)	3.7	3.7	12.6	1.5	78.5	0.0
2016-current (N=95)	0.0	1.1	4.2	0.0	94.7	0.0

Type of chemotherapy regimens



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=40)	20.0	17.5	5.0	0.0	57.5	0.0
2011-2015 (N=93)	5.4	6.5	7.5	2.2	78.5	0.0
2016-current (N=49)	2.0	0.0	4.1	2.0	91.8	0.0

Type of chemotherapy regimens



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=33)	24.2	30.3	42.4	0.0	3.0	0.0
2011-2015 (N=105)	10.5	9.5	55.2	10.5	3.8	10.5
2016-current (N=57)	1.8	10.5	52.6	19.3	14.0	1.8

Type of chemotherapy regimens

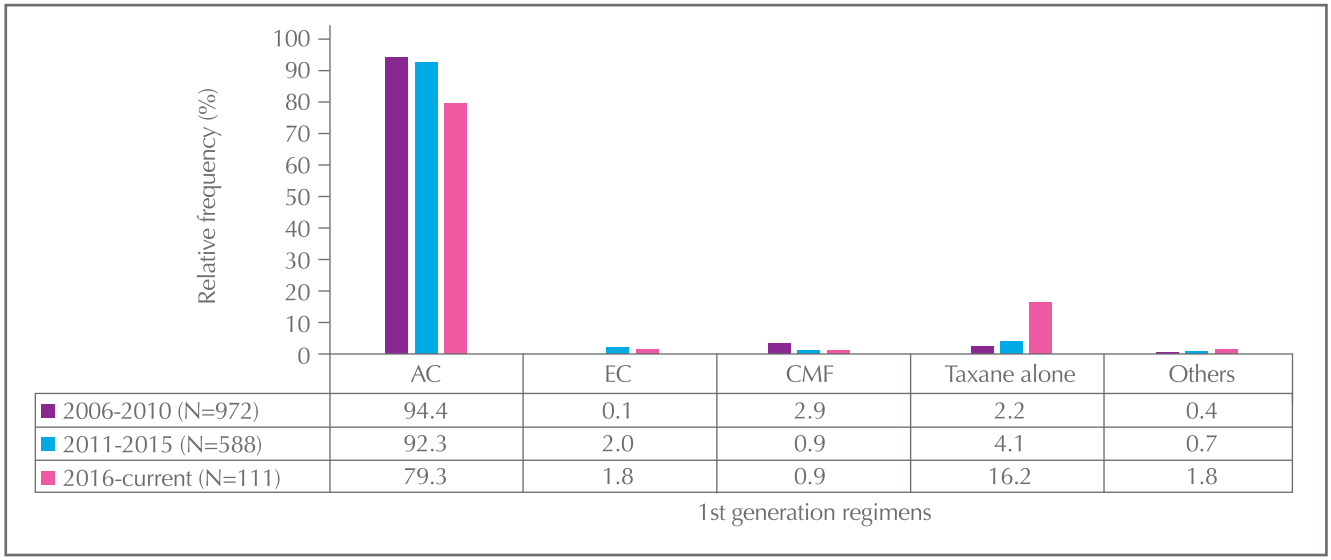
#AC+T: uncertain 2nd / 3rd generation due to uncertain week intervals

*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

ii. Adjuvant chemotherapy

2.58 Of the patients who underwent chemotherapy in each cohort, the majority (2006-2010: 90.0%; 2011-2015: 81.1%; 2016-current: 75.8%) of patients received it as adjuvant (stages I-III) treatment. Figures 2.16, 2.17 and 2.18 show the use of chemotherapy regimens of three generations in adjuvant setting among patients in the three cohorts. The use of HER2 regimens in adjuvant chemotherapy is shown in Figure 2.19. Figures 2.20 and 2.21 show the relative frequency for different types of regimens used by biological subtype and cancer stage, respectively.

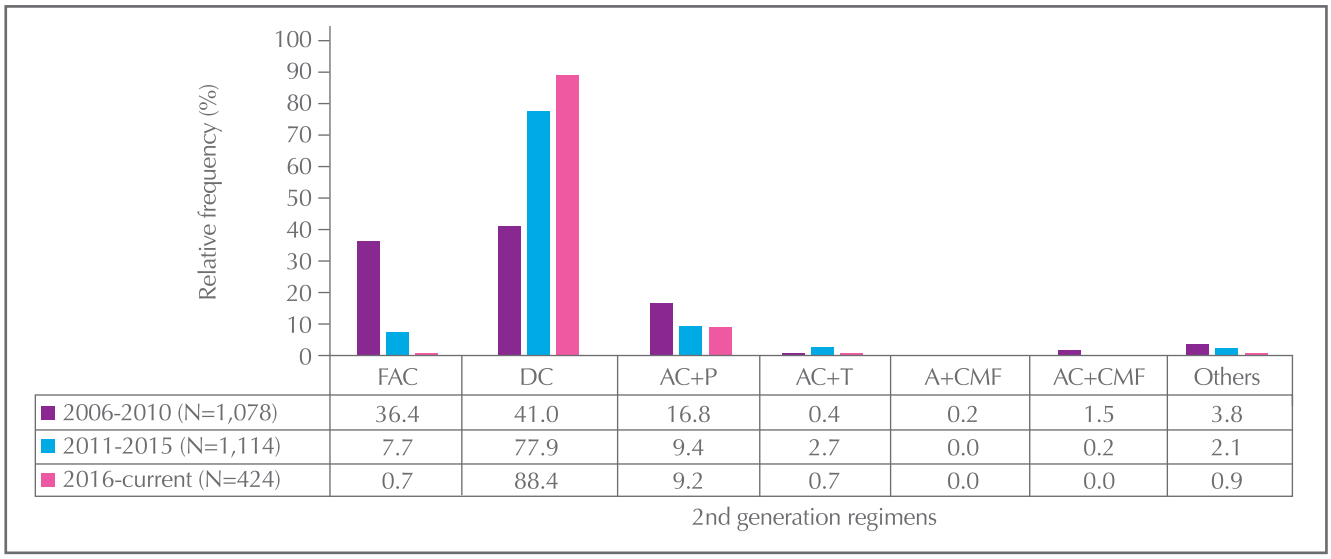
Figure 2.16: Type of first generation chemotherapy regimens (non-HER2) used in adjuvant setting (N=1,671)



	AC	EC	CMF	Taxane alone	Others
2006-2010 (N=972)	94.4	0.1	2.9	2.2	0.4
2011-2015 (N=588)	92.3	2.0	0.9	4.1	0.7
2016-current (N=111)	79.3	1.8	0.9	16.2	1.8

A: Adriamycin/Doxorubicin; E: Epirubicin; C: Cyclophosphamide; M: Methotrexate; F: 5FU; Taxane: Docetaxel or Paclitaxel

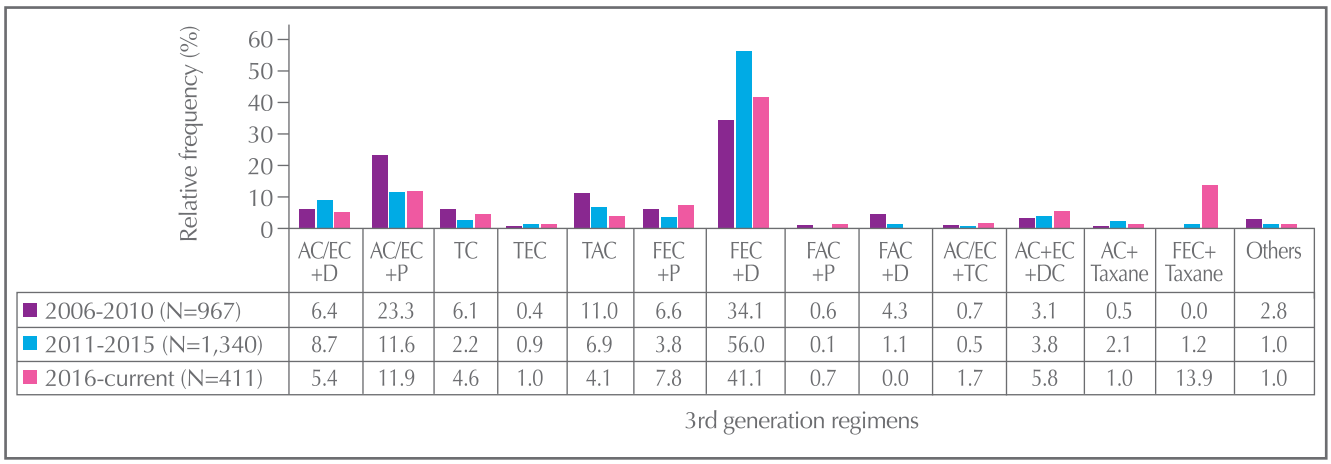
Figure 2.17: Type of second generation chemotherapy regimens (non-HER2) used in adjuvant setting (N=2,616)



