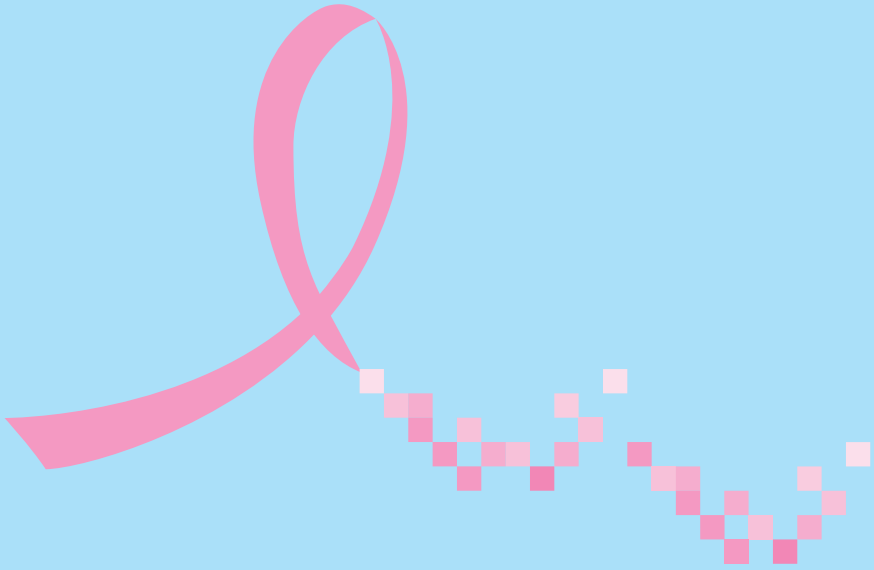

CHAPTER 2

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 18,358 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 covered in this report, according to their year of cancer diagnosis, were divided into three cohorts (2006-2010, 2011-2015 and 2016-current) and analysed separately.

Clinical presentation

- The primary method of first cancer detection in the patient cohorts was self-detection by chance (81.4%-84.2%). More stage 0 or I cancer cases (31.8%-36.6% and 11.9%-16.6% respectively) were detected by mammography screening than stage III or IV cancer cases (2.2%-2.9% and 0.7%-3.9% respectively).
- Most (90.8%-92.4%) patients who self-detected their cancer by chance found a painless lump on their breast(s). Pain is not usually a symptom of breast cancer; only 5.6%-8.0% of the patients felt pain in their breast(s) at initial presentation. Some patients (8.0%-9.6%) experienced changes in nipple (such as nipple discharge, nipple retraction, redness, scaliness or thickening of nipple).
- After the onset of symptoms, only about one-third (32.7%-38.2%) of the patients who self-detected their cancer by chance sought first medical consultation in less than one month. More than one quarter (27.9%-31.7%) waited more than three months before seeking first medical consultation.
- The majority (94.9%-95.6%) of the patients had unilateral breast cancer, while a small proportion (2.3%-2.8%) had synchronous bilateral breast cancer at first diagnosis. Another 1.9%-2.3% developed contralateral breast cancer after diagnosis of an initial primary breast cancer.
- The proportions of the patients with invasive breast cancer who did not have any cancer staging as part of their diagnosis and treatment ranged from 36.6% to 56.0% across the three cohorts. Among those patients who had cancer staging as part of their treatment, a combination of chest x-ray and ultrasound of abdomen (53.3%) was the most common method used for the 2006-2010 cohort, while positron emission tomography scan was the most common method used for the 2011-2015 (59.2%) and 2016-current (71.4%) cohorts.
- The most common cancer stage at diagnosis was stage II (35.7%-38.5%) followed by stages III-IV (14.9%-17.7%). In addition, 11.6%-12.5% of the patients were diagnosed with in situ cancer.

Cancer characteristics

- The mean size of tumours of invasive breast cancer in each patient cohort was 2.2 cm (standard deviation: ±1.5 cm). Tumours of one cm or less in size were found in 15.8%-16.8% of the patients, while tumours larger than two cm were found in 46.8%-48.0% of the patients. In each cohort, screen-detected tumours were significantly smaller

than those self-detected by chance (mean: 1.3±1.0 cm vs. 2.3±1.5cm; p<0.001). In addition, 56.3%-60.1% of the patients with invasive cancers had no positive lymph nodes, while 30.1%-34.5% had at least one positive lymph node with metastasis size larger than two mm. The most common type was invasive carcinoma of no specific type (86.9%-87.3%). Of the invasive breast cancer cases, 78.5%-83.4% were either estrogen receptor (ER) or progesterone receptor (PR) positive, while 17.5%-24.7% were c-erbB2/HER2 positive.

- The mean size of tumours of in situ breast cancer in each patient cohort was two cm (standard deviation: ±1.7 cm). Tumours larger than two cm in size were found in 30.4%-36.3% of the patients. Of the in situ breast cancer cases where mammogram was performed, 59.9%-62.3% showed microcalcification. Ductal cancer was the most common type of in situ breast cancer in each cohort (92.6%-93.6%). Of the in situ breast cancer cases, 81.7%-84.2% were either ER or PR positive, while 17.5%-28.9% were c-erbB2/HER2 positive.

Treatment

- Of the 18,358 patients, 10.0%-14.5% received care at private medical service, 46.6%-53.6% received care at public medical service, and 33.6%-38.8% received care at both private and public medical services.
- Surgery
  - The majority (97.4%-98.4%) of the patients underwent surgery as part of their treatment; 47.0%-53.5% of the patients had surgery at private medical facilities, while 46.5%-53.0% had surgery at public medical facilities.
  - For those patients with invasive tumours, more than half (58.8%-65.7%) had mastectomy and among them, 11.3%-12.9% had reconstruction. Almost all (94.8%-96.6%) the patients with invasive tumours received nodal surgery and among them, 23.1%-50.6% required axillary dissection, and 35.5%-62.3% required sentinel node biopsy only.
  - Less than half (39.4%-47.6%) of the patients with in situ tumours had mastectomy, and among them, 19.4%-27.4% had reconstruction. Among those who received nodal surgery, 76.7%-96.7% had sentinel node biopsy only and 2.3%-19.4% had axillary dissection without sentinel node biopsy.
  - The percentage of the patients who underwent mastectomy was positively correlated with both increasing age and cancer stage.
  - Regarding nodal surgery, sentinel node biopsy without axillary dissection was more commonly used on the patients with negative clinical nodal status (45.2%-79.9%) than those with positive clinical nodal status (10.0%-23.1%). The use of axillary dissection without sentinel node biopsy was positively correlated with increasing cancer stage.
- Radiotherapy
  - In the cohorts, two-thirds (62.6%-64.2%) of the patients had locoregional radiotherapy as part of their treatment. In addition, 85.7%-89.3% of the patients were treated with radiotherapy at public medical facilities, while 10.7%-14.3% had radiotherapy at private medical facilities.
  - The proportion of the invasive breast cancer patients who underwent breast-conserving surgery and also received locoregional radiotherapy was high (over 92%). On the other hand, the proportion of the invasive breast cancer patients who underwent mastectomy and also received locoregional radiotherapy increased significantly from stage I (9.3%-14.0%) to stage III (89.9%-94.4%).
  - Of the patients with in situ cancer who had breast-conserving surgery, over 90% received locoregional radiotherapy afterwards, while 2.8%-3.7% of the patients with in situ cancer who had mastectomy underwent locoregional radiotherapy.
  - Among the patients with metastatic breast cancer, 57.8%-63.2% underwent palliative radiotherapy, and of these patients, 6.9%-

27.3% received radiotherapy to the spine and 0.6%-14.8% to the pelvis.

- Chemotherapy
  - In the cohorts, 59.2%-70.7% of the patients with invasive cancer underwent chemotherapy. The majority (85.4%-87.0%) of them received chemotherapy at public medical facilities, and the remainder (13.0%-14.6%) at private medical facilities.
  - In the cohorts, the use of curative intent chemotherapy was positively correlated to progressing cancer stage from stages I to III. In contrast, the majority (73.5%-86.2%) of the stage IV patients underwent palliative chemotherapy. On the other hand, the use of neoadjuvant chemotherapy increased substantially with progressing cancer stage.
- Endocrine therapy
  - In the cohorts, 67.6%-69.1% of the patients were treated with endocrine therapy. In addition, 88.0%-92.6% of the patients received endocrine therapy at public medical facilities, while 7.4%-12.0% at private medical facilities.
  - Endocrine therapy was used in only 10.3%-12.8% of the in situ breast cancer cases. In contrast, high proportions (74.0%-85.0%) of the patients with invasive cancer received endocrine therapy.
- Anti-HER2 targeted therapy
  - Of the patients with invasive HER2 positive breast cancer in the three cohorts, 43.1%-79.5% underwent anti-HER2 targeted therapy. The majority (87.0%-90.3%) of the patients received anti-HER2 targeted therapy at public medical facilities, and the remainder (9.7%-13.0%) 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 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 for treating breast cancer effectively. In general, the number of treatment modalities increased with increasing cancer stage.
- Complementary and alternative therapies
  - A total of 6,827 (24.5%-41.6%) patients in the cohorts sought complementary and alternative therapies as part of their treatment. Among them, 64.1%-67.7% used traditional Chinese medicines.

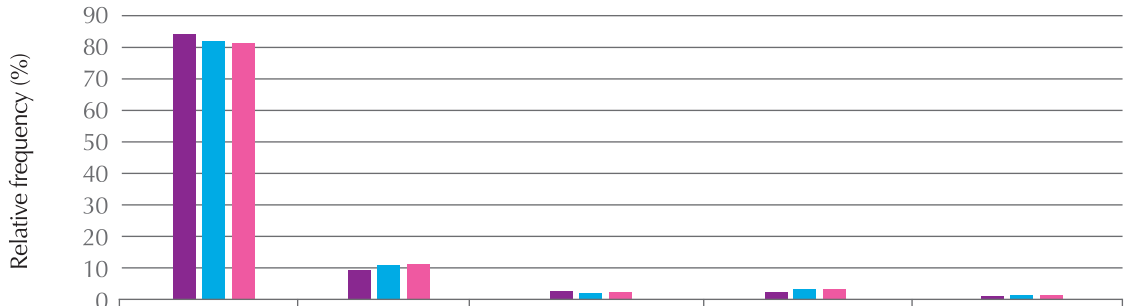
Patient status

- The mean and median follow-up period were 4.2 and 3.5 years, respectively.
- Of the patients who have been followed up, 1.4% experienced only locoreigonal recurrence, 1.9% experienced only distant recurrence, and 1.4% experienced both locoregional and distant recurrent concurrently or sequentially.
- The common sites for locoregional recurrence were chest wall (32.8%) and breast (29.9%). The top four organs involved in distant recurrence were bone (57.4%), lung (48.8%), liver (40.8%) and brain (17.1%).

II. Clinical presentation

2.2 The primary method of first breast cancer detection in the patient cohorts was self-detection by chance (81.4%-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%-17.6%). In the United States (US), a study reported that 43% of breast cancer cases were detected through MMG,[31] which is much higher than the 9.6%-11.3% of the patient cohorts.

Figure 2.1: Method of first breast cancer detection in the patient cohorts (N=17,360)



	Self-detection by chance	Mammography screening	Other screening methods (BSE and CBE)	Other imaging tests (USG and MRI)	Incidental surgery / Others
2006-2010 (N=6,441)	84.2	9.6	3.3	2.5	0.5
2011-2015 (N=8,337)	82.5	11.0	2.6	3.0	0.9
2016-current (N=2,582)	81.4	11.3	2.7	3.6	1.0

2.3 In terms of the types of medical service received, the proportion of the patients who self-detected their breast cancer by chance was higher among public medical service users (83.3%-85.6%) or mixed private/public medical service users (80.8%-86.6%) than among private medical service users (68.0%-72.9%). In contrast, the proportion of the patients who first detected their breast cancer through MMG was higher among private medical service users (14.3%-21.4%) than among public medical service users (8.7%-12.0%) or mixed private/public medical service users (7.1%-11.3%) (Table 2.1).

Table 2.1: Method of first breast cancer detection by type of medical service users (N=17,360)

	Type of medical service users % for 2006-2010, % for 2011-2015, % for 2016-current								
	Private			Public			Mixed private / public		
Self-detection by chance	72.9	72.3	68.0	85.6	83.3	85.3	86.6	84.1	80.8
Mammography screening	15.7	14.3	21.4	9.8	12.0	8.7	7.1	8.7	11.3
Other screening methods (BSE and CBE)	4.2	2.7	0.6	2.7	2.3	3.4	3.6	2.9	2.4
Other imaging tests (USG and MRI)	6.5	8.9	8.6	1.3	1.5	1.5	2.4	3.4	4.7
Incidental surgery / Others	0.7	1.7	1.4	0.6	0.9	1.0	0.4	0.8	0.7

Total number of patients in each group:

Private: 938 (for 2006-2010), 839 (for 2011-2015), 359 (for 2016-current)

Public: 3,005 (for 2006-2010), 4,446 (for 2011-2015), 1,358 (for 2016-current)

Mixed private / public: 2,498 (for 2006-2010), 3,052 (for 2011-2015), 865 (for 2016-current)

BSE: Breast self-examination; CBE: Clinical breast examination; USG: 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.[32] In the patient cohorts, the proportions of invasive breast cancer cases detected by MMG ranged from 6.4% to 8.3%, which were much lower than those of in situ breast cancer cases (31.8%-36.6%) (Table 2.2). In addition, more stage 0 or I cancer cases were detected by MMG than stage III or IV cancer cases (Table 2.3). On the other hand, the majority (91.1%-95.3%) of the patients with stage IIB, III or IV cancer self-detected their cancer by chance.

Table 2.2: Method of first breast cancer detection by type of cancer (N=17,236)

	Type of cancer % for 2006-2010, % for 2011-2015, % for 2016-current					
	Invasive cancer			In situ cancer		
Self-detection by chance	87.6	86.3	85.3	60.0	53.8	54.2
Mammography screening	6.4	7.7	8.3	31.8	36.6	32.5
Other screening methods (BSE and CBE)	3.2	2.4	2.5	3.9	3.3	3.4
Other imaging tests (USG and MRI)	2.2	2.7	3.0	4.1	5.0	8.4
Incidental surgery / Others	0.5	0.9	0.8	0.2	1.3	1.5

Total number of patients in each group:

Invasive cancer: 5,603 (for 2006-2010), 7,298 (for 2011-2015), 2,238 (for 2016-current)

In situ cancer: 803 (for 2006-2010), 971 (for 2011-2015), 323 (for 2016-current)

BSE: Breast self-examination; CBE: Clinical breast examination; USG: Ultrasound screening; MRI: Magnetic resonance imaging

Table 2.3: Method of first breast cancer detection by cancer stage (N=16,819)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current																	
	0			I			IIA			IIB			III			IV		
Self-detection by chance	59.9	53.8	54.1	79.6	76.8	73.7	89.9	88.7	90.0	93.8	93.6	94.3	93.6	93.9	93.2	92.9	91.1	95.3
Mammography screening	31.8	36.6	32.5	11.9	14.5	16.6	4.9	5.5	5.1	2.0	2.6	2.3	2.9	2.9	2.2	0.7	3.9	1.6
Other screening methods (BSE and CBE)	3.9	3.3	3.4	4.1	3.3	2.6	2.9	2.5	2.1	2.4	2.0	2.3	2.4	0.8	3.7	3.5	2.3	1.6
Other imaging tests (USG and MRI)	4.1	5.1	8.4	4.1	4.2	6.1	1.6	2.5	1.9	1.4	1.3	0.7	0.3	1.4	0.0	1.4	1.2	0.0
Incidental surgery / Others	0.2	1.2	1.6	0.4	1.2	1.0	0.6	0.7	1.0	0.5	0.5	0.3	0.8	0.9	0.9	1.4	1.6	1.6

Total number of patients in each group:

0: 801 (for 2006-2010), 968 (for 2011-2015), 320 (for 2016-current)

I: 2,000 (for 2006-2010), 2,578 (for 2011-2015), 801 (for 2016-current)

IIA: 1,668 (for 2006-2010), 1,971 (for 2011-2015), 629 (for 2016-current)

IIB: 804 (for 2006-2010), 1,063 (for 2011-2015), 299 (for 2016-current)

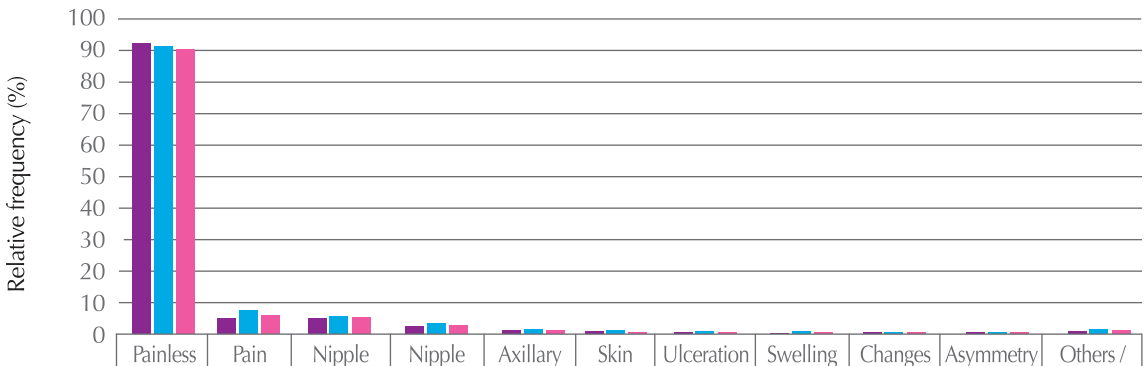
III: 909 (for 2006-2010), 1,223 (for 2011-2015), 323 (for 2016-current)

IV: 141(for 2006-2010), 257 (for 2011-2015), 64 (for 2016-current)

BSE: Breast self-examination; CBE: Clinical breast examination; USG: Ultrasound screening; MRI: Magnetic resonance imaging

2.5 Most (90.8%-92.4%) patients who self-detected their cancer by chance found a painless lump on their breast(s). Pain is not usually a symptom of breast cancer; only 5.6%-8.0% of the patients felt pain in their breast(s) at initial presentation. Some patients (8.0%-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=14,401)



	Painless lump	Pain	Nipple discharge	Nipple retraction	Axillary node	Skin change	Ulceration	Swelling	Changes in nipple	Asymmetry	Others / not known
2006-2010 (N=5,421)	92.4	5.6	5.4	2.3	1.0	0.8	0.4	0.2	0.3	0.4	0.8
2011-2015 (N=6,878)	91.5	8.0	6.3	2.9	1.1	1.0	0.7	0.8	0.4	0.3	1.3
2016-current (N=2,102)	90.8	6.6	5.9	2.6	0.9	0.4	0.4	0.4	0.3	0.2	1.0

*Self-detection by chance only

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.[33] After the onset of symptoms, only about one-third (32.7%-38.2%) of the patients who self-detected their cancer by chance sought first medical consultation in less than one month (Table 2.4). More than one quarter (27.9%-31.7%) waited more than three months before seeking first medical consultation.