	FAC	DC	AC+P	AC+T	A+CMF	AC+CMF	Others
2006-2010 (N=1,078)	36.4	41.0	16.8	0.4	0.2	1.5	3.8
2011-2015 (N=1,114)	7.7	77.9	9.4	2.7	0.0	0.2	2.1
2016-current (N=424)	0.7	88.4	9.2	0.7	0.0	0.0	0.9

DC: Docetaxel+Cyclophosphamide; P: Paclitaxel; T: Taxane

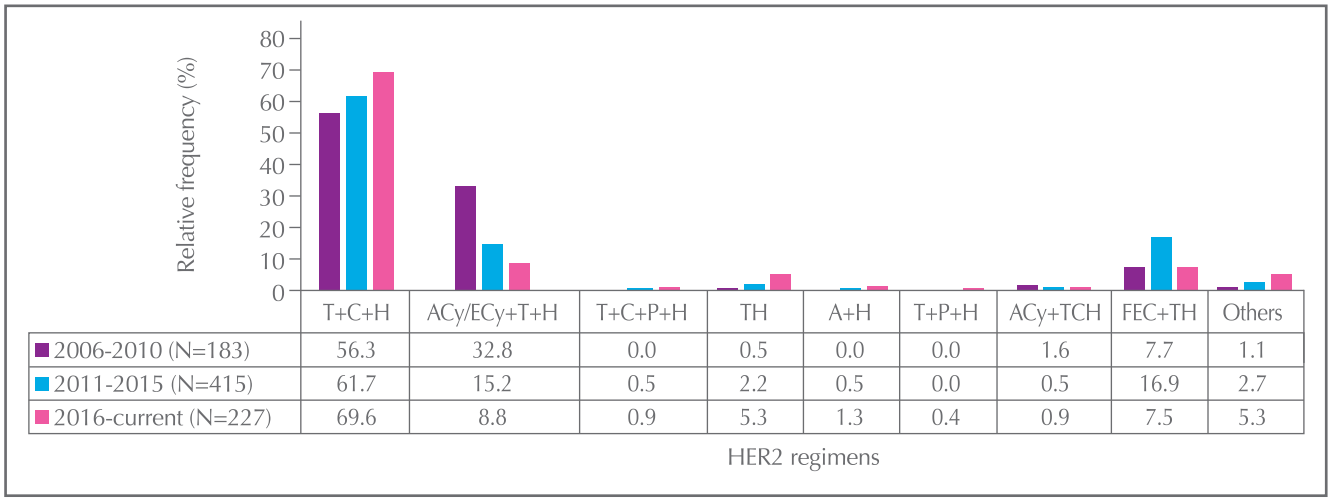
Figure 2.18: Type of third generation chemotherapy regimens (non-HER2) used in adjuvant setting (N=2,718)



	AC/EC +D	AC/EC +P	TC	TEC	TAC	FEC +P	FEC +D	FAC +P	FAC +D	AC/EC +TC	AC+EC +DC	AC+ Taxane	FEC+ Taxane	Others
2006-2010 (N=967)	6.4	23.3	6.1	0.4	11.0	6.6	34.1	0.6	4.3	0.7	3.1	0.5	0.0	2.8
2011-2015 (N=1,340)	8.7	11.6	2.2	0.9	6.9	3.8	56.0	0.1	1.1	0.5	3.8	2.1	1.2	1.0
2016-current (N=411)	5.4	11.9	4.6	1.0	4.1	7.8	41.1	0.7	0.0	1.7	5.8	1.0	13.9	1.0

D: Docetaxel; P: Paclitaxel; TC: Paclitaxel+Carboplatin; DC: Docetaxel+Cyclophosphamide

Figure 2.19: Type of HER2 regimens used in adjuvant setting (N=825)



	T+C+H	ACy/ECy+T+H	T+C+P+H	TH	A+H	T+P+H	ACy+TCH	FEC+TH	Others
2006-2010 (N=183)	56.3	32.8	0.0	0.5	0.0	0.0	1.6	7.7	1.1
2011-2015 (N=415)	61.7	15.2	0.5	2.2	0.5	0.0	0.5	16.9	2.7
2016-current (N=227)	69.6	8.8	0.9	5.3	1.3	0.4	0.9	7.5	5.3

A: Anthracycline; C: Carboplatin; T: Taxane; H: Trastuzumab; P: Pertuzumab; Cy: Cyclophosphamide

Figure 2.20: Type of chemotherapy regimens used by biological subtype in adjuvant setting (N=8,269)

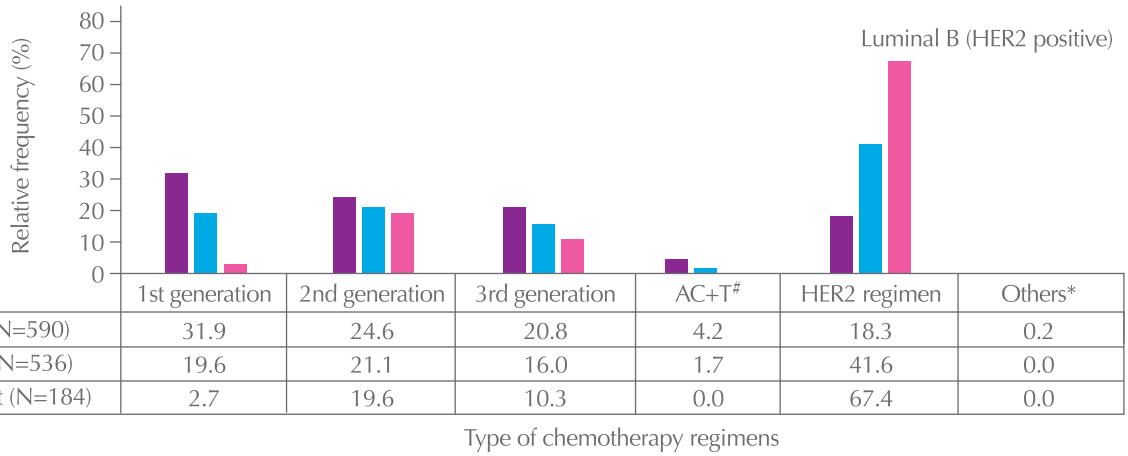
Luminal A	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=534)	23.0	33.5	30.1	12.5	0.6	0.2
2011-2015 (N=429)	12.1	33.8	44.5	8.4	0.9	0.2
2016-current (N=131)	9.2	38.2	38.2	10.7	3.1	0.8

Luminal B (HER2 negative)	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=703)	20.6	30.4	34.9	13.4	0.6	0.1
2011-2015 (N=913)	12.8	36.0	40.9	9.4	0.9	0.0
2016-current (N=491)	11.6	42.2	28.3	15.9	2.0	0.0

Luminal A/B (HER2 negative)	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=744)	34.0	33.6	29.4	2.4	0.1	0.4
2011-2015 (N=772)	20.9	26.4	50.3	1.4	1.0	0.0
2016-current (N=148)	17.6	20.9	57.4	2.7	1.4	0.0

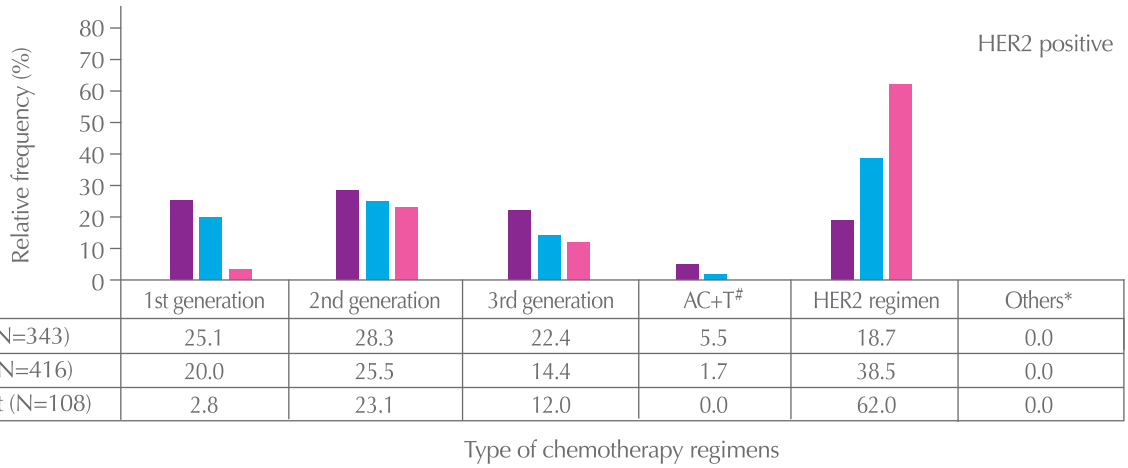
#AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

Figure 2.20: Type of chemotherapy regimens used by biological subtype in adjuvant setting (N=8,269) (cont'd)



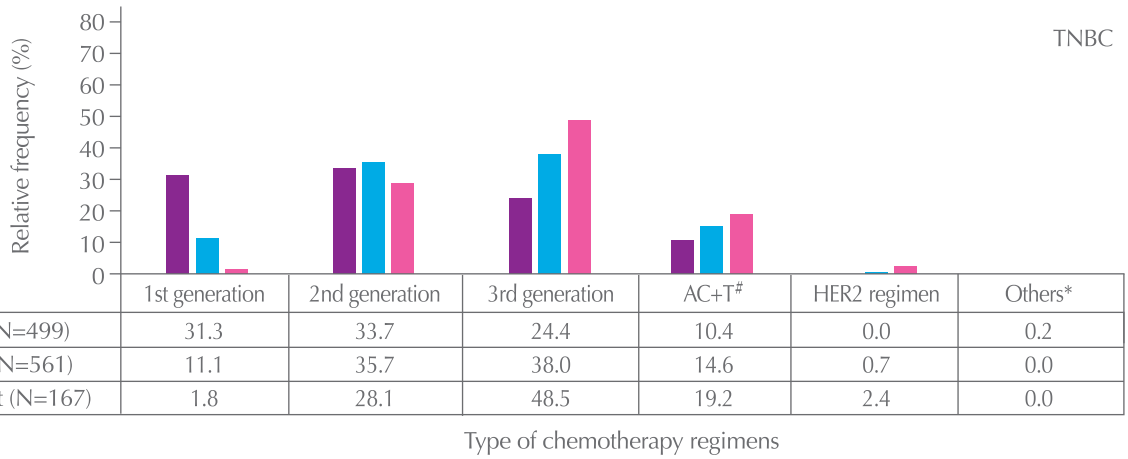
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=590)	31.9	24.6	20.8	4.2	18.3	0.2
2011-2015 (N=536)	19.6	21.1	16.0	1.7	41.6	0.0
2016-current (N=184)	2.7	19.6	10.3	0.0	67.4	0.0

Type of chemotherapy regimens



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=343)	25.1	28.3	22.4	5.5	18.7	0.0
2011-2015 (N=416)	20.0	25.5	14.4	1.7	38.5	0.0
2016-current (N=108)	2.8	23.1	12.0	0.0	62.0	0.0

Type of chemotherapy regimens

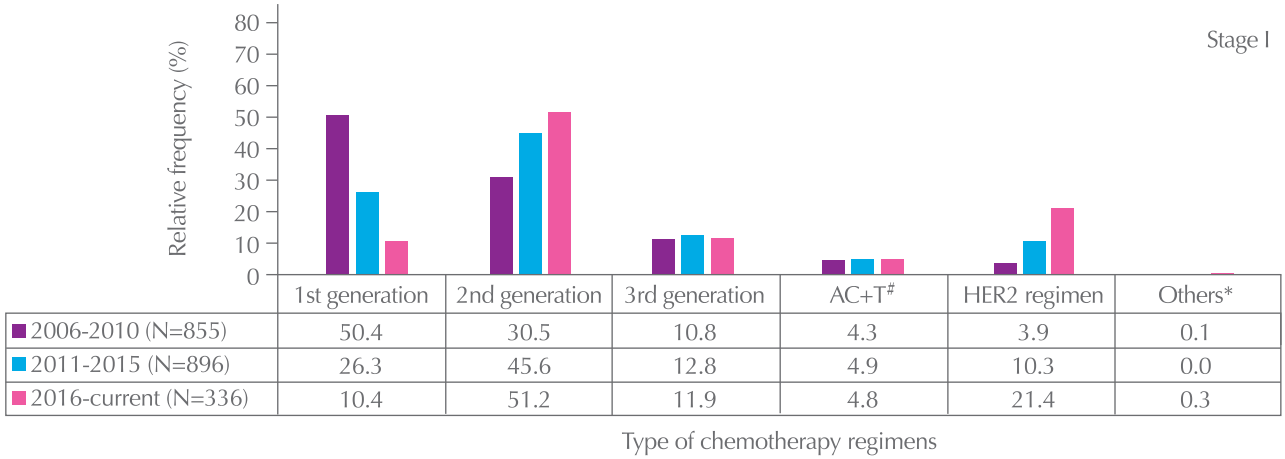


	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=499)	31.3	33.7	24.4	10.4	0.0	0.2
2011-2015 (N=561)	11.1	35.7	38.0	14.6	0.7	0.0
2016-current (N=167)	1.8	28.1	48.5	19.2	2.4	0.0

Type of chemotherapy regimens

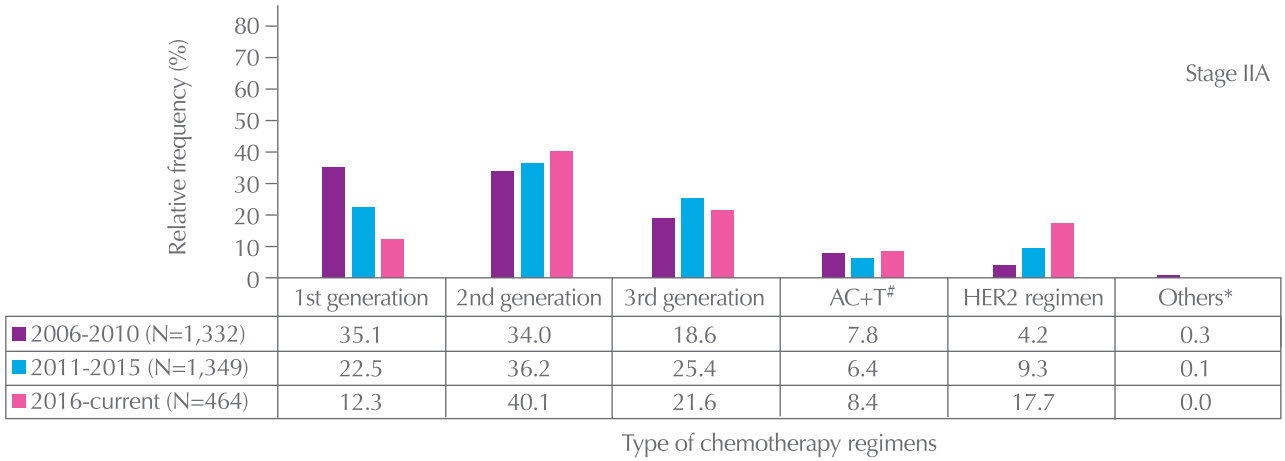
#AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

Figure 2.21: Type of chemotherapy regimens used by cancer stage in adjuvant setting (N=8,418)