2.7 The proportion of the patients who sought first medical consultation in less than one month was higher among private medical service users (39.9%-43.7%) than among public medical service users (26.8%-30.5%) (Table 2.5).

Table 2.4: Time interval between onset of symptoms and first medical consultation for patients who self-detected* their cancer (N=3,805)

	2006-2010 (N=1,614) %	2011-2015 (N=1,646) %	2016-current (N=545) %
Less than 1 month	38.2	32.7	33.4
1-3 months	30.1	35.5	38.7
4-12 months	19.9	22.2	18.9
More than 12 months	11.8	9.5	9.0

*Self-detection by chance only

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=3,805)

	Type of medical service users % for 2006-2010, % for 2011-2015, % for 2016-current								
	Private			Public			Mixed private / public		
Less than 1 month	43.7	39.9	40.7	30.5	26.8	25.9	40.7	41.7	44.1
1-3 months	29.0	32.7	37.3	28.4	35.3	42.4	32.2	36.7	32.8
4-12 months	17.5	19.0	20.3	25.6	25.8	20.7	16.9	16.5	15.3
More than 12 months	9.8	8.5	1.7	15.5	12.1	11.0	10.2	5.0	7.9

Total number of patients in each group:

Private: 428 (for 2006-2010), 153 (for 2011-2015), 59 (for 2016-current)

Public: 528 (for 2006-2010), 973 (for 2011-2015), 309 (for 2016-current)

Mixed private / public: 658 (for 2006-2010), 520 (for 2011-2015), 177 (for 2016-current)

*Self-detection by chance only

2.8 A much higher proportion (12.0%-14.0%) of the patients who sought first medical consultation after 12 months of symptom onset was diagnosed with stage IV cancer than those who sought first medical consultation in less than one month (0.6%-2.5%) (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=3,369)

	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	38.8	33.7	36.1	33.7	29.1	32.5	30.5	22.6	32.2	20.8	28.9	27.9
Stage IIA	33.9	33.3	32.3	35.1	30.8	33.5	28.7	33.6	32.2	24.7	21.1	39.5
Stage IIB	13.5	15.7	17.1	13.5	17.5	18.0	17.4	20.1	16.1	20.1	13.4	9.3
Stage III	12.0	16.7	12.0	16.3	18.1	13.4	19.9	18.9	13.8	20.8	24.6	9.3
Stage IV	1.8	0.6	2.5	1.4	4.6	2.6	3.5	4.7	5.7	13.6	12.0	14.0

Total number of patients in each group:

Less than 1 month: 557 (for 2006-2010), 478 (for 2011-2015), 158 (for 2016-current)

1-3 months: 430 (for 2006-2010), 526 (for 2011-2015), 194 (for 2016-current)

4-12 months: 282 (for 2006-2010), 318 (for 2011-2015), 87 (for 2016-current)

More than 12 months: 154 (for 2006-2010), 142 (for 2011-2015), 43 (for 2016-current)

*Self-detection by chance only

III. Cancer characteristics

2.9 Breast cancer can occur in one (unilateral) or both breasts (bilateral). The majority (2006-2010: 95.4%; 2011-2015: 94.9%; 2016-current: 95.6%) of the patients had unilateral breast cancer, while a small proportion (2006-2010: 2.3%; 2011-2015: 2.8%; 2016-current: 2.5%) had synchronous bilateral breast cancer at first diagnosis (Table 2.7). Another 1.9%-2.3% (2006-2010: 2.3%; 2011-2015: 2.3%; 2016-current: 1.9%) developed contralateral breast cancer after diagnosis of an initial primary breast cancer.

Table 2.7: Number of patients and breast cancer cases in the three patient cohorts

	No. of patients	No. of cases included in this report	Time interval for metachronous cases, median (range) (years)
2006-2010			
Unilateral	**6,387**	**6,387**	**—**
Bilateral (synchronous)	**151**	**302**	**—**
All bilateral (metachronous) cases	**154**	**195**	**5.5 (0.5 – 34.5)**
Bilateral (metachronous) Initial diagnosis happened within 2006-2010	*41*	*82*	*2.4 (0.6 – 3.8)*
Bilateral (metachronous) Initial diagnosis happened before 2006	*113*	*113*	*7.7 (0.5 – 34.5)*
2011-2015			
Unilateral	**8,066**	**8,066**	**—**
Bilateral (synchronous)	**238**	**476**	**—**
All bilateral (metachronous) cases	**192**	**220**	**7.0 (0.5 – 36.1)**
Bilateral (metachronous) Initial diagnosis happened within 2011-2015	*28*	*56*	*2.1 (0.5 – 4.3)*
Bilateral (metachronous) Initial diagnosis happened within 2006-2010	*74*	*74*	*5.0 (0.5 – 8.8)*
Bilateral (metachronous) Initial diagnosis happened before 2006	*90*	*90*	*11.8 (5.4 – 36.1)*
2016-current			
Unilateral	**2,527**	**2,527**	**—**
Bilateral (synchronous)	**67**	**134**	**—**
All bilateral (metachronous) cases	**49**	**51**	**7.8 (1.2 – 21.1)**
Bilateral (metachronous) Initial diagnosis happened within 2016-current	*2*	*4*	*1.3 (1.2 – 1.5)*
Bilateral (metachronous) Initial diagnosis happened within 2011-2015	*13*	*13*	*4.8 (1.4 – 7.2)*
Bilateral (metachronous) Initial diagnosis happened within 2006-2010	*22*	*22*	*8.1 (5.5 – 10.8)*
Bilateral (metachronous) Initial diagnosis happened before 2006	*12*	*12*	*14.1 (11.0 – 21.1)*

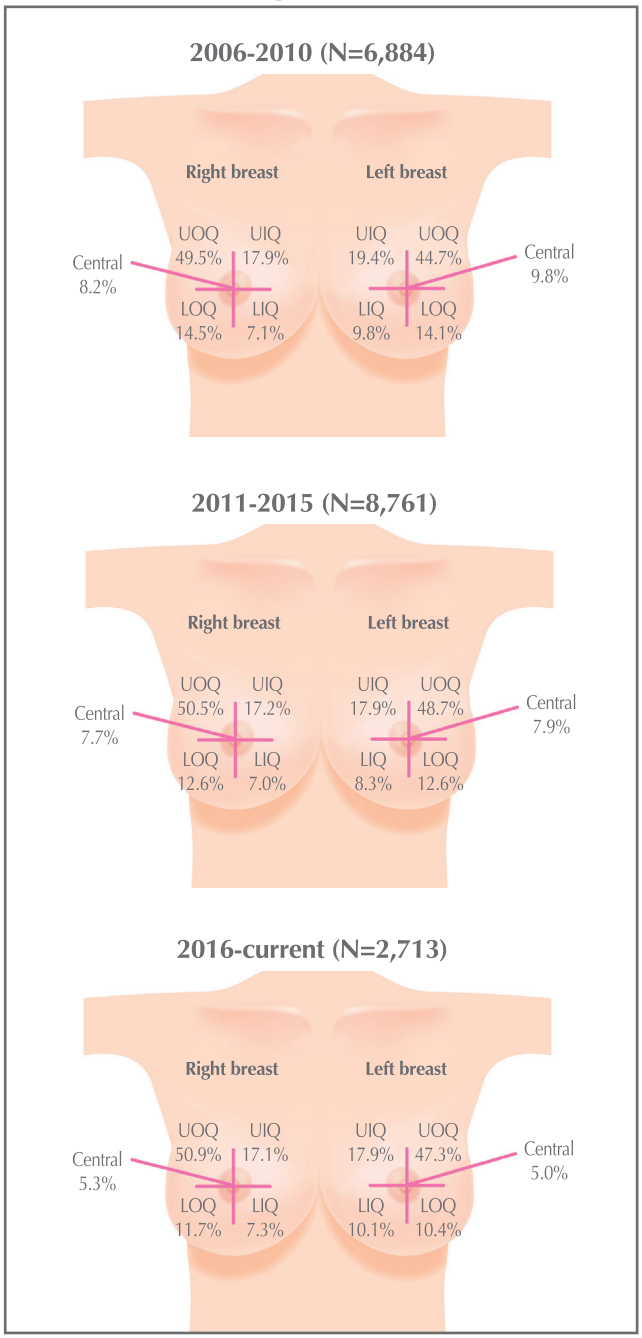
2.10 As regards the location of malignant breast tumour, about half of the breast cancer cases in either the left or the right breast (44.7%-48.7% and 49.5%-50.9% respectively), the tumour was detected in the upper outer quadrant (Figure 2.3).

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 83.6%-88.5% of the patients, and USG on 77.1%-86.8%, while MRI was used on only 6.0%-12.9% of the patients (Table 2.8). Results of imaging tests are classified into categories using a system called 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=18,358)



UOQ: Upper outer quadrant UIQ: Upper inner quadrant
LOQ: Lower outer quadrant LIQ: Lower inner quadrant
Note: Figures include multicentric cancers

Table 2.8: Sensitivity and diagnostic results of breast imaging tests (N=18,358)

	2006-2010 (N=6,884) %	2011-2015 (N=8,761) %	2016-current (N=2,713) %
Mammography			
Proportion of patients using the test	83.6	86.4	88.5
Overall sensitivity*	79.3	85.8	89.8
BIRADS category			
Diagnostic / malignant (BIRADS 5)	28.4	35.4	30.0
Suspicious abnormality (BIRADS 4)	50.9	50.5	59.8
Probably benign (BIRADS 3)	7.4	4.1	3.3
Benign (BIRADS 2)	5.1	3.2	3.5
Normal (BIRADS 1)	7.9	6.0	2.9
Incomplete (BIRADS 0)	0.3	0.9	0.5
Breast ultrasound			
Proportion of patients using the test	77.1	81.5	86.8
Overall sensitivity*	88.4	92.8	94.6
BIRADS category			
Diagnostic / malignant (BIRADS 5)	35.5	39.2	32.0
Suspicious abnormality (BIRADS 4)	52.9	53.6	62.6
Probably benign (BIRADS 3)	6.8	4.6	3.6
Benign (BIRADS 2)	2.1	1.2	1.4
Normal (BIRADS 1)	2.6	1.4	0.5
Incomplete (BIRADS 0)	0.1	0.1	<0.1
MRI			
Proportion of patients using the test	6.0	11.8	12.9
Overall sensitivity*	95.4	97.3	98.3
BIRADS category			
Diagnostic / malignant (BIRADS 5)	69.8	82.7	82.2
Suspicious abnormality (BIRADS 4)	25.5	14.6	16.0
Probably benign (BIRADS 3)	1.9	1.3	1.1
Benign (BIRADS 2)	1.5	0.4	0.3
Normal (BIRADS 1)	1.2	1.0	0.3
Incomplete (BIRADS 0)	0.0	0.1	0.0

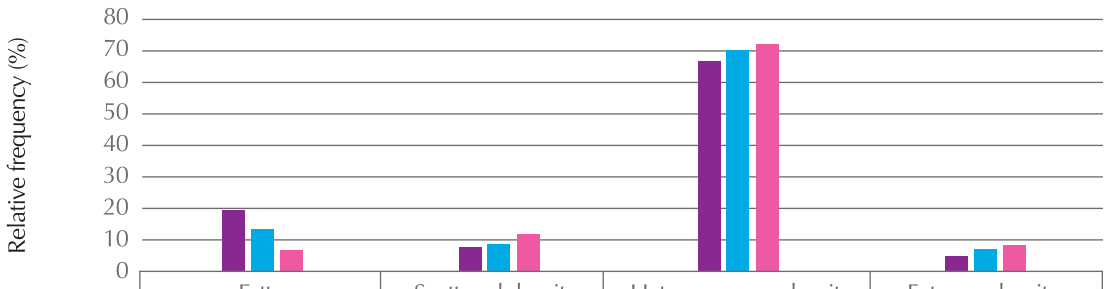
MRI: Magnetic resonance imaging; BIRADS: Breast Imaging Reporting and Data System
*Sensitivity: Number of true positives (BIRADS 4-5) divided by total number of patients who had the test

2.13 Opacity was observed in 58.3%-75.0% of the patients in the three cohorts with BIRADS 4 or 5 mammograms, while microcalcification was observed in 42.3%-50.4% (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%-72.3%) had heterogeneously dense breasts, while a small proportion (5.3%-8.6%) 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%-28.6% among patients aged between 20 and 29 to 0.5%-4.2% among patients aged 70 and above (Table 2.10).

Table 2.9: Mammographic findings of patients diagnosed through mammography (N=13,220)

	2006-2010 (N=4,561) %	2011-2015 (N=6,497) %	2016-current (N=2,162) %
Opacity	58.3	67.0	75.0
Microcalcification	50.4	50.2	42.3
Architectural distortion	13.2	15.2	15.4
Asymmetric density	10.3	7.4	4.1
Unclassified	5.2	3.5	5.1

Figure 2.4: Mammographic density of breasts of patients diagnosed through mammogram (N=9,317)



	Fatty	Scattered density	Heterogeneous density	Extreme density
2006-2010 (N=3,291)	19.5	8.1	67.1	5.3
2011-2015 (N=4,664)	13.6	9.1	70.0	7.3
2016-current (N=1,362)	7.0	12.0	72.3	8.6

Mammographic breast density

Table 2.10: Mammographic density of breasts of patients diagnosed through mammogram by age group (N=9,069)

	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	6.8	5.6	1.0	10.7	7.7	3.7	20.6	12.3	5.0	31.7	19.9	10.9	47.0	31.7	18.3
Scattered density	5.3	0.0	14.3	4.3	3.4	5.0	6.4	5.6	8.7	9.0	9.4	10.4	10.5	12.2	16.8	10.0	17.3	20.0
Heterogeneous density	73.7	75.0	57.1	79.9	76.8	76.2	75.4	76.9	71.7	65.9	71.9	78.6	55.0	63.7	68.4	42.5	49.0	57.5
Extreme density	10.5	20.0	28.6	9.0	14.2	17.8	7.5	9.9	15.9	4.5	6.4	6.1	2.8	4.2	3.8	0.5	2.0	4.2

Total number of patients in each group:

20-29: 19 (for 2006-2010), 20 (for 2011-2015), 7 (for 2016-current)

30-39: 278 (for 2006-2010), 323 (for 2011-2015), 101 (for 2016-current)

40-49: 1,120 (for 2006-2010), 1,332 (for 2011-2015), 321 (for 2016-current

50-59: 1,077 (for 2006-2010), 1,588 (for 2011-2015), 444 (for 2016-current)

60-69: 458 (for 2006-2010), 956 (for 2011-2015), 339 (for 2016-current)

70+: 219 (for 2006-2010), 347 (for 2011-2015), 120 (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: 83.6%; 2011-2015: 87.5%; 2016-current: 90.0%) of the patients in the three cohorts and among them, less than one-third (2006-2010: 36.5%; 2011-2015: 19.0%; 2016-current: 10.2%) received only FNA, one-third to two-thirds (2006-2010: 43.2%; 2011-2015: 56.7%; 2016-current: 66.5%) received only CNB, while about one-fifth (2006-2010: 20.3%; 2011-2015: 24.3%; 2016-current: 23.2%) received both FNA and CNB. In addition, 5.6%-13.7% of the patients had excisional biopsy. Excisional biopsy had the highest overall sensitivity of 100%, followed by CNB (98.8%-99.5%) and FNA (90.1%-91.0%) (Table 2.11).