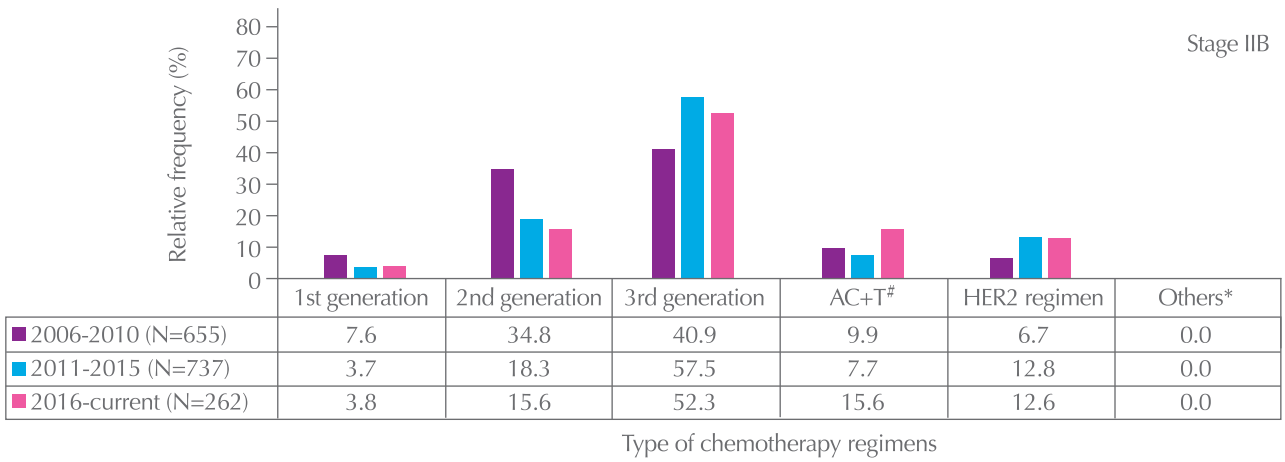
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=855)	50.4	30.5	10.8	4.3	3.9	0.1
2011-2015 (N=896)	26.3	45.6	12.8	4.9	10.3	0.0
2016-current (N=336)	10.4	51.2	11.9	4.8	21.4	0.3

Type of chemotherapy regimens



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=1,332)	35.1	34.0	18.6	7.8	4.2	0.3
2011-2015 (N=1,349)	22.5	36.2	25.4	6.4	9.3	0.1
2016-current (N=464)	12.3	40.1	21.6	8.4	17.7	0.0

Type of chemotherapy regimens

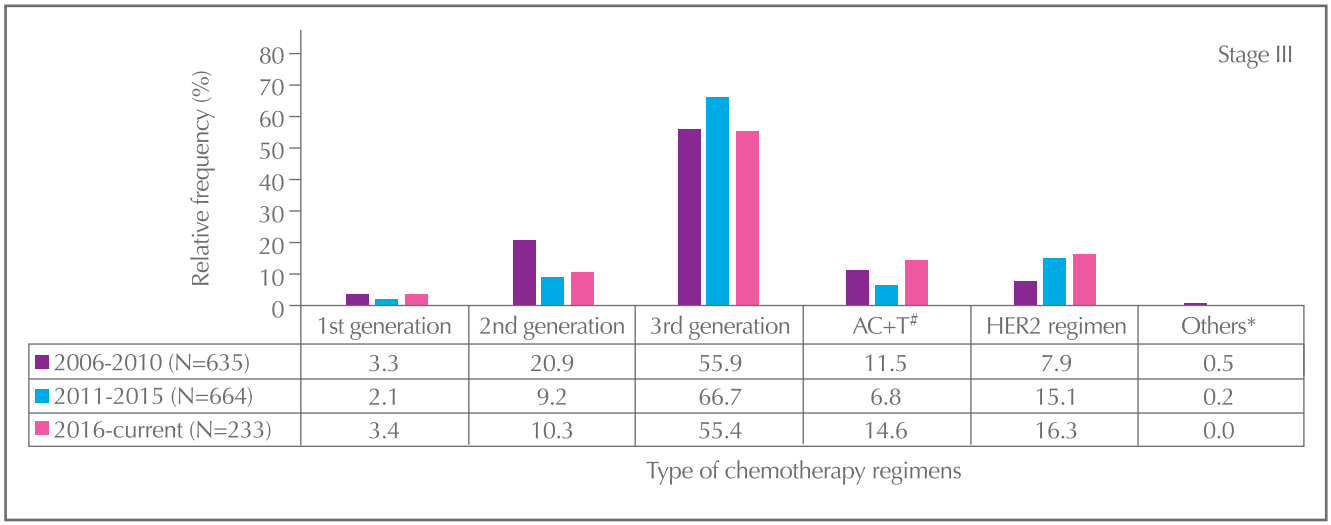


	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=655)	7.6	34.8	40.9	9.9	6.7	0.0
2011-2015 (N=737)	3.7	18.3	57.5	7.7	12.8	0.0
2016-current (N=262)	3.8	15.6	52.3	15.6	12.6	0.0

Type of chemotherapy regimens

#AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

Figure 2.21: Type of chemotherapy regimens used by cancer stage in adjuvant setting (N=8,418) (cont'd)



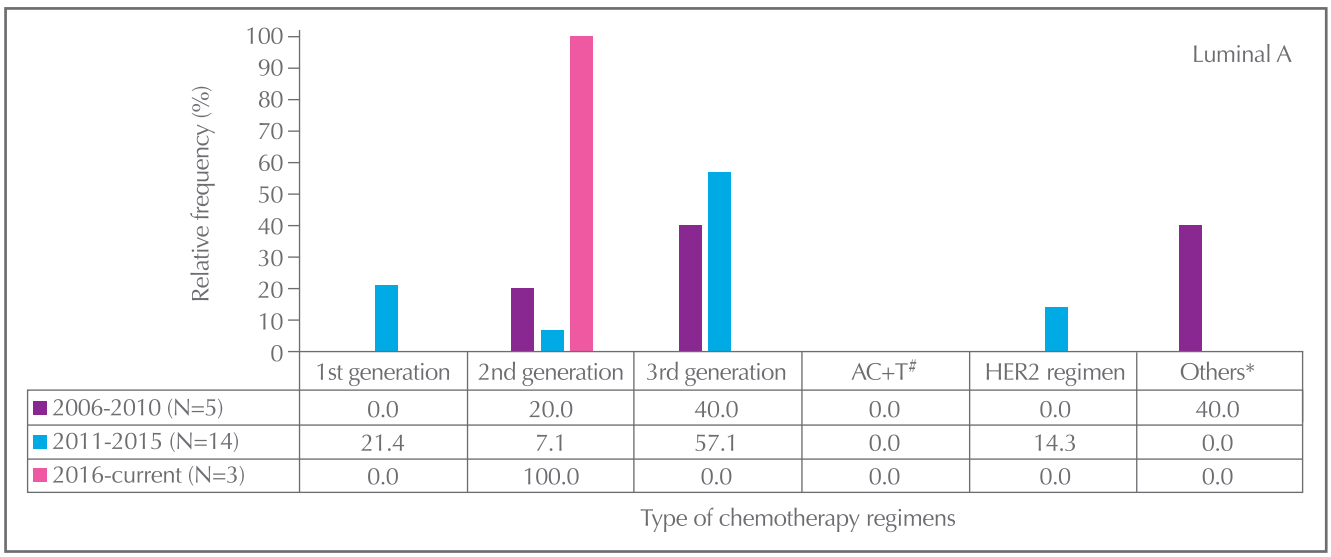
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=635)	3.3	20.9	55.9	11.5	7.9	0.5
2011-2015 (N=664)	2.1	9.2	66.7	6.8	15.1	0.2
2016-current (N=233)	3.4	10.3	55.4	14.6	16.3	0.0

#AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

iii. Palliative chemotherapy

2.59 Of the patients who underwent chemotherapy in each cohort, a small proportion (2006-2010: 3.1%; 2011-2015: 4.7%; 2016-current: 4.2%) of patients received it as palliative (stage IV) treatment. Figure 2.22 shows the relative frequency for different types of regimens used by biological subtype.