Table 2.11: Sensitivity and diagnostic results of breast tissue biopsies (N=18,358)

	2006-2010 (N=6,884) %	2011-2015 (N=8,761) %	2016-current (N=2,713) %
Fine needle aspiration			
Proportion of patients using the test	47.1	37.6	29.9
Overall sensitivity*	90.5	90.1	91.0
Class			
Diagnostic / malignant (Class V)	60.0	65.2	66.1
Suspicious (Class IV)	18.8	13.1	14.3
Atypical (Class III)	11.7	11.7	10.6
Benign (Class II)	4.8	3.4	2.8
Scanty benign (Class I)	3.3	4.7	5.5
Incomplete (Class 0)	1.5	1.8	0.6
Core needle biopsy			
Proportion of patients using the test	52.7	70.5	80.4
Overall sensitivity*	98.8	98.8	99.5
Class			
Diagnostic / malignant (Class V)	94.6	95.8	96.5
Suspicious (Class IV)	2.5	1.2	2.0
Atypical (Class III)	1.7	1.7	1.1
Benign (Class II)	0.7	0.9	0.2
Scanty benign (Class I)	0.5	0.2	0.2
Incomplete (Class 0)	0.0	0.0	0.0
Excisional biopsy			
Proportion of patients using the test	13.7	9.0	5.6
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)	–	–	–

* 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 usually 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 the patients with invasive breast cancer who did not have any cancer staging as part of their diagnosis and treatment ranged from 36.6% to 56.0% across the three cohorts (2006-2010: 36.6%; 2011-2015: 53.6%; 2016-current: 56.0%). Among those patients who had cancer staging as part of their treatment, a combination of chest x-ray and ultrasound of abdomen was the most common method used for the 2006-2010 cohort (53.3%), while positron emission tomography scan (PET scan) was the most common method used for the 2011-2015 (59.2%) and 2016-current (71.4%) cohorts (Table 2.12). 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.[34] 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, 12.1%-44.0% of stage I and 26.8%-69.0% 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=7,352)

	2006-2010 (N=3,139) %	2011-2015 (N=3,239) %	2016-current (N=974) %
Positron emission tomography scan (PET scan)	34.2	59.2	71.4
Chest X-Ray (CXR) and ultrasound abdomen (USG Abd)	53.3	27.9	16.9
Computed tomography of body parts*	4.2	7.9	11.0
Bone scan	3.6	3.0	2.5
Magnetic resonance imaging whole body (MRI whole body)	0.7	0.6	1.8
Others (e.g. bone x-ray)	6.4	9.8	5.4
Not known	11.4	1.2	0.7

*Body parts include abdomen, thorax, pelvis, brain, or whole body

Table 2.13: Use of PET scan as a form of staging method among patients by cancer stage (N=7,352)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current					
	I	IIA	IIB	III	IV	Unstaged
PET scan used	12.1 25.2 44.0	26.8 47.1 69.0	39.6 70.3 80.9	62.9 82.6 85.8	82.7 90.3 83.3	68.0 79.8 94.4

Total number of patients in each group:

I: 1,029 (for 2006-2010), 786 (for 2011-2015), 234 (for 2016-current)

IIA: 832 (for 2006-2010), 735 (for 2011-2015), 242 (for 2016-current)

IIB: 467 (for 2006-2010), 498 (for 2011-2015), 141 (for 2016-current)

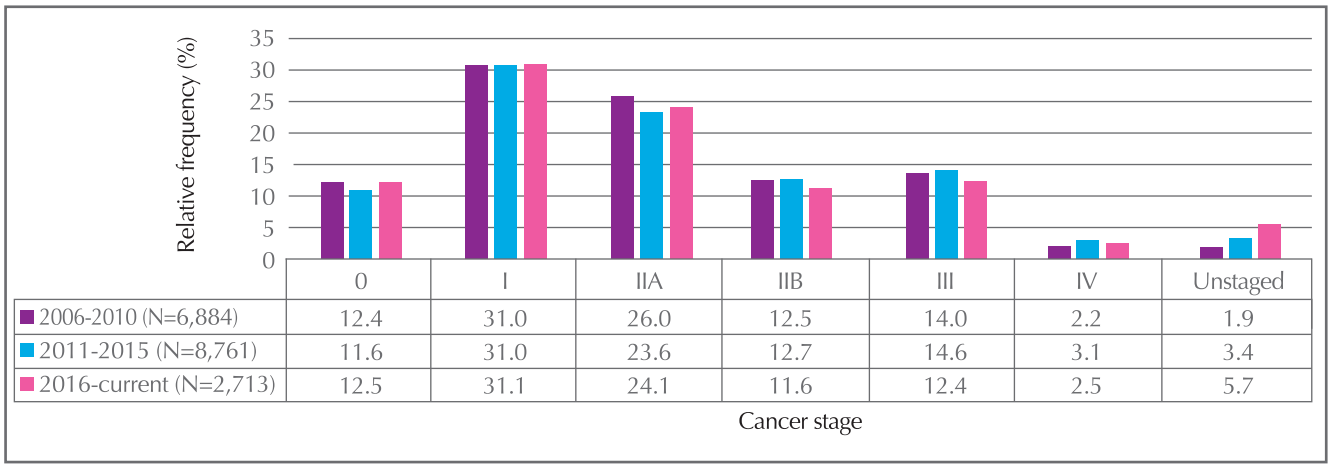
III: 628 (for 2006-2010), 867 (for 2011-2015), 226 (for 2016-current)

IV: 133 (for 2006-2010), 259 (for 2011-2015), 60 (for 2016-current)

Unstaged: 50 (for 2006-2010), 94 (for 2011-2015), 71 (for 2016-current)

2.17 The American Joint Committee on Cancer (AJCC) Anatomic Breast Cancer Staging (8th edition)[35] is used for determining cancer staging in the patient cohorts. There are two stage groups according to this system: anatomic stage 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. Although prognostic stage group was recommended for patient care and was used for reporting of all cancer patients in the US starting from 2018, it was not used in this report. The reason for this was that patients in the cohorts were mostly diagnosed in 2006 to 2016 and treatment offered to the patients in the cohorts 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 (35.7%-38.5%) followed by stages III-IV (14.9%-17.7%). In addition, 11.6%-12.5% of the patients were diagnosed with in situ cancer (Figure 2.5).

Figure 2.5: Cancer stage at diagnosis (N=18,358)



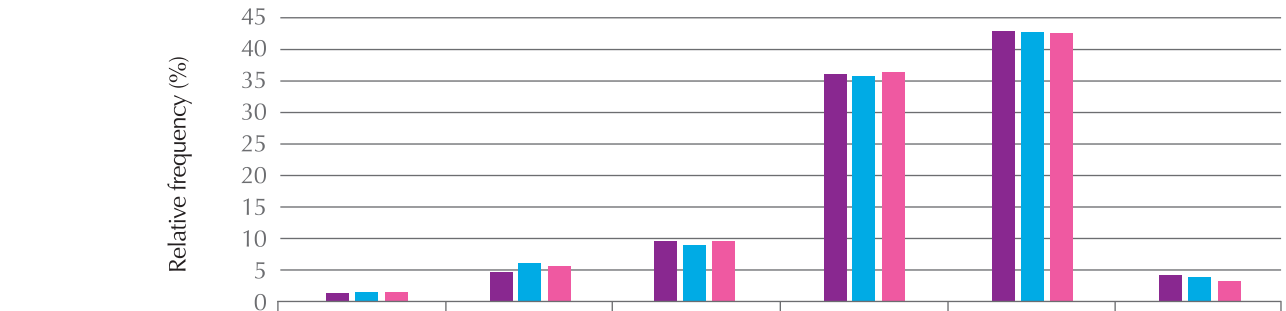
	0	I	IIA	IIB	III	IV	Unstaged
2006-2010 (N=6,884)	12.4	31.0	26.0	12.5	14.0	2.2	1.9
2011-2015 (N=8,761)	11.6	31.0	23.6	12.7	14.6	3.1	3.4
2016-current (N=2,713)	12.5	31.1	24.1	11.6	12.4	2.5	5.7

2.18 Of the 18,358 breast cancer cases analysed, data from 17,753 cases with available pathology data were used for subsequent analyses on cancer characteristics. A total of 15,368 (2006-2010: 86.4%; 2011-2015: 86.8%; 2016-current: 86.1%) patients were diagnosed with invasive cancer, while 2,373 (2006-2010: 13.5%; 2011-2015: 13.1%; 2016-current: 13.8%) patients were diagnosed with in situ cancer. In addition, 12 (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

2.19 The mean size of tumours of invasive breast cancer in each patient cohort was 2.2 cm (range: 0.01 to 19.1 cm; standard deviation: ±1.5 cm). Tumours of one cm or less in size were found in about 16% of the patients, while tumours of sizes one to two cm and two to five cm were respectively found in about 36% and 43% of the patients in all the three cohorts (Figure 2.6). Only a small proportion (3.7%-4.3%) of the 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 (mean: 1.3±1.0 cm vs. 2.3±1.5 cm; p<0.001).

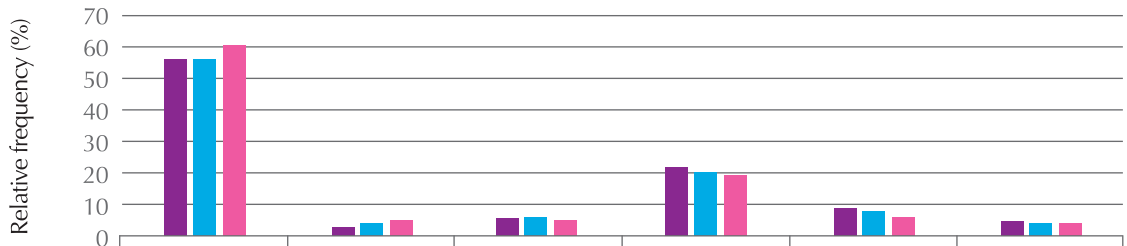
Figure 2.6: Distribution of tumour size (cm) of invasive breast cancer (N=14,250)



	≤ 0.10	0.11-0.50	0.51-1.00	1.01-2.00	2.01-5.00	> 5.00
2006-2010 (N=5,541)	1.6	4.7	9.5	36.1	43.7	4.3
2011-2015 (N=6,708)	1.7	6.0	9.0	35.9	43.3	4.2
2016-current (N=2,001)	1.7	5.6	9.5	36.3	43.1	3.7

2.20 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%-60.1% had no positive axillary lymph nodes, 3.2%-5.0% had isolated tumour cells, 4.8%-6.6% had micrometastasis (metastasis size > 0.2 mm to ≤ 2 mm), while 30.1%-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=14,862)



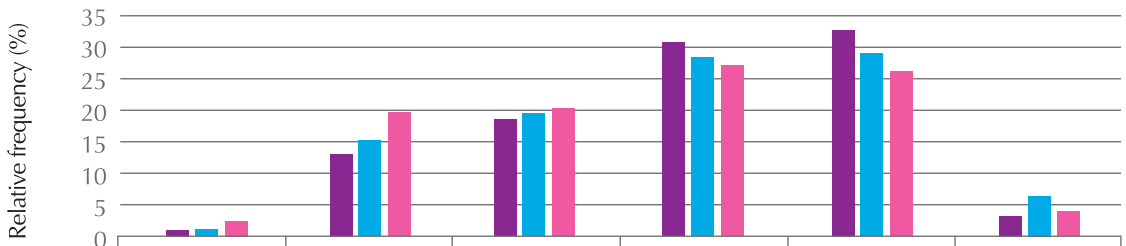
	0+ve nodes	Isolated tumour cell (ITC)	Micrometastasis (0.2-2mm)	1-3 +ve nodes	4-9 +ve nodes	10 or above +ve nodes
2006-2010 (N=5,693)	56.3	3.2	6.0	21.0	8.9	4.6
2011-2015 (N=7,068)	56.4	4.4	6.6	20.1	8.1	4.3
2016-current (N=2,101)	60.1	5.0	4.8	19.6	6.6	3.9

Axillary nodal status

D. Characteristics of in situ breast cancer

2.21 The mean size of tumours of in situ breast cancer in each patient cohort was two cm (range: 0.02 to 25.0 cm; standard deviation: ±1.7 cm). Tumours of one cm or less in size were found in 33.2%-42.6% of the patients, while tumours of two to five cm in size were found in 26.3%-33.0% of the patients (Figure 2.8). A small proportion (3.3%-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: 62.3%; 2016-current: 59.9%) showed microcalcification.

Figure 2.8: Distribution of tumour size (cm) of in situ breast cancer (N=1,965)



	≤ 0.10	0.11-0.50	0.51-1.00	1.01-2.00	2.01-5.00	> 5.00
2006-2010 (N=789)	1.0	13.7	18.5	30.5	33.0	3.3
2011-2015 (N=883)	1.1	15.2	19.6	28.4	29.1	6.6
2016-current (N=293)	2.7	19.8	20.1	27.0	26.3	4.1

Tumour size (cm)

IV. Histological and biological characteristics

2.22 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

2.23 As far as histological characteristics, grading, multifocality and multicentricity of invasive breast cancer in the patient cohorts are concerned, the most common type was invasive carcinoma of no specific type (86.9%-87.3%) (Table 2.14), and about one-third (31.4%-34.0%) of the invasive tumours are of grade 3 (Table 2.15).

Table 2.14: Histological type of invasive breast cancer (N=15,368)

	2006-2010 (N=5,787) %	2011-2015 (N=7,330) %	2016-current (N=2,251) %
Invasive carcinoma of no specific type	86.9	87.2	87.3
Lobular	3.6	3.4	4.3
Mucinous (colloid)	3.7	3.2	2.6
Papillary	0.8	1.1	1.0
Tubular	0.8	0.6	0.4
Carcinoma with medullary features	0.6	0.6	0.3
Borderline / malignant phyllodes	0.4	0.5	0.5
Mixed ductal and lobular	0.5	0.3	0.6
Micropapillary	0.4	0.4	0.5
Metaplastic	0.3	0.4	0.4
Carcinoma with neuroendocrine features	0.2	0.2	0.1
Carcinoma with apocrine features	0.2	0.1	<0.1
Adenoid cystic	<0.1	0.2	0.1
Paget's disease of nipple	0.1	0.1	0.0
Cribriform	0.1	<0.1	0.1
Tubulo-lobular	<0.1	0.1	<0.1
Inflammatory	<0.1	<0.1	<0.1
Squamous cell	<0.1	<0.1	0.0
Lipid rich carcinoma	<0.1	<0.1	<0.1
Secretory carcinoma	<0.1	0.0	0.0
Acinic cell carcinoma	0.0	<0.1	0.0
Sarcoma	0.0	<0.1	<0.1
Others (e.g. mixed types)	0.4	1.2	1.2
Not known	1.0	0.5	0.4

Table 2.15: Grading, multifocality and multicentricity of invasive breast cancer (N=15,368)

	2006-2010 (N=5,787) %	2011-2015 (N=7,330) %	2016-current (N=2,251) %
Grade			
Grade 1	16.6	16.1	17.5
Grade 2	39.2	41.0	37.9
Grade 3	34.0	31.4	31.4
Not known	10.2	11.5	13.1
Lymphovascular invasion	**28.9**	**25.2**	**23.1**
Multifocality	**9.8**	**8.8**	**9.4**
Number of foci			
2	53.3	54.3	54.5
3-4	18.3	16.1	16.6
≥5	12.3	7.3	9.5
Not known	16.2	22.3	19.4
Multicentricity	**2.7**	**2.7**	**2.3**
Number of quadrants			
2	85.2	85.6	90.2
3	7.1	5.1	2.0
4	5.2	1.0	2.0
Not known	2.6	8.2	5.9

2.24 In each cohort, nearly all (2006-2010: 97.6%; 2011-2015: 97.8%; 2016-current: 96.7%) the patients with invasive breast cancer were tested for ER or PR status. Among them, more than three-quarters (2006-2010: 79.3%; 2011-2015: 78.5%; 2016-current: 83.4%) were either ER or PR positive. Amplification or over-expression of HER2 oncogene is associated with the development of certain types of breast cancer. A patient with immunohistochemistry (IHC) score 3 is considered as HER2 positive, while score 0 or 1 is considered as negative. For patients with IHC score 2, In Situ Hybridization (ISH) test will be further conducted. Patients who had positive results in ISH are also considered as HER2 positive. In each of the three patient cohorts, less than one-quarter (2006-2010: 24.7%; 2011-2015: 21.5%; 2016-current: 17.5%) 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=15,368)

	2006-2010 (N=5,787) %	2011-2015 (N=7,330) %	2016-current (N=2,251) %
Estrogen receptor (ER) [% had the test]	**[97.5]**	**[97.8]**	**[96.7]**
Positive	76.3	77.7	82.8
Negative	23.7	22.3	17.2
Progesterone receptor (PR) [% had the test]	**[97.3]**	**[97.6]**	**[96.3]**
Positive	63.9	65.1	69.3
Negative	36.1	34.9	30.7
c-erbB2 / HER2 [% had the test]	**[96.7]**	**[97.0]**	**[94.0]**
Positive (IHC Score 3)	23.7	18.3	14.6
Equivocal (IHC Score 2) ISH positive	1.0	3.2	2.9
Equivocal (IHC Score 2) ISH equivocal	0.2	1.2	1.8
Equivocal (IHC Score 2) ISH negative	10.4	22.0	17.0
Equivocal (IHC Score 2) ISH not done	14.2	10.6	9.3
Negative (IHC Score 0 / 1)	50.4	44.6	54.4
Ki-67 index [% had the test]	**[51.2]**	**[54.9]**	**[70.7]**
<14%	42.8	34.9	31.3
≥14%	57.2	65.1	68.7

HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; ISH: In situ hybridization

2.25 Breast cancer is not considered to be a single disease and can be further classified into several biological subtypes[36] by immunohistochemical staining of several biological markers (Table 2.16). 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 set out in Table 2.17.

Table 2.17: Biological subtypes of invasive tumours by cancer stage (N=14,497)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current														
	I			IIA			IIB			III			IV		
Luminal A*	27.7	25.7	33.3	17.0	16.2	18.4	18.6	12.3	11.0	11.3	10.7	12.8	6.1	8.8	13.2
Luminal B (HER2-ve)#	13.2	17.5	32.3	16.9	22.0	35.7	17.9	21.8	38.5	19.8	21.6	29.3	12.1	22.3	36.8
Luminal A/B (HER2-ve)†	28.1	29.1	13.5	27.2	26.1	16.7	27.8	30.8	21.3	26.2	28.2	23.0	30.3	20.9	13.2
Luminal B (HER2+ve)^	13.5	9.6	8.4	15.3	11.1	12.1	15.7	12.8	8.6	20.1	17.1	14.5	28.8	18.9	15.8
HER2 Positive❉	7.7	8.1	5.4	8.8	9.9	5.3	9.5	8.6	6.5	11.7	11.9	8.6	16.7	16.9	10.5
TND§	9.6	9.9	7.1	14.8	14.7	11.8	10.6	13.7	14.1	11.0	10.5	11.8	6.1	12.2	10.5

Total number of patients in each group:

I: 2,026 (for 2006-2010), 2,587 (for 2011-2015), 784 (for 2016-current)

IIA: 1,710 (for 2006-2010), 1,983 (for 2011-2015), 603 (for 2016-current)

IIB: 823 (for 2006-2010), 1,061 (for 2011-2015), 291 (for 2016-current

III: 906 (for 2006-2010), 1,170 (for 2011-2015), 301 (for 2016-current)

IV: 66 (for 2006-2010), 148 (for 2011-2015), 38 (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

§ TND (Triple Negative Disease): ER and PR-, HER2-, and any Ki-67 index

B. In situ breast cancer

2.26 Ductal cancer was found to be the most common (92.6%-93.6%) type of in situ breast cancer in each cohort. Table 2.18 shows the histological characteristics, grading, multifocality and multicentricity of in situ breast cancer in the three patient cohorts.

2.27 In each cohort, one-half to three-quarters (2006-2010: 74.5%; 2011-2015: 70.4%; 2016-current: 54.3%) of the patients with in situ breast cancer were tested for ER or PR status. Among them, the majority (2006-2010: 82.5%; 2011-2015: 81.7%; 2016-current: 84.2%) were either ER or PR positive. Table 2.19 shows the biological characteristics of in situ breast cancer in the three patient cohorts. C-erbB2/HER2 positive was found in 17.5%-28.9% of the in situ breast cancer patients in the three cohorts.

Table 2.18: Histological type, grading, multifocality and multicentricity of in situ breast cancer (N=2,373)

	2006-2010 (N=903) %	2011-2015 (N=1,109) %	2016-current (N=361) %
Histological type			
Ductal	93.6	92.6	93.1
Mixed	3.0	2.6	1.1
Papillary	1.3	1.7	1.9
Intracystic papillary	0.8	0.8	0.3
Encapsulated papillary	0.1	0.7	0.8
Apocrine	0.1	0.5	0.6
Neuroendocrine	0.1	0.2	0.0
Cribriform	0.0	0.1	0.3
Micropapillary	0.1	0.0	0.0
Not known	0.9	0.8	1.9
Necrosis	**39.0**	**30.7**	**24.7**
Nuclear grade			
Low	24.6	25.0	27.1
Intermediate	33.1	31.6	33.2
High	37.8	36.4	31.3
Not known	4.6	7.1	8.4
Multifocality	**12.4**	**11.5**	**9.7**
Number of foci			
2	50.9	39.8	62.9
3	7.1	8.6	8.6
4 or more	4.5	3.9	0.0
Not known	37.5	47.7	28.6
Multicentricity	**2.4**	**2.3**	**1.4**
Number of quadrants			
2	81.8	84.6	100.0
3	4.5	7.7	0.0
Not known	13.6	7.7	0.0

Table: 2.19: Biological characteristics of in situ breast cancer (N=2,373)

	2006-2010 (N=903) %	2011-2015 (N=1,109) %	2016-current (N=361) %
Estrogen receptor (ER) [% had the test]	**[74.5]**	**[70.3]**	**[54.3]**
Positive	80.4	81.4	84.2
Negative	19.6	18.6	15.8
Progesterone receptor (PR) [% had the test]	**[73.5]**	**[68.6]**	**[51.5]**
Positive	71.2	72.4	78.5
Negative	28.8	27.6	21.5
c-erbB2 / HER2 [% had the test]	**[70.2]**	**[62.0]**	**[46.0]**
Positive (IHC Score 3)	28.7	24.7	17.5
Equivocal (IHC Score 2) ISH positive	0.2	0.1	0.0
Equivocal (IHC Score 2) ISH equivocal	0.0	0.1	0.0
Equivocal (IHC Score 2) ISH negative	1.4	1.3	1.2
Equivocal (IHC Score 2) ISH not done	28.1	38.1	34.9
Negative (IHC Score 0 / 1)	41.6	35.6	46.4
Ki-67 index [% had the test]	**[44.9]**	**[37.6]**	**[40.7]**
<14%	71.9	60.7	52.4
≥14%	28.1	39.3	47.6

HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; ISH: In situ hybridization

V. Treatment methods

2.28 In each patient cohort, about one-eighth (2006-2010: 14.5%; 2011-2015: 10.0%; 2016-current: 14.0%) received care at private medical service, around half (2006-2010: 46.6%; 2011-2015: 53.6%; 2016-current: 52.4%) received care at public medical service, and one-third (2006-2010: 38.8%; 2011-2015: 36.4%; 2016-current: 33.6%) received care at both private and public medical services. Patients with invasive tumours are usually given multimodality treatments, which may include surgery, chemotherapy, anti-HER2 targeted therapy, endocrine therapy and radiotherapy. In contrast, patients with in situ tumours require less aggressive treatments including surgery, endocrine therapy, and radiotherapy. Chemotherapy and anti-HER2 targeted therapy are generally not required for patients with in situ tumour. These treatments, except surgery, may be applied in adjuvant (after surgery), neoadjuvant (before surgery) or palliative (for metastatic disease) settings, according to the cancer stage at diagnosis.

A. Surgical treatment

2.29 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.

2.30 Nodal surgery is usually performed together with breast surgery to ascertain the extent of the 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.

2.31 In the cohorts, about half (2006-2010: 53.5%; 2011-2015: 47.0%; 2016-current: 49.5%) of the patients had surgery at private medical facilities, while the other half (2006-2010: 46.5%; 2011-2015: 53.0%; 2016-current: 50.5%) had surgery at public medical facilities.

2.32 For those patients with invasive tumour, the majority (97.5%-98.4%) underwent surgery as part of their treatment (Table 2.20). Among them, about two-thirds (58.8%-65.7%) had mastectomy, while the remainder (32.5%-38.2%) had breast-conserving surgery. Among the patients who had mastectomy, 11.3%-12.9% had either immediate or delayed reconstruction. The most common type of reconstruction was TRAM flap (67.9%-70.0%). Almost all (94.8%-96.6%) the patients with invasive tumours received nodal surgery and among them, 23.1%-50.6% required AD, and 35.5%-62.3% required SNB only.

2.33 For the patients with in situ tumour, almost all (97.2%-99.5%) underwent surgery (Table 2.21). About half (51.9%-56.9%) of them had breast-conserving surgery, while about a quarter (19.4%-27.4%) had reconstruction after mastectomy. In addition, about one-third (32.0%-37.3%) of them did not receive nodal surgery. Among those who received nodal surgery, 76.7%-96.7% had SNB only and 2.3%-19.4% had AD without SNB.

Table 2.20: Type of surgery for patients with invasive cancer

	2006-2010 %	2011-2015 %	2016-current %
Type of surgery (N=16,004)	**(N=5,988)**	**(N=7,667)**	**(N=2,349)**
No surgery	1.4	1.7	1.9
Breast-conserving surgery	32.5	33.0	38.2
Mastectomy	65.7	64.7	58.8
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	0.3	0.6
Type of mastectomy (N=10,272)	**(N=3,935)**	**(N=4,955)**	**(N=1,382)**
Total mastectomy	94.0	94.5	93.8
Skin sparing	5.0	3.6	2.3
Areolar sparing	0.2	0.2	0.0
Nipple sparing	0.5	1.5	3.7
Type not known	0.3	0.2	0.1
Type of reconstruction (N=1,233)	**(N=495)**	**(N=560)**	**(N=178)**
TRAM flap	67.9	70.0	68.0
Implant	14.1	16.8	21.3
LD flap	9.1	7.5	5.1
LD flap & implant	7.5	3.2	3.4
Type not known	1.4	2.5	2.2
Type of nodal surgery (N=15,387)	**(N=5,787)**	**(N=7,372)**	**(N=2,228)**
Sentinel node biopsy only	35.5	48.6	62.3
Axillary dissection only	50.6	33.5	23.1
Sentinel node biopsy followed by axillary dissection	13.5	16.4	14.1
Type not known	0.4	1.5	0.5

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

	2006-2010 %	2011-2015 %	2016-current %
Type of surgery (N=2,220)	**(N=856)**	**(N=1,021)**	**(N=343)**
No surgery	0.5	0.0	0.0
Breast-conserving surgery	51.9	52.4	56.9
Mastectomy	47.6	46.4	39.4
Nodal surgery only	0.0	0.0	0.0
Type of surgery not known	0.0	0.4	0.9
Not known if surgery done	0.0	0.9	2.9
Type of mastectomy (N=1,016)	**(N=408)**	**(N=473)**	**(N=135)**
Total mastectomy	88.2	85.6	85.2
Skin sparing	10.8	9.5	8.1
Areolar sparing	0.0	0.8	0.0
Nipple sparing	0.7	4.0	6.7
Type not known	0.2	0.0	0.0
Type of reconstruction (N=234)	**(N=79)**	**(N=118)**	**(N=37)**
TRAM flap	67.1	59.3	54.1
Implant	21.5	31.4	35.1
LD flap	3.8	5.9	8.1
LD flap & implant	7.6	2.5	0.0
Type not known	0.0	0.8	2.7
Type of nodal surgery (N=1,480)	**(N=571)**	**(N=694)**	**(N=215)**
Sentinel node biopsy only	76.7	91.2	96.7
Axillary dissection only	19.4	5.9	2.3
Sentinel node biopsy followed by axillary dissection	3.3	1.3	0.9
Type not known	0.5	1.6	0.0

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

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

Table 2.22: Type of surgery by age group (N=17,412)

	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	0.0	0.0	44.2	55.6	70.0	48.0	46.8	49.7	41.3	44.6	49.9	32.2	36.1	44.6	26.9	25.4	32.8	12.9	18.8	19.2	14.7	10.7	10.5
Mastectomy	0.0	0.0	0.0	32.7	11.1	15.0	33.4	32.3	29.3	47.1	43.0	34.7	62.4	58.8	48.6	71.3	72.6	66.2	86.8	81.0	80.8	85.3	89.3	89.5
Mastectomy + Reconstruction	0.0	100.0	0.0	23.1	33.3	15.0	18.5	20.8	21.0	11.6	12.4	15.3	5.4	5.0	6.7	1.8	2.1	1.0	0.3	0.2	0.0	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), 45 (for 2011-2015), 20 (for 2016-current)
30-39: 664 (for 2006-2010), 662 (for 2011-2015), 181 (for 2016-current)
40-49: 2,464 (for 2006-2010), 2,510 (for 2011-2015), 685 (for 2016-current)
50-59: 2,099 (for 2006-2010), 2,830 (for 2011-2015), 831 (for 2016-current)
60-69: 850 (for 2006-2010), 1,699 (for 2011-2015), 628 (for 2016-current)
70-79: 318 (for 2006-2010), 504 (for 2011-2015), 172 (for 2016-current)
80+: 75 (for 2006-2010), 84 (for 2011-2015), 38 (for 2016-current)

Table 2.23: Type of surgery by tumour size (N=16,193)

	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	34.0	37.7	42.9	42.9	46.3	52.7	50.7	48.8	66.1	45.2	47.1	53.2	26.4	26.4	30.4	6.1	8.3	9.5
Mastectomy	44.0	54.9	50.0	47.0	44.5	37.1	43.5	43.1	27.8	49.2	47.9	41.2	64.3	65.2	61.1	72.6	75.1	65.5
Mastectomy + Reconstruction	22.0	7.4	7.1	10.1	9.2	10.2	5.8	8.1	6.0	5.7	5.0	5.6	9.4	8.4	8.6	21.3	16.6	25.0

Total number of patients in each group:

≤0.10 cm: 100 (for 2006-2010), 122 (for 2011-2015), 42 (for 2016-current)
0.11-0.50 cm: 368 (for 2006-2010), 533 (for 2011-2015), 167 (for 2016-current)
0.51-1.00 cm: 672 (for 2006-2010), 778 (for 2011-2015), 248 (for 2016-current)
1.01-2.00 cm: 2,243 (for 2006-2010), 2,657 (for 2011-2015), 803 (for 2016-current)
2.01-5.00 cm: 2,680 (for 2006-2010), 3,160 (for 2011-2015), 935 (for 2016-current)
>5.00 cm: 264 (for 2006-2010), 337 (for 2011-2015), 84 (for 2016-current)

Table 2.24: Type of surgery by cancer stage (N=17,464)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current														
	0			I			II			III			IV		
Breast-conserving surgery	52.1	53.1	59.0	46.9	47.3	56.0	30.6	31.6	34.7	12.8	14.3	14.9	6.9	7.9	19.0
Mastectomy	38.6	35.5	30.3	46.7	47.0	38.0	61.1	61.5	57.2	76.1	74.9	75.9	81.6	79.2	76.2
Mastectomy + Reconstruction	9.3	11.3	10.7	6.4	5.8	6.0	8.3	7.0	8.1	11.0	10.8	9.1	11.5	12.9	4.8

Total number of patients in each group:

0: 849 (for 2006-2010), 1,005 (for 2011-2015), 327 (for 2016-current)
I: 2,127 (for 2006-2010), 2,711 (for 2011-2015), 836 (for 2016-current)
II: 2,642 (for 2006-2010), 3,164 (for 2011-2015), 960 (for 2016-current)
II: 960 (for 2006-2010), 1,248 (for 2011-2015), 328 (for 2016-current)
IV: 87 (for 2006-2010), 178 (for 2011-2015), 42 (for 2016-current)

2.36 The proportion of those 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).

2.37 A higher proportion of the patients who had surgery at private medical facilities (44.9%-53.1%) underwent breast-conserving surgery than those who had surgery at public medical facilities (25.6%-31.4%) (Table 2.25).

Table 2.25: Type of surgery by type of medical service users (N=17,299)

	Type of medical service users % for 2006-2010, % for 2011-2015, % for 2016-current					
	Private			Public		
Breast-conserving surgery	44.9	45.5	53.1	25.6	28.1	31.4
Mastectomy	46.0	45.1	36.4	66.3	65.2	62.7
Mastectomy + Reconstruction	9.0	9.3	10.5	8.0	6.7	5.9

Total number of patients in each group:

Private: 3,493 (for 2006-2010), 3,878 (for 2011-2015), 1,258 (for 2016-current)

Public: 3,036 (for 2006-2010), 4,360 (for 2011-2015), 1,274 (for 2016-current)

2.38 SNB without AD was more commonly performed on the patients with negative clinical nodal status (45.2%-79.9%) than those with positive clinical nodal status (10.0%-23.1%). On the other hand, AD without SNB was more commonly performed on the patients with positive clinical nodal status (58.3%-80.5%) than those with negative clinical nodal status (9.0%-41.5%). Table 2.26 shows the type of nodal surgery received by the patients with positive or negative clinical nodal status in the three patient cohorts.

2.39 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=16,773)

	Clinical nodal status % for 2006-2010, % for 2011-2015, % for 2016-current					
	Negative			Positive		
SNB	45.2	63.7	79.9	10.0	19.5	23.1
SNB followed by AD	13.2	15.9	11.2	9.5	13.5	18.6
AD	41.5	20.4	9.0	80.5	67.0	58.3

Total number of patients in each group:

Negative: 5,282 (for 2006-2010), 6,044 (for 2011-2015), 1,827 (for 2016-current)

Positive: 1,068 (for 2006-2010), 1,933 (for 2011-2015), 619 (for 2016-current)

SNB: sentinel node biopsy; AD: axillary dissection

Table 2.27: Type of nodal surgery for invasive cancer by cancer stage (N=14,959)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current														
	I			IIA			IIB			III			IV		
SNB	62.7	82.8	91.7	35.8	53.6	72.3	9.5	15.9	25.3	3.0	5.7	12.2	2.3	9.1	25.6
SNB followed by AD	5.1	5.8	2.7	16.8	17.9	15.3	27.9	36.5	39.0	14.2	21.5	20.4	4.6	9.1	10.3
AD	32.1	11.5	5.7	47.5	28.6	12.4	62.6	47.6	35.7	82.8	72.8	67.4	93.1	81.8	64.1

Total number of patients in each group:

I: 2,087 (for 2006-2010), 2,646 (for 2011-2015), 830 (for 2016-current)

IIA: 1,753 (for 2006-2010), 2,013 (for 2011-2015), 635 (for 2016-current)

IIB: 850 (for 2006-2010), 1,083 (for 2011-2015), 300 (for 2016-current)

III: 939 (for 2006-2010), 1,213 (for 2011-2015), 319 (for 2016-current)

IV: 87 (for 2006-2010), 165 (for 2011-2015), 39 (for 2016-current)

SNB: sentinel node biopsy; AD: axillary dissection

2.40 About half (56.4%-60.1%) of the patients with node positive invasive cancer had tumours of two to five cm in size, while about one-tenth (8.0%-9.0%) had tumours larger than five cm. In the patient cohorts, more patients with node negative invasive cancer (62.2%-64.7%) had tumours of less than two cm compared to patients with node positive invasive cancer (31.1%-34.6%) (Table 2.28).