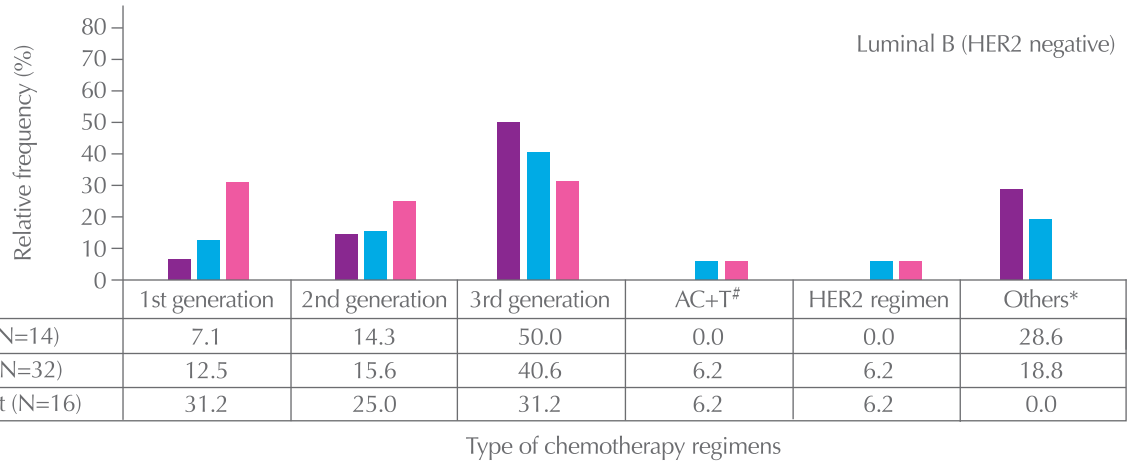
Figure 2.22: Type of chemotherapy regimens used by biological subtype in palliative setting (N=283)



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=5)	0.0	20.0	40.0	0.0	0.0	40.0
2011-2015 (N=14)	21.4	7.1	57.1	0.0	14.3	0.0
2016-current (N=3)	0.0	100.0	0.0	0.0	0.0	0.0

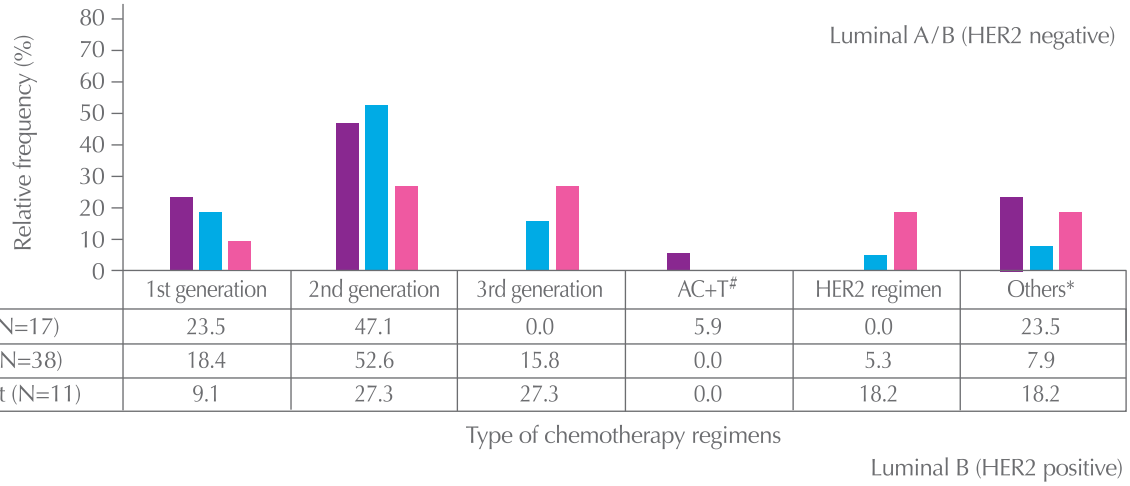
#AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

Figure 2.22: Type of chemotherapy regimens used by biological subtype in palliative setting (N=283) (cont'd)



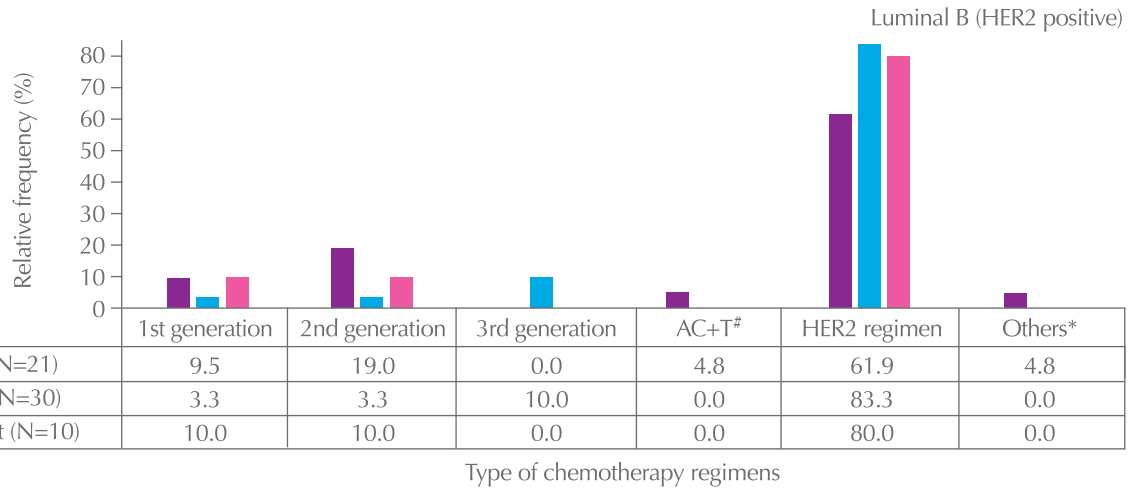
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=14)	7.1	14.3	50.0	0.0	0.0	28.6
2011-2015 (N=32)	12.5	15.6	40.6	6.2	6.2	18.8
2016-current (N=16)	31.2	25.0	31.2	6.2	6.2	0.0

Type of chemotherapy regimens



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=17)	23.5	47.1	0.0	5.9	0.0	23.5
2011-2015 (N=38)	18.4	52.6	15.8	0.0	5.3	7.9
2016-current (N=11)	9.1	27.3	27.3	0.0	18.2	18.2

Type of chemotherapy regimens



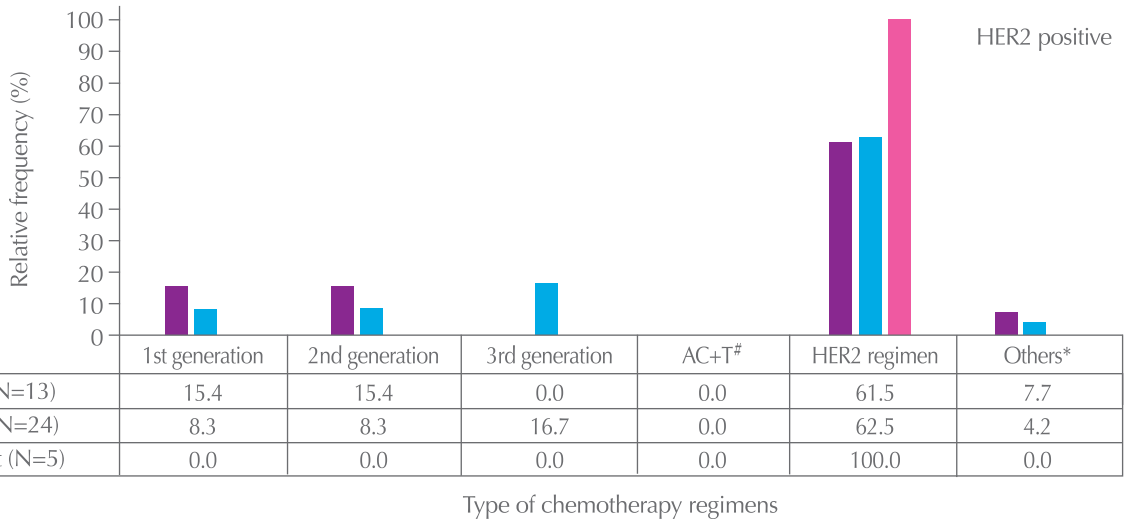
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=21)	9.5	19.0	0.0	4.8	61.9	4.8
2011-2015 (N=30)	3.3	3.3	10.0	0.0	83.3	0.0
2016-current (N=10)	10.0	10.0	0.0	0.0	80.0	0.0