2.41 Of the patients in the cohorts, 94.6%-96.9% who underwent only SNB had no positive lymph node, while 32.8%-51.2% who underwent only AD and 8.5%-20.6% who underwent AD after SNB had no positive lymph node (Table 2.29).

Table 2.28: Distribution of tumour size in invasive cancer with negative or positive nodal status (N=12,652)

	Nodal status % for 2006-2010, % for 2011-2015, % for 2016-current					
	Negative			Positive		
≤ 0.10 cm	2.4	2.3	2.7	0.5	0.3	0.0
0.11-0.50 cm	6.8	8.5	8.1	1.7	2.1	1.3
0.51-1.00 cm	13.0	12.7	13.9	4.0	3.8	2.2
1.01-2.00 cm	40.0	40.9	40.0	28.4	27.3	27.6
2.01-5.00 cm	35.9	33.8	33.7	56.4	58.5	60.1
>5.00 cm	1.9	1.7	1.6	9.0	8.0	8.8

Total number of patients in each group:

Negative: 3,065 (for 2006-2010), 3,663 (for 2011-2015), 1,154 (for 2016-current)

Positive: 1,936 (for 2006-2010), 2,240 (for 2011-2015), 594 (for 2016-current)

Table 2.29: Number of positive nodes by types of nodal surgery (N=14,852)

	Types of nodal surgery % for 2006-2010, % for 2011-2015, % for 2016-current								
	SNB			SNB followed by AD			AD		
0 +ve nodes	96.9	96.5	94.6	20.6	14.3	8.5	51.2	40.8	32.8
1-3 +ve nodes	2.7	3.1	4.3	60.9	63.3	70.7	25.9	30.3	35.5
4-9 +ve nodes	0.4	0.4	0.8	14.8	16.6	13.5	14.2	17.9	19.0
10+ +ve nodes	0.0	0.1	0.3	3.7	5.8	7.3	8.7	11.0	12.7

Total number of patients in each group:

SNB: 2,218 (for 2006-2010), 3,699 (for 2011-2015), 1,374 (for 2016-current)

SNB followed by AD: 2,887 (for 2006-2010), 2,326 (for 2011-2015), 473 (for 2016-current)

AD: 647 (for 2006-2010), 969 (for 2011-2015), 259 (for 2016-current)

SNB: sentinel node biopsy; AD: axillary dissection

B. Radiotherapy

2.42 Radiotherapy is a treatment to kill cancer cells using ionizing radiation. Radiation is capable of inflicting damage at the DNA level of a cell and can stop cells from reproducing. Radiotherapy can be administered in two settings: firstly, locoregional radiotherapy where breast, chest wall, and/or regional lymph nodes are radiated with curative intention; 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

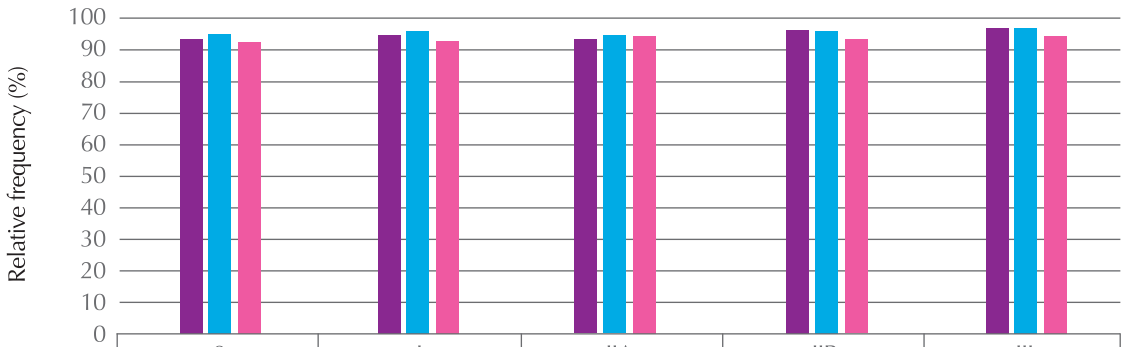
2.43 Locoregional radiotherapy to the breast following breast-conserving surgery is an integral part of breast-conserving therapy in order to achieve an outcome equivalent to mastectomy. This applies to all patients with invasive breast cancer and most patients with in situ cancer. Some patients whose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

2.44 In the patient cohorts, two-thirds (2006-2010: 62.7%; 2011-2015: 62.6%; 2016-current: 64.2%) had locoregional radiotherapy as part of their treatment, with almost all (2006-2010: 99.9%; 2011-2015: 99.7%; 2016-current: 99.9%) being adjuvant and the remainder (2006-2010: <0.1%; 2011-2015: 0.2%; 2016-current: 0.0%) neoadjuvant. About four-fifths (2006-2010: 86.9%; 2011-2015: 89.3%; 2016-current: 85.7%) of the patients were treated with radiotherapy at public medical facilities, while the remainder (2006-2010: 13.1%; 2011-2015: 10.7%; 2016-current: 14.3%) had radiotherapy at private medical facilities.

2.45 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. A high proportion (over 92%) 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 the invasive breast cancer patients who underwent mastectomy and also received locoregional radiotherapy increased significantly with progressing cancer stage (Figure 2.10).

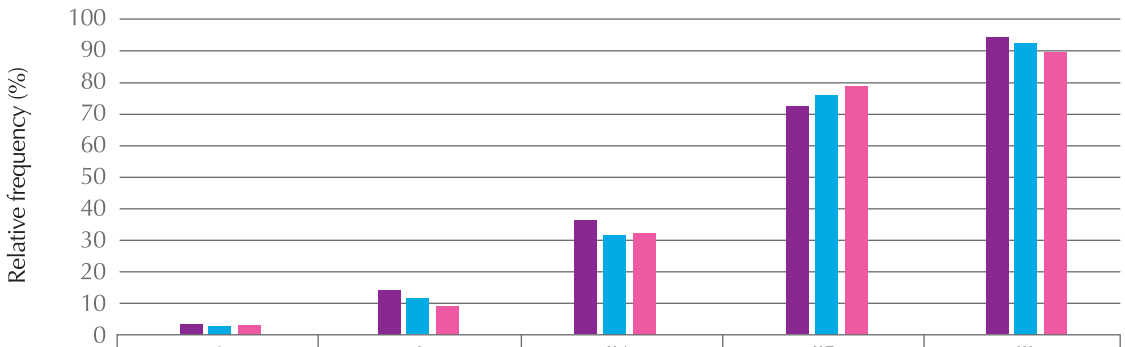
2.46 Of the patients with in situ cancer who had breast-conserving surgery, the majority (92.2%-95.3%) received locoregional radiotherapy afterwards (Figure 2.9), while only a small proportion (2.8%-3.7%) of the patients with in situ cancer who had mastectomy underwent radiotherapy (Figure 2.10).

Figure 2.9: Use of locoregional radiotherapy among patients who underwent breast-conserving surgery by cancer stage (N=6,406)



	0	I	IIA	IIB	III
2006-2010 (N=2,373)	92.8	94.6	93.7	96.3	97.6
2011-2015 (N=2,991)	95.3	95.9	94.5	96.0	97.8
2016-current (N=1,042)	92.2	92.9	94.5	93.6	93.9

Figure 2.10: Use of locoregional radiotherapy among patients who underwent mastectomy by cancer stage (N=10,725)



	0	I	IIA	IIB	III
2006-2010 (N=4,198)	3.7	14.0	37.7	73.1	94.4
2011-2015 (N=5,130)	2.8	11.4	31.9	77.3	93.3
2016-current (N=1,397)	3.0	9.3	32.8	78.6	89.9

2.47 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=7,123)

	2006-2010 (N=3,084) %	2011-2015 (N=3,195) %	2016-current (N=844) %
Breast-conserving surgery			
Breast alone	84.0	82.9	89.9
Breast and regional lymph nodes	16.0	17.1	10.1
Mastectomy			
Chest wall alone	27.6	23.2	22.8
Chest wall and regional lymph nodes	72.4	76.8	77.2

ii. Palliative radiotherapy

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

2.49 Among the patients with metastatic breast cancer, about three-fifths (2006-2010: 58.7%; 2011-2015: 57.8%; 2016-current: 63.2%) underwent palliative radiotherapy, and of these patients, 6.9%-27.3% received radiotherapy to the spine (2006-2010: 27.3%; 2011-2015: 6.9%; 2016-current: 9.3%) and 0.6%-14.8% to the pelvis (2006-2010: 14.8%; 2011-2015: 0.6%; 2016-current: 2.3%).

C. Chemotherapy

2.50 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 multiply. Chemotherapy is generally not required for patients with in situ tumour. Chemotherapy drugs are classified into three generations[37] 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.

2.51 In each cohort, about two-thirds (2006-2010: 70.7%; 2011-2015: 66.6%; 2016-current: 59.2%) of the patients with invasive cancer underwent chemotherapy. Of these patients, 77.4%-90.0% (2006-2010: 90.0%; 2011-2015: 81.1%; 2016-current: 77.4%) had adjuvant chemotherapy, 6.9%-18.8% (2006-2010: 6.9%; 2011-2015: 14.2%; 2016-current: 18.8%) had neoadjuvant chemotherapy and 3.0%-4.7% (2006-2010: 3.0%; 2011-2015: 4.7%; 2016-current: 3.8%) had palliative chemotherapy. The majority (2006-2010: 85.4%; 2011-2015: 87.0%; 2016-current: 86.9%) of the patients received chemotherapy at public medical facilities, and the remainder (2006-2010: 14.6%; 2011-2015: 13.0%; 2016-current: 13.1%) at private medical facilities.

2.52 In each patient cohort, the use of curative intent chemotherapy was positively correlated to progressing cancer stage from stage I to III (Table 2.31). In contrast, the majority (73.5%-86.2%) of the patients with stage IV breast cancer underwent palliative chemotherapy.

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

Table 2.31: Chemotherapy treatment by cancer stage (N=15,454)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current														
	I			IIA			IIB			III			IV		
Yes, neoadjvuant	<0.1	0.3	1.2	1.5	4.5	4.0	6.2	13.7	12.5	19.4	32.5	33.3	–	–	–
Yes, adjuvant	42.2	36.1	28.7	81.4	72.9	63.8	85.4	75.4	70.4	75.5	60.9	58.2	–	–	–
Yes, palliative	–	–	–	–	–	–	–	–	–	–	–	–	84.8	86.2	73.5
Not done	57.7	63.7	70.1	17.1	22.6	32.2	8.4	11.0	17.0	5.1	6.6	8.5	15.2	13.8	26.5

Total number of patients in each group:

I: 2,118 (for 2006-2010), 2,706 (for 2011-2015), 829 (for 2016-current)
IIA: 1,777 (for 2006-2010), 2,051 (for 2011-2015), 643 (for 2016-current)
IIB: 856 (for 2006-2010), 1,113 (for 2011-2015), 311 (for 2016-current)
III: 959 (for 2006-2010), 1,267 (for 2011-2015), 330 (for 2016-current)
IV: 151 (for 2006-2010), 275 (for 2011-2015), 68 (for 2016-current)

Table 2.32: Use of chemotherapy by age group and cancer stage at diagnosis (N=15,041)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current														
	I			IIA			IIB			III			IV		
20-29	76.5	54.5	36.4	93.3	80.0	100.0	100.0	100.0	100.0	100.0	100.0	–	100.0	100.0	–
30-39	61.4	57.3	46.8	89.7	91.4	89.1	100.0	98.9	94.4	100.0	99.1	96.4	100.0	91.7	62.5
40-49	49.2	43.8	31.2	93.7	86.2	79.1	97.4	95.7	94.7	99.2	98.0	98.8	96.2	95.1	85.0
50-59	42.6	37.8	38.0	91.9	85.9	77.4	97.1	96.1	92.0	97.6	98.0	95.3	88.9	85.6	88.9
60-69	22.3	28.0	21.1	70.7	71.8	59.7	87.3	92.1	83.3	96.4	93.1	94.4	87.5	82.9	66.7
70+	2.7	2.5	9.0	7.7	11.0	14.3	10.0	17.1	21.2	36.5	40.8	33.3	29.4	42.9	33.3

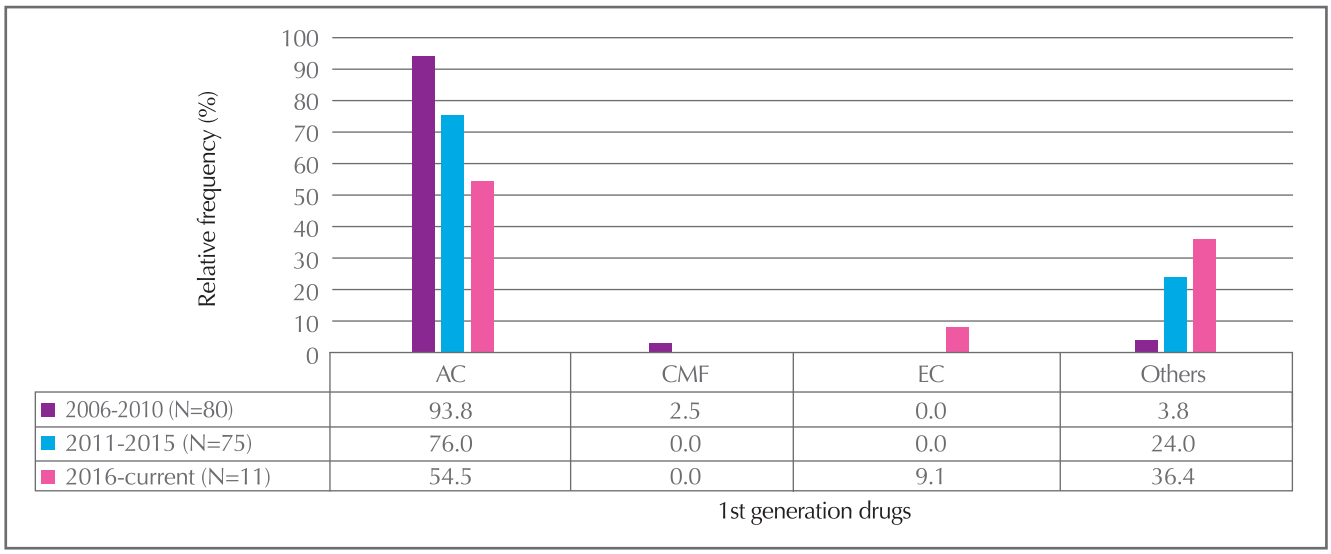
Total number of patients in each group:

I & 20-29: 18 (for 2006-2010), 11 (for 2011-2015), 11 (for 2016-current)
I & 30-39: 220 (for 2006-2010), 192 (for 2011-2015), 62 (for 2016-current)
I & 40-49: 799 (for 2006-2010), 827 (for 2011-2015), 221 (for 2016-current)
I & 50-59: 629 (for 2006-2010), 875 (for 2011-2015), 237 (for 2016-current)
I & 60-69: 247 (for 2006-2010), 522 (for 2011-2015), 204 (for 2016-current)
I & 70+: 117 (for 2006-2010), 199 (for 2011-2015), 67 (for 2016-current)
IIA & 20-29: 15 (for 2006-2010), 10 (for 2011-2015), 2 (for 2016-current)
IIA & 30-39: 194 (for 2006-2010), 163 (for 2011-2015), 46 (for 2016-current)
IIA & 40-49: 601 (for 2006-2010), 549 (for 2011-2015), 153 (for 2016-current)
IIA & 50-59: 557 (for 2006-2010), 680 (for 2011-2015), 208 (for 2016-current)
IIA & 60-69: 232 (for 2006-2010), 468 (for 2011-2015), 159 (for 2016-current)
IIA & 70+: 130 (for 2006-2010), 145 (for 2011-2015), 56 (for 2016-current)
IIB & 20-29: 10 (for 2006-2010), 6 (for 2011-2015), 2 (for 2016-current)
IIB & 30-39: 82 (for 2006-2010), 89 (for 2011-2015), 18 (for 2016-current)
IIB & 40-49: 305 (for 2006-2010), 329 (for 2011-2015), 75 (for 2016-current)
IIB & 50-59: 280 (for 2006-2010), 357 (for 2011-2015), 113 (for 2016-current)
IIB & 60-69: 118 (for 2006-2010), 228 (for 2011-2015), 66 (for 2016-current)
IIB & 70+: 40 (for 2006-2010), 78 (for 2011-2015), 33 (for 2016-current)
III & 20-29: 6 (for 2006-2010), 6 (for 2011-2015), 0 (for 2016-current)
III & 30-39: 73 (for 2006-2010), 117 (for 2011-2015), 28 (for 2016-current)
III & 40-49: 374 (for 2006-2010), 352 (for 2011-2015), 80 (for 2016-current)
III & 50-59: 295 (for 2006-2010), 445 (for 2011-2015), 106 (for 2016-current)
III & 60-69: 138 (for 2006-2010), 247 (for 2011-2015), 89 (for 2016-current)
III & 70+: 52 (for 2006-2010), 76 (for 2011-2015), 21 (for 2016-current)
IV & 20-29: 1 (for 2006-2010), 3 (for 2011-2015), 0 (for 2016-current)
IV & 30-39: 6 (for 2006-2010), 24 (for 2011-2015), 8 (for 2016-current)
IV & 40-49: 53 (for 2006-2010), 81 (for 2011-2015), 20 (for 2016-current)
IV & 50-59: 54 (for 2006-2010), 104 (for 2011-2015), 18 (for 2016-current)
IV & 60-69: 16 (for 2006-2010), 41 (for 2011-2015), 15 (for 2016-current)
IV & 70+: 17 (for 2006-2010), 14 (for 2011-2015), 6 (for 2016-current)

i. Neoadjuvant chemotherapy

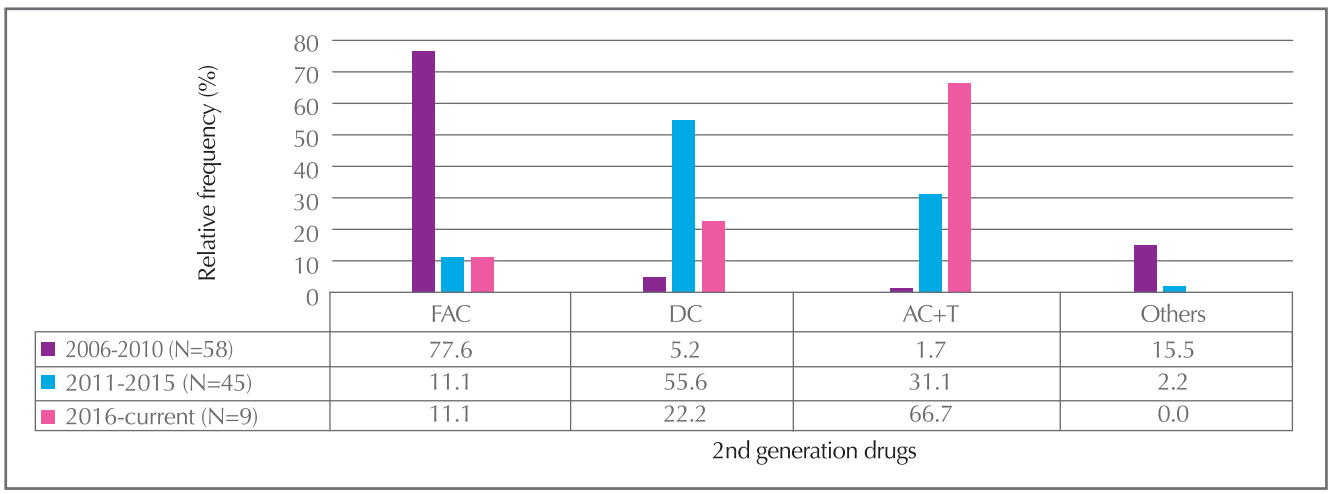
2.54 Of the patients who underwent chemotherapy in each cohort, 6.9%-18.8% (2006-2010: 6.9%; 2011-2015: 14.2%; 2016-current: 18.8%) received it as neoadjuvant treatment. The use of neoadjuvant chemotherapy increased substantially with progressing cancer stage (Table 2.31). Figures 2.11, 2.12 and 2.13 show the use of chemotherapy drugs of the three generations in neoadjuvant setting in the three cohorts. The use of HER2 regimens is shown in Figure 2.14. The generations of chemotherapy drugs used by the patients with different biological subtype in the three cohorts are shown in Figure 2.15.

Figure 2.11: Type of first generation chemotherapy drugs (non-HER2 regimen) used in neoadjuvant setting (N=166)



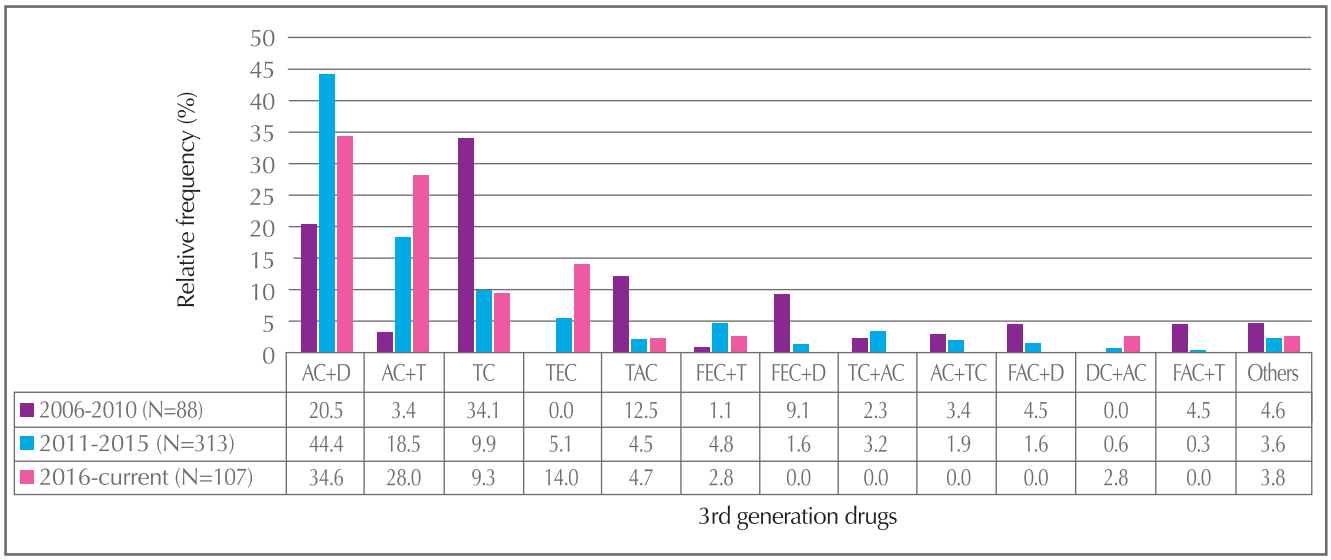
	AC	CMF	EC	Others
2006-2010 (N=80)	93.8	2.5	0.0	3.8
2011-2015 (N=75)	76.0	0.0	0.0	24.0
2016-current (N=11)	54.5	0.0	9.1	36.4

Figure 2.12: Type of second generation chemotherapy drugs (non-HER2 regimen) used in neoadjuvant setting (N=112)



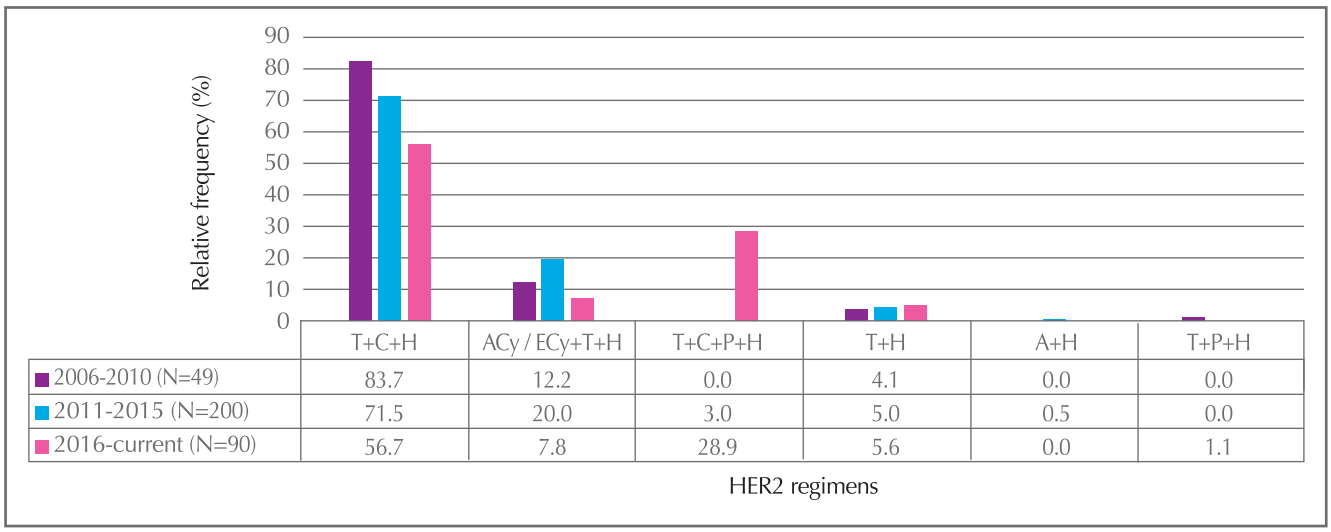
	FAC	DC	AC+T	Others
2006-2010 (N=58)	77.6	5.2	1.7	15.5
2011-2015 (N=45)	11.1	55.6	31.1	2.2
2016-current (N=9)	11.1	22.2	66.7	0.0

Figure 2.13: Type of third generation chemotherapy drugs (non-HER2 regimen) used in neoadjuvant setting (N=508)



	AC+D	AC+T	TC	TEC	TAC	FEC+T	FEC+D	TC+AC	AC+TC	FAC+D	DC+AC	FAC+T	Others
2006-2010 (N=88)	20.5	3.4	34.1	0.0	12.5	1.1	9.1	2.3	3.4	4.5	0.0	4.5	4.6
2011-2015 (N=313)	44.4	18.5	9.9	5.1	4.5	4.8	1.6	3.2	1.9	1.6	0.6	0.3	3.6
2016-current (N=107)	34.6	28.0	9.3	14.0	4.7	2.8	0.0	0.0	0.0	0.0	2.8	0.0	3.8

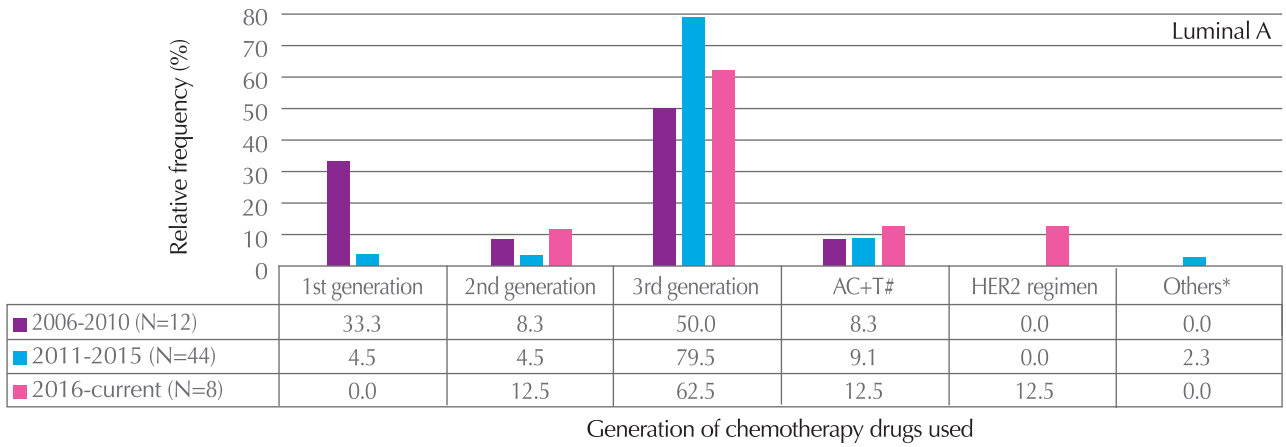
Figure 2.14: Type of HER2 regimens used in neoadjuvant setting (N=339)



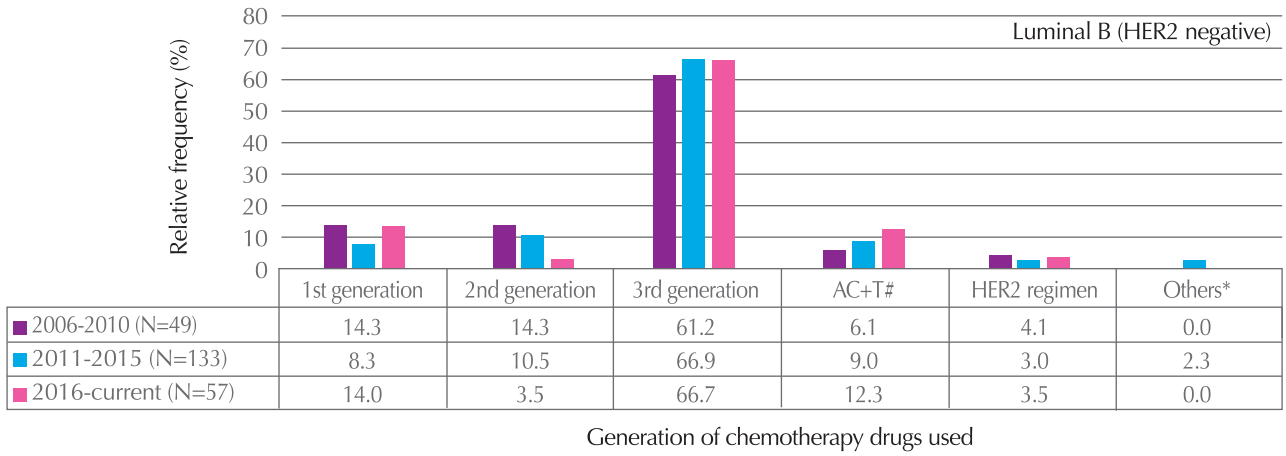
	T+C+H	ACy / ECy+T+H	T+C+P+H	T+H	A+H	T+P+H
2006-2010 (N=49)	83.7	12.2	0.0	4.1	0.0	0.0
2011-2015 (N=200)	71.5	20.0	3.0	5.0	0.5	0.0
2016-current (N=90)	56.7	7.8	28.9	5.6	0.0	1.1

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

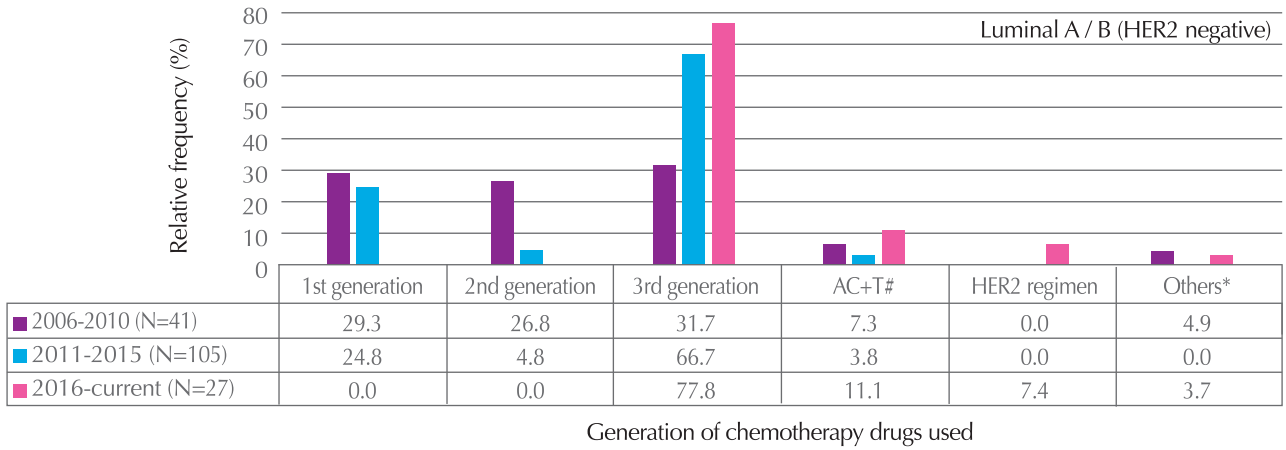
Figure 2.15: Generation of chemotherapy drugs used by biological subtype in neoadjuvant setting (N=1,025)



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=12)	33.3	8.3	50.0	8.3	0.0	0.0
2011-2015 (N=44)	4.5	4.5	79.5	9.1	0.0	2.3
2016-current (N=8)	0.0	12.5	62.5	12.5	12.5	0.0