Type of chemotherapy regimens

#AC+T: uncertain 2nd/3rd generation due to uncertain week intervals

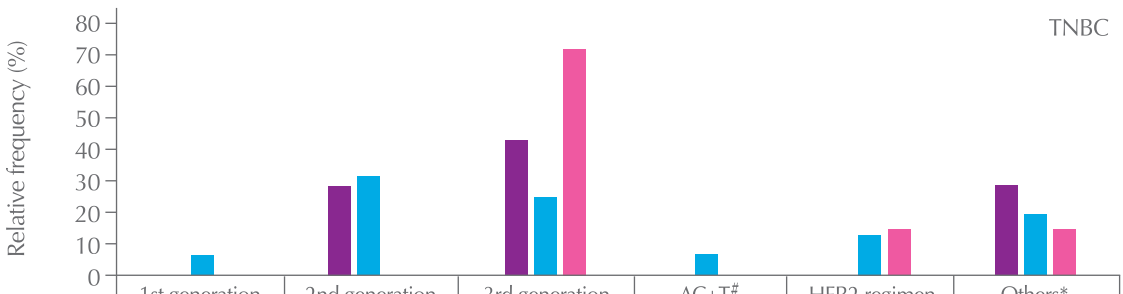
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

Figure 2.22: Type of chemotherapy regimens used by biological subtype in palliative setting (N=283) (cont'd)



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=13)	15.4	15.4	0.0	0.0	61.5	7.7
2011-2015 (N=24)	8.3	8.3	16.7	0.0	62.5	4.2
2016-current (N=5)	0.0	0.0	0.0	0.0	100.0	0.0

Type of chemotherapy regimens



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=7)	0.0	28.6	42.9	0.0	0.0	28.6
2011-2015 (N=16)	6.2	31.2	25.0	6.2	12.5	18.8
2016-current (N=7)	0.0	0.0	71.4	0.0	14.3	14.3

Type of chemotherapy regimens

#AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

D. Endocrine therapy

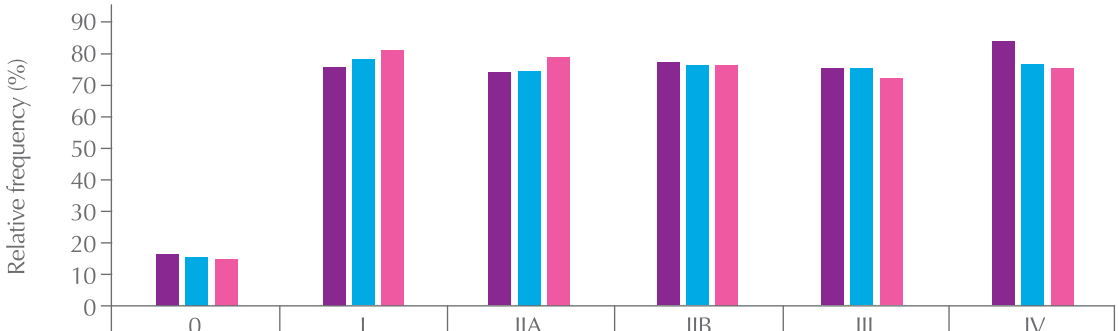
2.60 Endocrine therapy plays an important role in all stages of the treatment and prevention strategy for hormone receptor-positive breast cancer. Breast cancer develops from abnormal breast cells that are often sensitive to sex hormones, such as estrogen and progesterone. Endocrine therapy acts on the hormone receptors of cancer cells.

2.61 In the cohorts, about two-thirds (2006-2010: 67.7%; 2011-2015: 68.1%; 2016-current: 68.8%) of the patients were treated with endocrine therapy. Among them, the majority (2006-2010: 96.4%; 2011-2015: 95.2%; 2016-current: 95.7%) were adjuvant, neoadjuvant (2006-2010: <0.1%; 2011-2015: 0.3%; 2016-current: 0.6%) and palliative (2006-2010: 3.5%; 2011-2015: 4.5%; 2016-current: 3.7%) accounted for small proportions. In addition, the majority (2006-2010: 88.5%; 2011-2015: 92.2%; 2016-current: 85.8%) of the patients received endocrine therapy at public medical facilities, while the remainder (2006-2010: 11.5%; 2011-2015: 7.8%; 2016-current: 14.2%) received at private medical facilities.

2.62 For patients with invasive breast cancer, high proportions (72.0%-84.0%) received endocrine therapy, while for patients with in situ breast cancer, less than one-fifth (14.8%-16.6%) received endocrine therapy (Figure 2.23).

2.63 Two types of drugs are commonly used: anti-estrogens and aromatase inhibitors. Anti-estrogen drugs slow down breast cancer growth by binding to ER on breast cancer cells. The most common anti-estrogen is tamoxifen which is used in both pre-menopausal and post-menopausal women. Aromatase inhibitors decreases the level of estrogen in the body. Aromatase inhibitors, including anastrozole, letrozole and exemestane, are only effective for women who are post-menopausal. Table 2.33 shows the use of tamoxifen and aromatase inhibitors by age group in the three patient cohorts.

Figure 2.23: Use of endocrine therapy by cancer stage (N=19,309)



	0	I	IIA	IIB	III	IV
2006-2010 (N=6,780)	16.6	75.9	74.3	77.5	75.5	84.0
2011-2015 (N=8,583)	15.2	78.2	74.6	76.6	75.4	77.1
2016-current (N=3,946)	14.8	81.3	79.0	76.7	72.0	75.5

Cancer stage

Table 2.33: Forms of endocrine therapy by age group (N=12,422)

	Age group % for 2006-2010, % for 2011-2015, % for 2016-current								
	<45			45-55			≥55		
Tamoxifen	94.0	97.6	95.7	74.5	86.5	80.0	41.0	52.0	28.9
Tamoxifen → aromatase inhibitors	5.0	1.3	0.9	15.3	4.5	1.6	23.5	8.7	4.2
Aromatase inhibitors	1.0	1.1	3.4	10.3	9.0	18.4	35.4	39.3	66.9

Total number of patients in each group:
<45: 1,094 (for 2006-2010), 1,082 (for 2011-2015), 470 (for 2016-current)
45-55: 1,781 (for 2006-2010), 1,976 (for 2011-2015), 790 (for 2016-current)
≥55: 1,491 (for 2006-2010), 2,507 (for 2011-2015), 1,231 (for 2016-current)

E. Targeted therapy

2.64 Targeted therapy uses a drug that specifically inhibits the abnormal growth pathway of cancer cells by blocking specific molecules required for tumour growth or anti-apoptosis. Anti-HER2 targeted therapy is used for treating patients with invasive breast cancer cells that over-express HER2 oncogene (HER2-positive breast cancer).