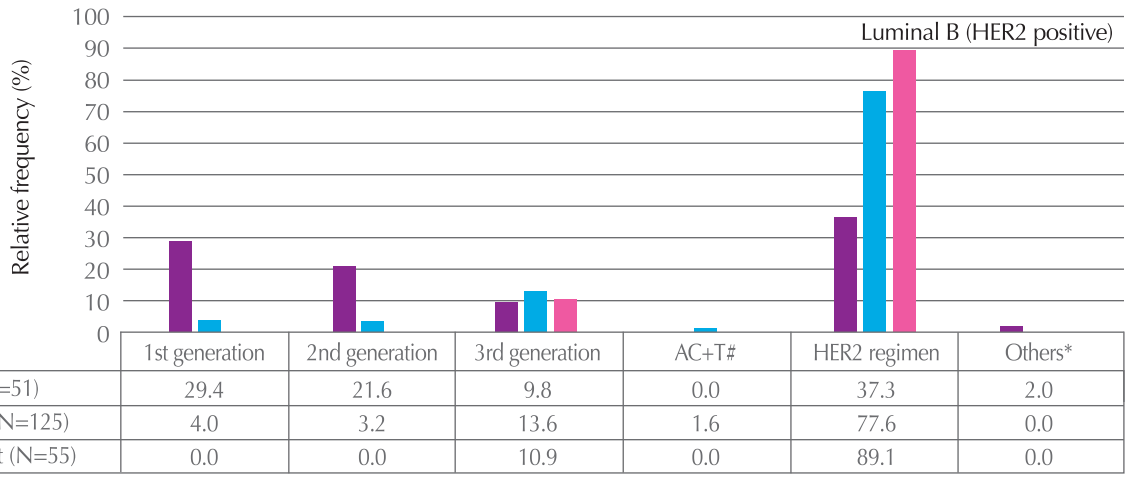
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=49)	14.3	14.3	61.2	6.1	4.1	0.0
2011-2015 (N=133)	8.3	10.5	66.9	9.0	3.0	2.3
2016-current (N=57)	14.0	3.5	66.7	12.3	3.5	0.0



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=41)	29.3	26.8	31.7	7.3	0.0	4.9
2011-2015 (N=105)	24.8	4.8	66.7	3.8	0.0	0.0
2016-current (N=27)	0.0	0.0	77.8	11.1	7.4	3.7

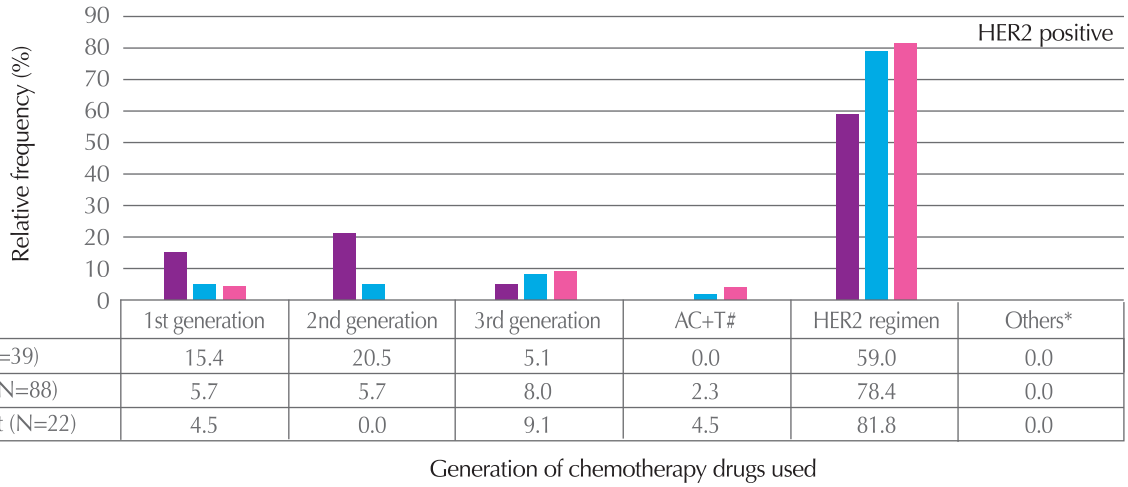
#AC+T: uncertain 2nd / 3rd generation due to uncertain week intervals
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

Figure 2.15: Generation of chemotherapy drugs used by biological subtype in neoadjuvant setting (N=1,025) (cont'd)



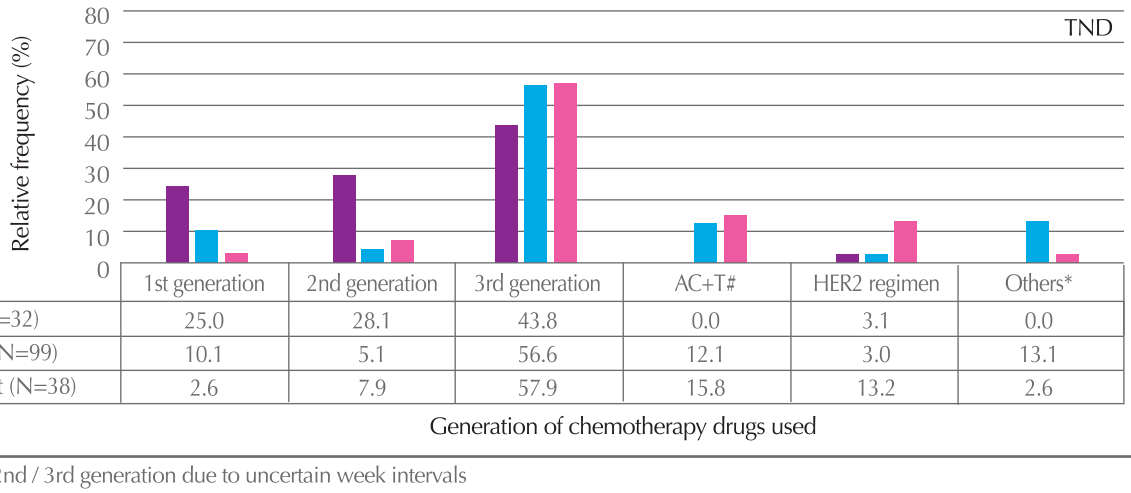
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=51)	29.4	21.6	9.8	0.0	37.3	2.0
2011-2015 (N=125)	4.0	3.2	13.6	1.6	77.6	0.0
2016-current (N=55)	0.0	0.0	10.9	0.0	89.1	0.0

Generation of chemotherapy drugs used



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=39)	15.4	20.5	5.1	0.0	59.0	0.0
2011-2015 (N=88)	5.7	5.7	8.0	2.3	78.4	0.0
2016-current (N=22)	4.5	0.0	9.1	4.5	81.8	0.0

Generation of chemotherapy drugs used



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=32)	25.0	28.1	43.8	0.0	3.1	0.0
2011-2015 (N=99)	10.1	5.1	56.6	12.1	3.0	13.1
2016-current (N=38)	2.6	7.9	57.9	15.8	13.2	2.6

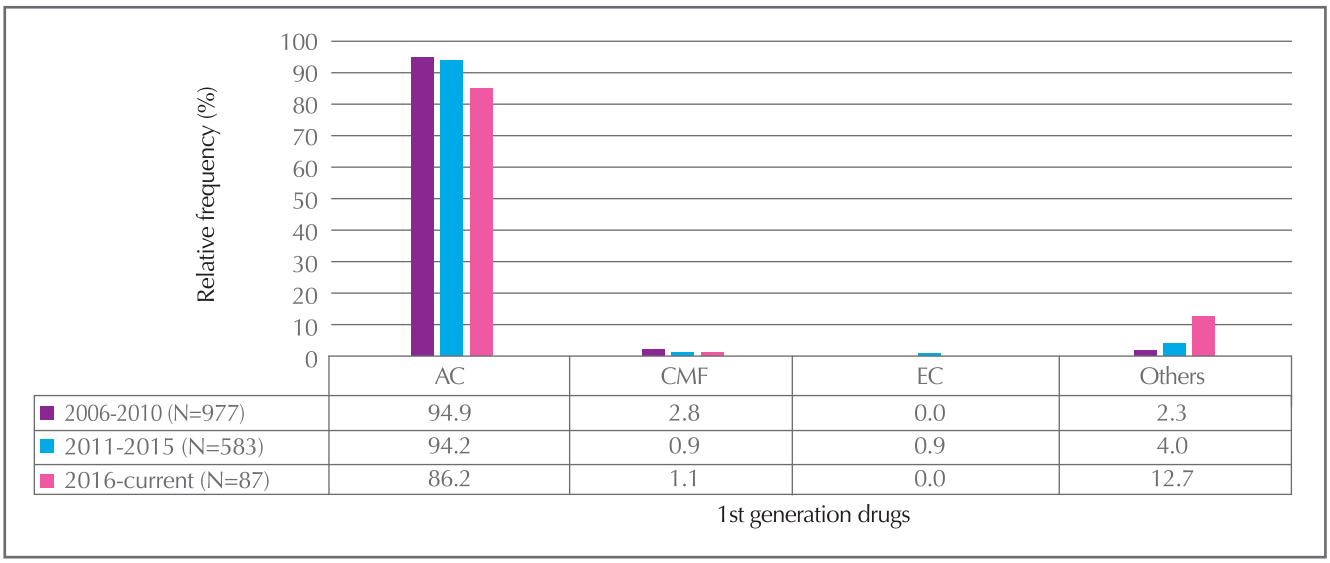
Generation of chemotherapy drugs used

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

ii. Adjuvant chemotherapy

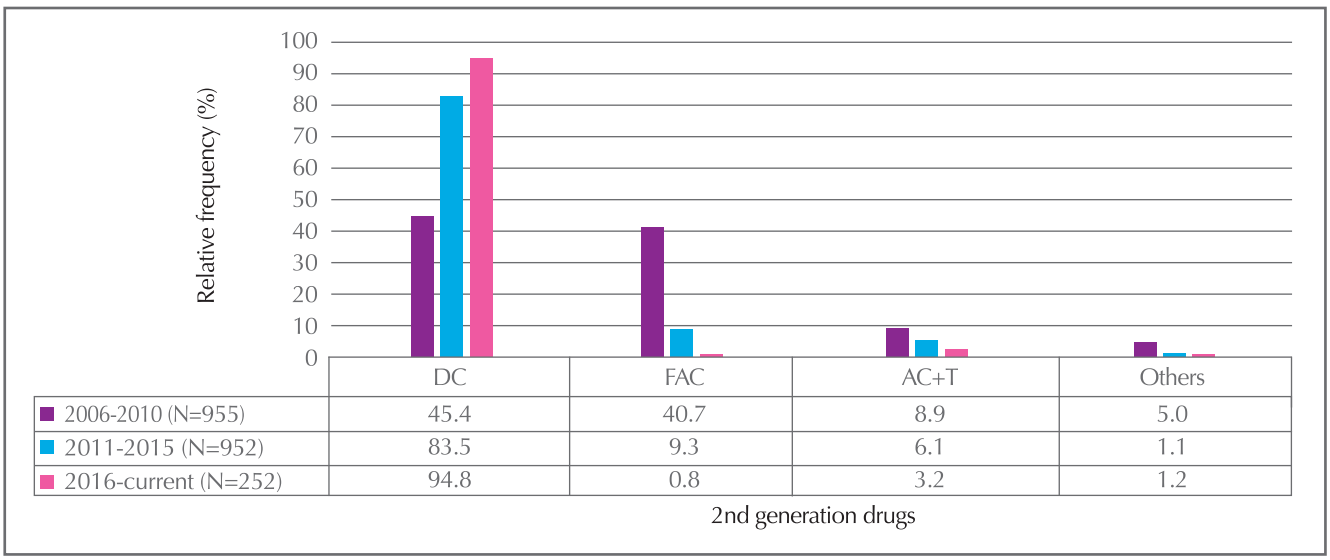
2.55 Of the patients who underwent chemotherapy in each cohort, the majority (2006-2010: 90.0%; 2011-2015: 81.1%; 2016-current: 77.4%) received it as adjuvant (stages I-III) treatment. Figures 2.16, 2.17 and 2.18 show the use of chemotherapy drugs of the three generations in adjuvant setting among the 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 drug generations used by biological subtype and cancer stage respectively.

Figure 2.16: Type of first generation chemotherapy drugs (non-HER2 regimen) used in adjuvant setting (N=1,647)



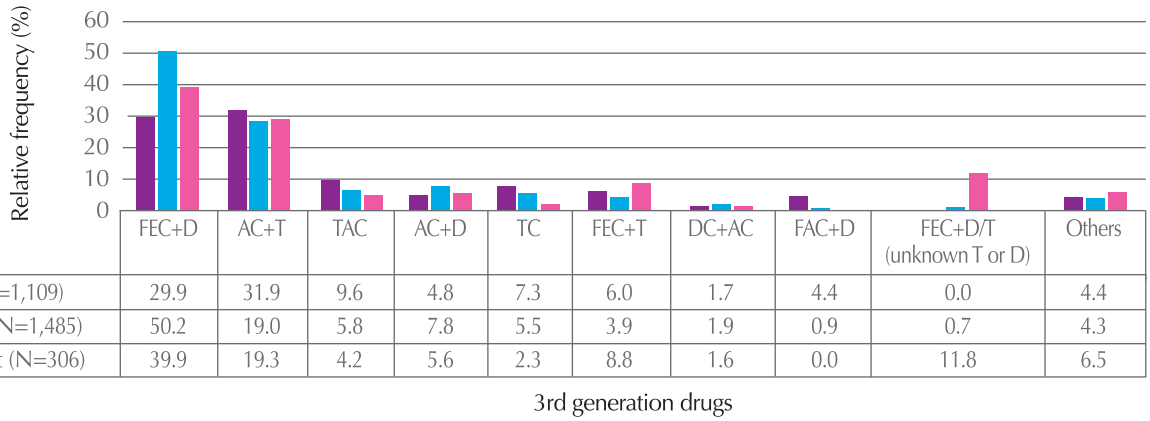
	AC	CMF	EC	Others
2006-2010 (N=977)	94.9	2.8	0.0	2.3
2011-2015 (N=583)	94.2	0.9	0.9	4.0
2016-current (N=87)	86.2	1.1	0.0	12.7

Figure 2.17: Type of second generation chemotherapy drugs (non-HER2 regimen) used in adjuvant setting (N=2,159)



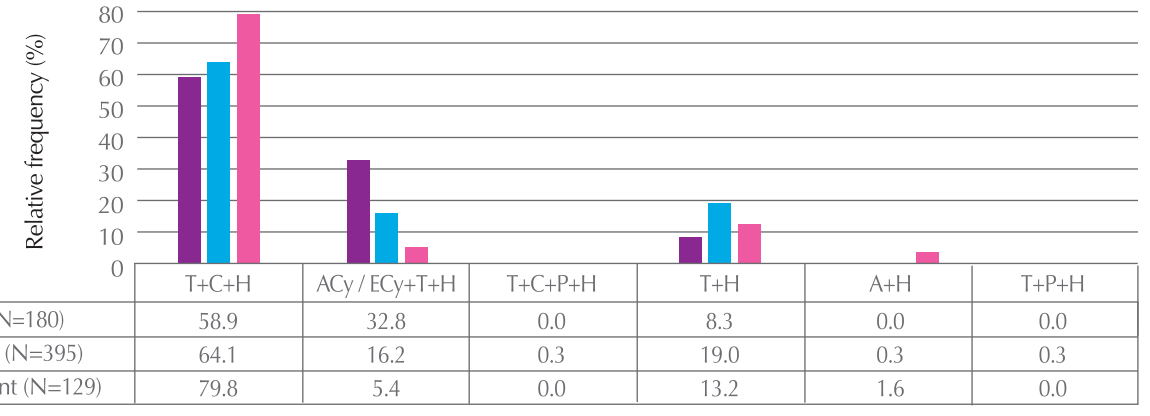
	DC	FAC	AC+T	Others
2006-2010 (N=955)	45.4	40.7	8.9	5.0
2011-2015 (N=952)	83.5	9.3	6.1	1.1
2016-current (N=252)	94.8	0.8	3.2	1.2

Figure 2.18: Type of third generation chemotherapy drugs (non-HER2 regimen) used in adjuvant setting (N=2,900)



	FEC+D	AC+T	TAC	AC+D	TC	FEC+T	DC+AC	FAC+D	FEC+D/T (unknown T or D)	Others
2006-2010 (N=1,109)	29.9	31.9	9.6	4.8	7.3	6.0	1.7	4.4	0.0	4.4
2011-2015 (N=1,485)	50.2	19.0	5.8	7.8	5.5	3.9	1.9	0.9	0.7	4.3
2016-current (N=306)	39.9	19.3	4.2	5.6	2.3	8.8	1.6	0.0	11.8	6.5

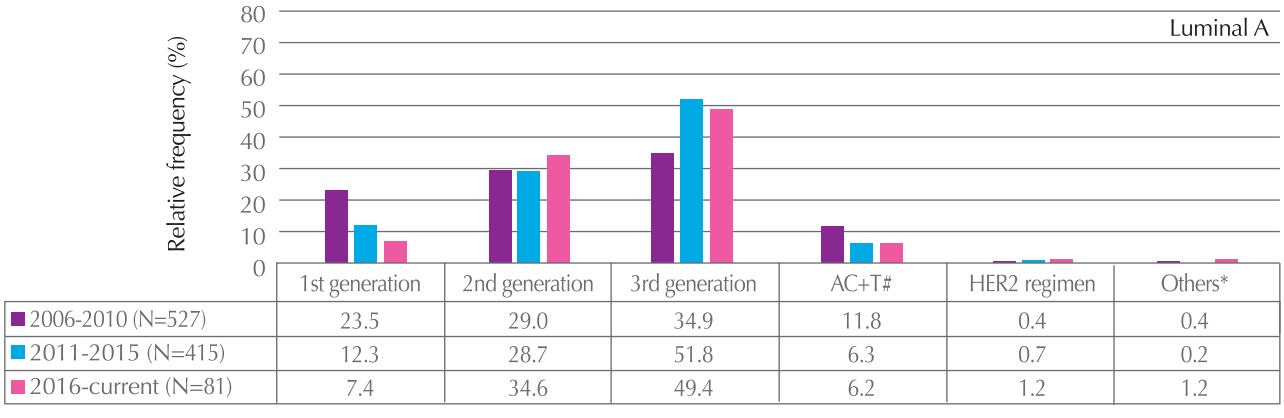
Figure 2.19: Type of HER2 regimens used in adjuvant setting (N=704)