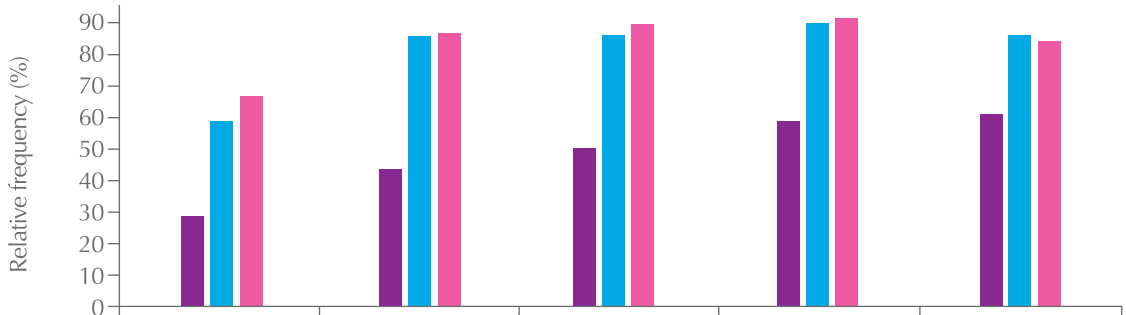
2.65 Among all patients, 10.1%-16.3% received targeted therapy, in particular HER2-targeted agents (94.3%-95.8%) (Table 2.34). Of the patients with invasive HER2-positive breast cancer in the three cohorts, 38.4%-74.7% (2006-2010: 38.4%; 2011-2015: 70.7%; 2016-current: 74.7%) underwent anti-HER2 targeted therapy. Among them, 74.9%-93.0% (2006-2010: 93.0%; 2011-2015: 89.9%; 2016-current: 74.9%) were adjuvant, 2.8%-20.5% (2006-2010: 2.8%; 2011-2015: 5.0%; 2016-current: 20.5%) were neoadjuvant and 4.2%-5.1% (2006-2010: 4.2%; 2011-2015: 5.1%; 2016-current: 4.6%) were palliative. In addition, the majority (2006-2010: 87.7%; 2011-2015: 90.6%; 2016-current: 86.8%) of the patients received anti-HER2 targeted therapy at public medical facilities, and the remainder (2006-2010: 12.3%; 2011-2015: 9.4%; 2016-current: 13.2%) at private medical facilities. In each cohort, the use of anti-HER2 targeted therapy was much lower for stage I patients, and the proportions of stage II or above patients who had anti-HER2 targeted therapy were similar for the 2011-2015 and 2016-current cohorts (Figure 2.24).

Table 2.34: Type of targeted therapy drugs used (N=2,795)

	2006-2010 (N=697) %	2011-2015 (N=1,463) %	2016-current (N=635) %
HER2-targeted agents	95.8	94.7	94.3
Angiogenesis inhibitors	0.7	0.0	0.0
CDK4/6 inhibitors	0.0	0.2	1.4
mTOR inhibitors	0.0	0.1	0.0
Unclassified	3.4	5.1	4.3

HER2: human epidermal growth factor receptor 2; CDK: cyclin-dependent kinase; mTOR: mammalian target of rapamycin

Figure 2.24: Use of anti-HER2 targeted therapy in HER2 positive patients by cancer stage (N=3,480)



	I	IIA	IIB	III	IV
2006-2010 (N=1,397)	28.7	43.9	50.0	58.5	61.5
2011-2015 (N=1,553)	58.1	85.7	86.7	89.9	86.4
2016-current (N=530)	66.3	86.5	89.7	90.7	84.2

Cancer stage

F. Multimodality treatment

2.66 Combinations of treatments, including surgery, radiotherapy, chemotherapy, endocrine therapy and targeted therapy, are usually used to treat breast cancer effectively. Table 2.35 shows the multimodality treatment pattern of the patients. In general, the number of modalities increased with increasing cancer stage. In the cohorts, the majority (90.0%-91.0%) of patients with stage 0 disease received two or less treatments. On the other hand, more than three-quarters of the patients with stage IIA (77.2%-81.8%), IIB (86.3%-93.0%) or III (93.4%-96.7%) disease received three or more modalities.

Table 2.35 Number of treatment modalities by cancer stage (N=19,309)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current																	
	0			I			IIA			IIB			III			IV		
0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.4	0.1	0.1	0.0	0.0	0.8	0.0
1	40.4	40.4	38.2	6.4	6.7	6.3	2.3	2.3	4.2	0.8	1.4	2.3	0.8	0.7	2.3	6.2	7.1	18.1
2	50.5	49.6	51.9	32.0	32.6	31.2	15.9	19.0	18.4	7.1	5.5	11.1	2.5	2.5	4.3	18.1	13.0	17.0
3	7.5	8.6	8.8	42.1	41.0	45.2	39.0	35.1	37.6	27.5	26.5	24.3	18.1	16.5	18.7	36.8	32.4	14.9
4	1.3	1.2	0.9	18.0	15.7	13.5	39.1	37.4	32.5	57.7	54.7	52.1	66.9	63.4	61.5	33.3	34.8	34.0
5	0.1	0.2	0.2	1.5	4.0	3.7	3.7	6.2	7.1	6.8	11.8	9.9	11.6	16.8	13.2	5.6	11.9	16.0

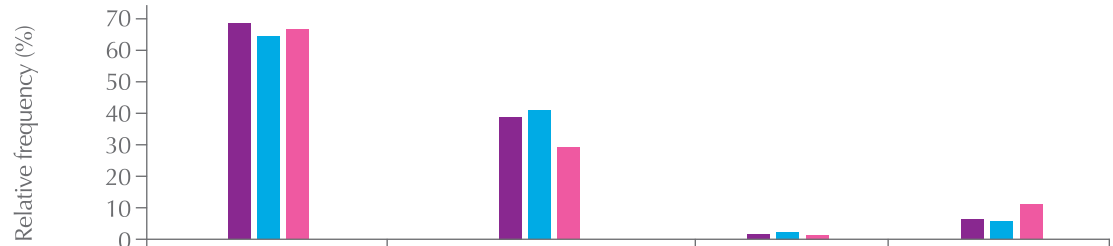
Total number of patients in each group:

0: 918 (for 2006-2010), 1,112 (for 2011-2015), 566 (for 2016-current)
I: 2,161 (for 2006-2010), 2,781 (for 2011-2015), 1,360 (for 2016-current)
IIA: 1,766 (for 2006-2010), 2,069 (for 2011-2015), 954 (for 2016-current)
IIB: 840 (for 2006-2010), 1,110 (for 2011-2015), 486 (for 2016-current)
III: 951 (for 2006-2010), 1,258 (for 2011-2015), 486 (for 2016-current)
IV: 144 (for 2006-2010), 253 (for 2011-2015), 94 (for 2016-current)

G. Complementary and alternative therapies

2.67 Apart from the standard medical treatments and care of breast cancer described in the previous sections of this chapter, patients may seek different kinds of complementary and alternative therapies, such as taking traditional Chinese medicines, health foods and supplements. A total of 7,201 (2006-2010: 41.6%; 2011-2015: 37.4%; 2016-current: 22.8%) of the patients in the three cohorts sought complementary and alternative therapies as part of their treatment. Among them, about 97% (2006-2010: 97.2%; 2011-2015: 96.1%; 2016-current: 97.0%) were adjuvant, neoadjuvant (2006-2010: 0.6%; 2011-2015: 0.5%; 2016-current: 0.2%) and palliative (2006-2010: 2.2%; 2011-2015: 3.5%; 2016-current: 2.8%) accounted for only small proportions. In addition, about two-thirds (64.4%-67.9%) of the patients used traditional Chinese medicines (Figure 2.25).

Figure 2.25: Type of complementary and alternative therapies used (N=7,201)



	Chinese medicine	Health food / supplements	Others*	Not known
2006-2010 (N=2,883)	67.9	38.6	1.8	6.2
2011-2015 (N=3,355)	64.4	40.7	2.1	5.8
2016-current (N=963)	67.1	28.7	1.6	10.4

Complementary and alternative therapies

*Others included tai chi, qigong, naturopathy, acupuncture and moxibustion, massage and yoga

VI. Patient status

2.68 Once treatment is completed, the HKBCR will follow up with the registered patients annually to ascertain the efficacy of the treatment. To date, a total of 18,155 patients in the three cohorts completed at least one follow-up. About a quarter (25.8%) of them had the last follow-up within the past two years and less than half (43.3%) have been followed up for five or more years (Table 2.36). The mean and median follow-up period were 4.7 and 4.1 years respectively.

2.69 Of the patients who have been followed up, 1.8% experienced only locoregional recurrence (LR), 2.4% experienced only distant recurrence (DR), and 1.7% experienced both locoregional and distant recurrence concurrently or sequentially. The mean and median time to recurrence are shown in Table 2.36.

Table 2.36: Follow-up of patients (N=18,155)

	Number	%
Follow-up period		
<1 year	2,092	11.5
1-2 years	2,776	15.3
2-5 years	5,435	29.9
5-10 years	6,421	35.4
≥10 years	1,431	7.9
Mean (95% CI)	4.7 years (4.68-4.78)	
Median (95% CI)	4.1 years (4.00-4.20)	
Locoregional recurrence only		
No. of locoregional recurrence only	319	1.8
Mean time (95% CI)	3.6 years (3.24-3.85)	
Median time (95% CI)	3.0 years (2.70-3.40)	
Distant recurrence only		
No. of distant recurrence only	442	2.4
Mean time (95% CI)	3.4 years (3.14-3.58)	
Median time (95% CI)	2.8 years (2.30-3.10)	
Locoregional and distant recurrence		
No. of locoregional and distant recurrence	308	1.7
Mean time (95% CI)	3.3 years (2.99-3.60)	
Median time (95% CI)	2.9 years (2.70-3.20)	
Mortality*		
No. of deaths from breast cancer	233	1.3
No. of deaths from unrelated causes	116	0.6
No. of deaths with causes not known	158	0.9

CI: confidence interval

*Data as of Feb 2021 with traceable medical records only.

2.70 Table 2.37 shows the number of invasive breast cancer patients with LR in different subgroups specified by surgery type and cancer stage at diagnosis in the patient cohort. Patients with stage I and II disease who received breast-conserving surgery without radiotherapy had higher LR rates than those who received breast-conserving surgery with radiotherapy. Overall, patients who received mastectomy had lower LR rates than those who received breast-conserving surgery without radiotherapy (Table 2.37). The common sites for LR were chest wall (32.2%) and breast (31.7%) (Table 2.38).

Table 2.37: Locoregional recurrence by type of surgery received and cancer stage at diagnosis

	Cancer stage, Number (% of patients with the same surgery type and cancer stage)				
	I	IIA	IIB	III	Total
BCS with RT	38/2,864 (1.3)	51/1,643 (3.1)	11/569 (1.9)	19/368 (5.2)	119/5,444 (2.2)
BCS without RT	8/132 (6.1)	8/87 (9.2)	1/27 (3.7)	0/10 (0.0)	17/256 (6.6)
MTX	63/3,024 (2.1)	76/3,021 (2.5)	58/1,843 (3.1)	137/2,280 (6.0)	334/10,168 (3.3)

BCS: breast-conserving surgery; MTX: mastectomy; RT: radiotherapy

Table 2.38: Sites involved in locoregional recurrence (N=627)

	Number	%
Chest wall	202	32.2
Breast	199	31.7
Axilla	202	32.2
Supraclavicular fossa	127	20.3
Internal mammary node	42	6.7
Infraclavicular fossa	7	1.1
Others	65	10.4

Note: the total percentages may exceed 100 as multiple sites may be involved in locoregional recurrence.

2.71 In the cohort, 750 (4.1%) patients experienced distant recurrence. Among them, the top four organs involved were bone (55.7%), lung (45.3%), liver (37.7%) and brain (18.8%) (Table 2.39). The median time for distant recurrence to bone, lung, liver and brain and the distribution of biological subtypes of the patients involved are shown in Table 2.40.

Table 2.39: Organs involved in distant recurrence (N=750)

	Number	%
Bone	418	55.7
Lung	340	45.3
Liver	283	37.7
Brain	141	18.8
Mediastinal node	120	16.0
Neck node	57	7.6
Pleural cavity	53	7.1
Distant lymph node	25	3.3
Peritoneum	18	2.4
Kidney	18	2.4
Adrenal gland	15	2.0
Contralateral axillary node	5	0.7
Ovary	6	0.8
Spleen	6	0.8
Thyroid gland	3	0.4
Uterus	3	0.4
Pancreas	1	0.1
Unspecified	26	3.5

Note: the total percentages may exceed 100 as multiple sites may be involved in distant recurrence.

Table 2.40: Time for organ specific metastasis and distribution of the biological subtypes of patients

	Bone (N=418)	Lung (N=340)	Liver (N=283)	Brain (N=141)
Time for distant recurrence, median years (range)	**3.4 (0.1-11.2)**	**3.4 (0.2-11.2)**	**2.9 (0.2-9.6)**	**2.8 (0.2-10.1)**
Biological subtypes				
Luminal A	41 (9.8)	24 (7.1)	23 (8.1)	9 (6.4)
Luminal B (HER2 negative)	99 (23.7)	59 (17.4)	59 (20.8)	20 (14.2)
Luminal A/B (HER2 negative)	110 (26.3)	78 (22.9)	77 (27.2)	15 (10.6)
Luminal B (HER2 positive)	70 (16.7)	55 (16.2)	46 (16.3)	27 (19.1)
HER2 positive	27 (6.5)	30 (8.8)	28 (9.9)	28 (19.9)
TNBC	38 (9.1)	60 (17.6)	29 (10.2)	24 (17.0)
Not known	33 (7.9)	34 (10.0)	21 (7.4)	18 (12.8)

Luminal A: ER and/or PR+, HER2-, and low Ki-67 index (<14%)
Luminal B (HER2 negative): ER and/or PR+, HER2-, and high Ki-67 index (≥14%)
Luminal A/B (HER2 negative): ER and/or PR+, HER2-, and Ki-67 index not known
Luminal B (HER2 positive): ER and/or PR+, HER2+, and any Ki-67 index
HER2 positive: ER and PR-, HER2+, and any Ki-67 index
TNBC (Triple Negative Breast Cancer): ER and PR-, HER2-, and any Ki-67 index

2.72 In the cohort, the proportion of patients with only LR did not show any association with cancer stage at diagnosis. However, the proportion of the patients with only DR increased from 0.9% of stage I patients to 6.1% of stage III patients. Stage III patients also had higher rates of only DR (6.1%) and combination of LR and DR (4.0%) than those with lower cancer stages (Table 2.41).

2.73 In the cohort, 232 (1.3%) patients died from breast cancer. More than half (58.2%) of them were stage III or IV at initial diagnosis. Survival time ranged from 0.6 to 11.3 years. Information on biological subtypes of these patients is shown in Table 2.42.

Table 2.41: Locoregional and distant recurrence among invasive breast cancer patients by cancer stage (N=15,950)

	Cancer stage, Number (%)			
	I (N=6,032)	IIA (N=4,770)	IIB (N=2,452)	III (N=2,696)
Locoregional recurrence only	81 (1.3)	72 (1.5)	21 (0.9)	50 (1.9)
Distant recurrence only	54 (0.9)	73 (1.5)	67 (2.7)	164 (6.1)
Locoregional and distant recurrence	29 (0.5)	64 (1.3)	49 (2.0)	109 (4.0)

Table 2.42: Characteristics of breast cancer-specific deaths (N=232)

	Cancer stage at initial diagnosis						
	0	I	IIA	IIB	III	IV	Unstaged
No. of cases (% of breast cancer death cases)	**3 (1.3)**	**22 (9.5)**	**32 (13.8)**	**25 (10.8)**	**97 (41.8)**	**38 (16.4)**	**15 (6.5)**
Survival time (range in years)	**4.5 – 7.3**	**1.8 – 9.6**	**1.6 – 11.3**	**2.1 – 11.3**	**0.8 – 9.5**	**0.6 – 8.1**	**0.6 – 6.2**
Time from first diagnosis of distant recurrence to death (years), mean (range)	**1.2 (0.9 - 1.5)**	**1.9 (0.7 - 4.6)**	**1.3 (0.1 - 5.9)**	**1.8 (0.1 - 6.2)**	**1.2 (0.0 - 5.9)**	**1.4 (0.1 - 3.9)**	**1.1 (0.3 - 3.1)**
Biological subtypes							
Luminal A	0	1	3	3	6	0	0
Luminal B (HER2 negative)	0	5	4	5	14	5	1
Luminal A/B (HER2 negative)	1	4	10	10	24	6	2
Luminal B (HER2 positive)	2	2	3	1	18	6	5
HER2 positive	0	4	4	0	14	7	1
TNBC	0	6	6	6	14	4	0
Not known	0	0	2	0	7	10	6

Luminal A: ER and/or PR+, HER2-, and low Ki-67 index (<14%)
Luminal B (HER2 negative): ER and/or PR+, HER2-, and high Ki-67 index (≥14%)
Luminal A/B (HER2 negative): ER and/or PR+, HER2-, and Ki-67 index not known
Luminal B (HER2 positive): ER and/or PR+, HER2+, and any Ki-67 index
HER2 positive: ER and PR-, HER2+, and any Ki-67 index
TNBC (Triple Negative Breast Cancer): ER and PR-, HER2-, and any Ki-67 index