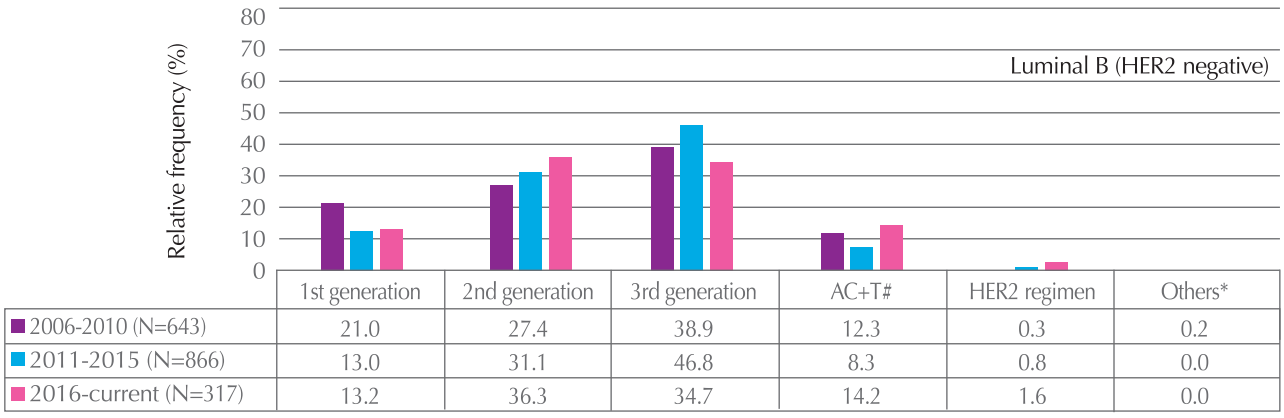
	T+C+H	ACy / ECy+T+H	T+C+P+H	T+H	A+H	T+P+H
2006-2010 (N=180)	58.9	32.8	0.0	8.3	0.0	0.0
2011-2015 (N=395)	64.1	16.2	0.3	19.0	0.3	0.3
2016-current (N=129)	79.8	5.4	0.0	13.2	1.6	0.0

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

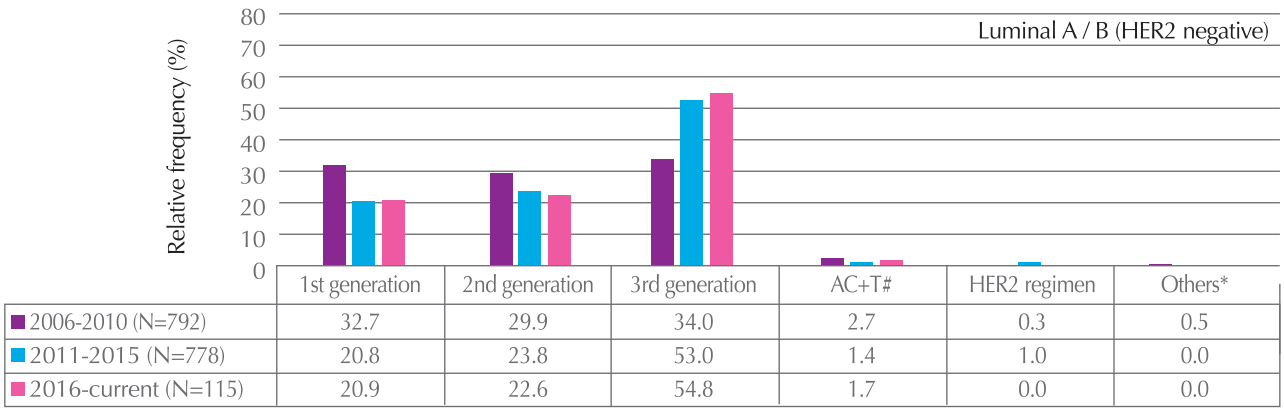
Figure 2.20: Generation of chemotherapy drugs used by biological subtype in adjuvant setting (N=7,722)



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=527)	23.5	29.0	34.9	11.8	0.4	0.4
2011-2015 (N=415)	12.3	28.7	51.8	6.3	0.7	0.2
2016-current (N=81)	7.4	34.6	49.4	6.2	1.2	1.2



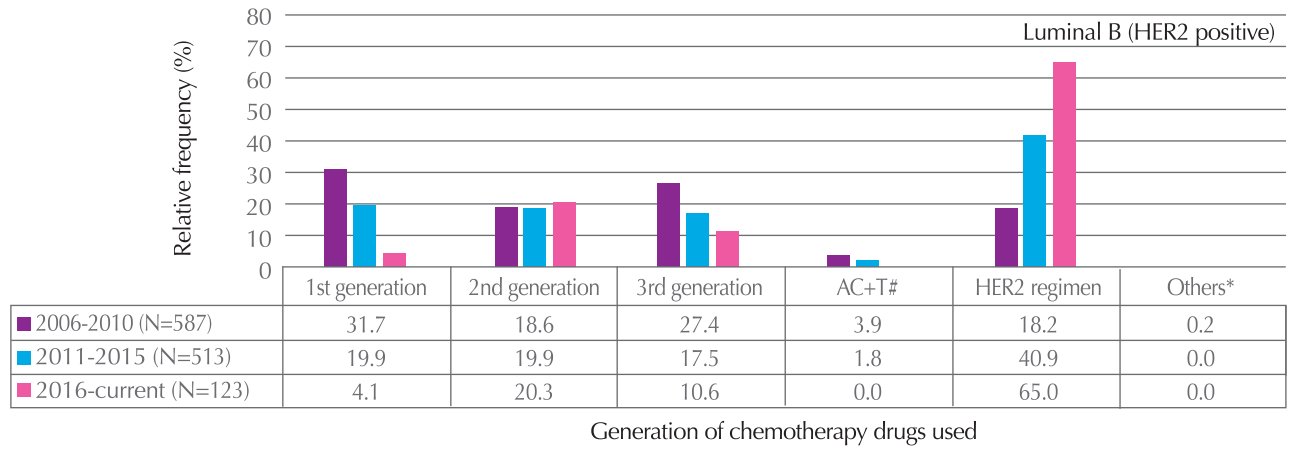
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=643)	21.0	27.4	38.9	12.3	0.3	0.2
2011-2015 (N=866)	13.0	31.1	46.8	8.3	0.8	0.0
2016-current (N=317)	13.2	36.3	34.7	14.2	1.6	0.0



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=792)	32.7	29.9	34.0	2.7	0.3	0.5
2011-2015 (N=778)	20.8	23.8	53.0	1.4	1.0	0.0
2016-current (N=115)	20.9	22.6	54.8	1.7	0.0	0.0

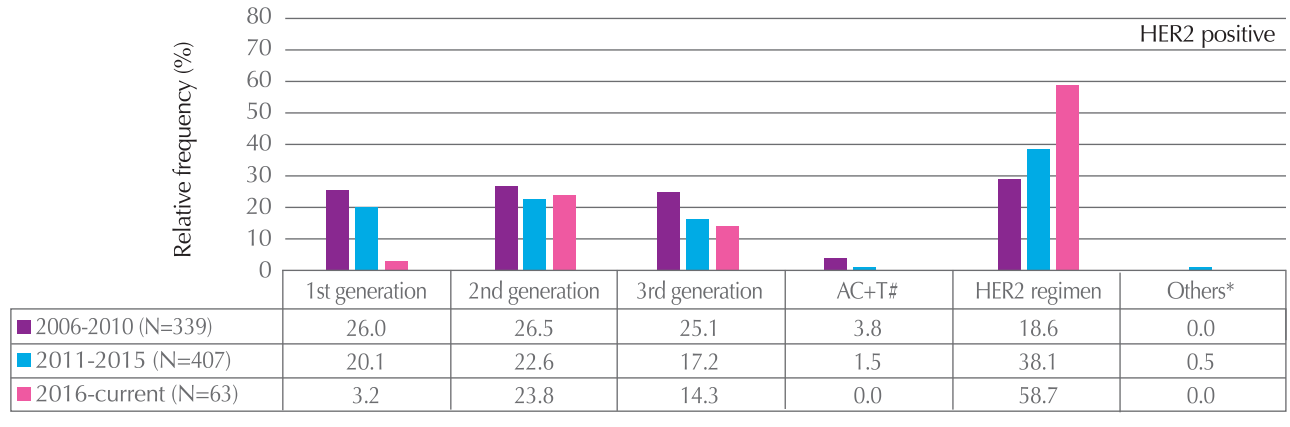
#AC+T: uncertain 2nd/3rd generation due to uncertain week intervals
*Others included any regimens containing Capecitabine, Gemcitabine, or Vinorelbine

Figure 2.20: Generation of chemotherapy drugs used by biological subtype in adjuvant setting (N=7,722) (cont'd)



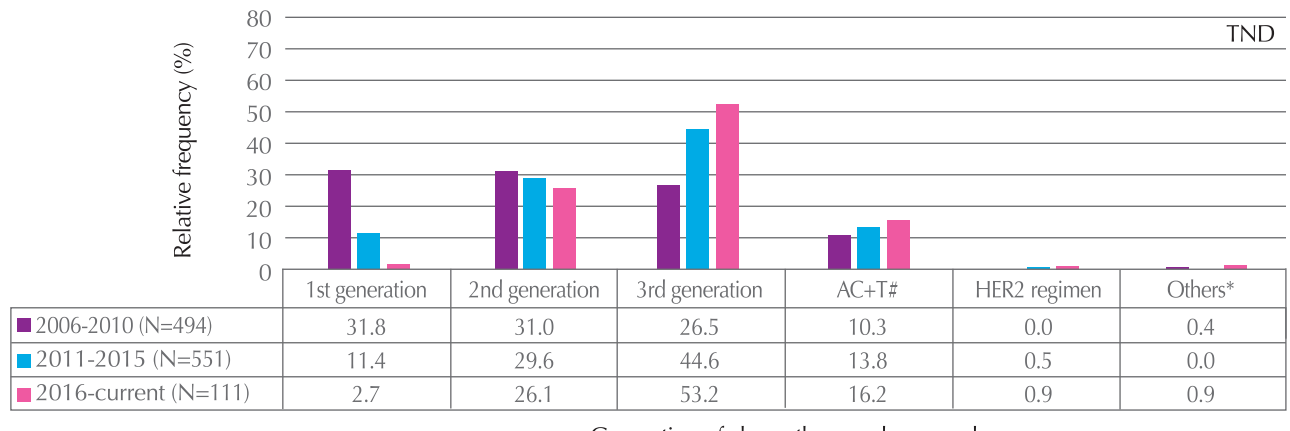
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=587)	31.7	18.6	27.4	3.9	18.2	0.2
2011-2015 (N=513)	19.9	19.9	17.5	1.8	40.9	0.0
2016-current (N=123)	4.1	20.3	10.6	0.0	65.0	0.0

Generation of chemotherapy drugs used



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=339)	26.0	26.5	25.1	3.8	18.6	0.0
2011-2015 (N=407)	20.1	22.6	17.2	1.5	38.1	0.5
2016-current (N=63)	3.2	23.8	14.3	0.0	58.7	0.0

Generation of chemotherapy drugs used

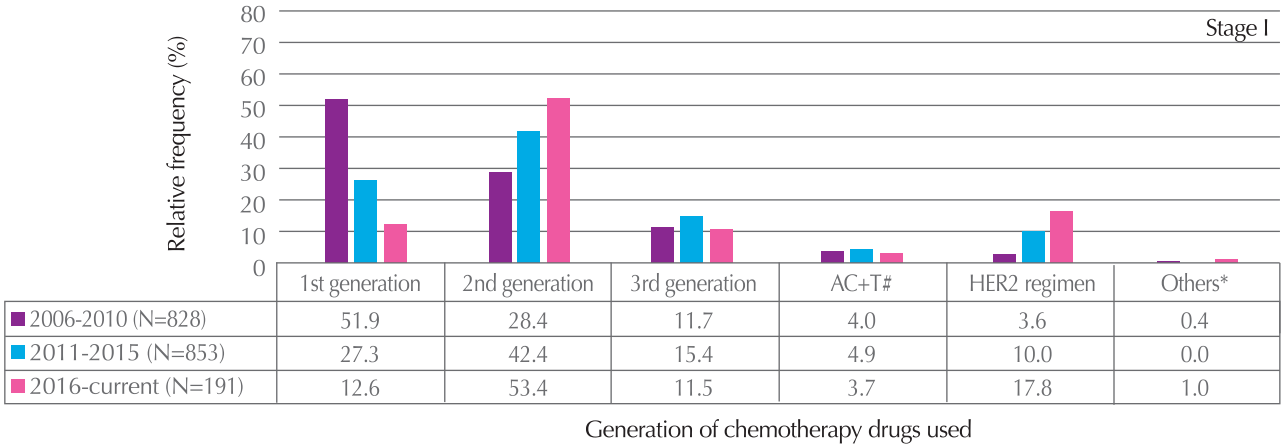


	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=494)	31.8	31.0	26.5	10.3	0.0	0.4
2011-2015 (N=551)	11.4	29.6	44.6	13.8	0.5	0.0
2016-current (N=111)	2.7	26.1	53.2	16.2	0.9	0.9

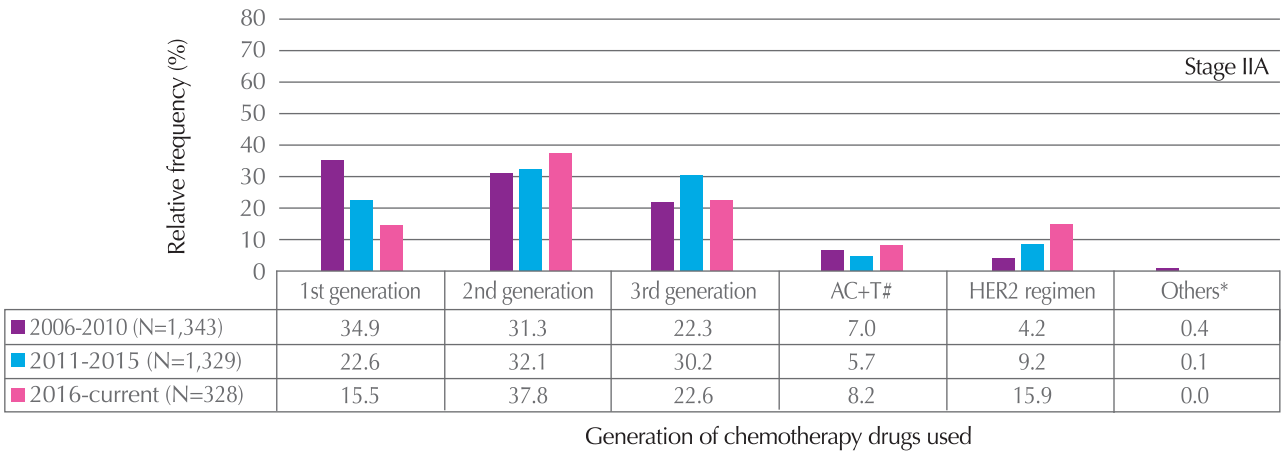
Generation of chemotherapy drugs used

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

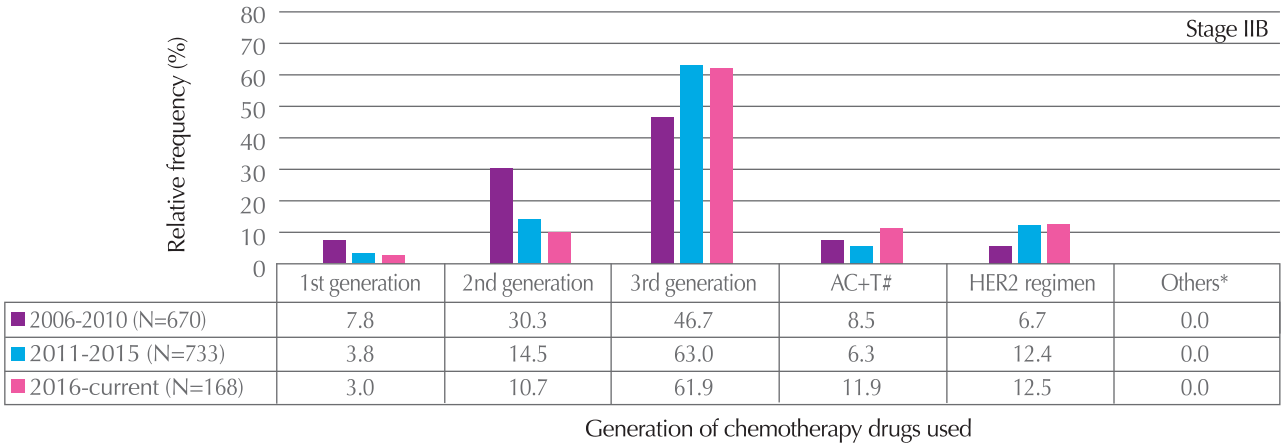
Figure 2.21: Generation of chemotherapy drugs used by cancer stage in adjuvant setting (N=7,899)



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=828)	51.9	28.4	11.7	4.0	3.6	0.4
2011-2015 (N=853)	27.3	42.4	15.4	4.9	10.0	0.0
2016-current (N=191)	12.6	53.4	11.5	3.7	17.8	1.0



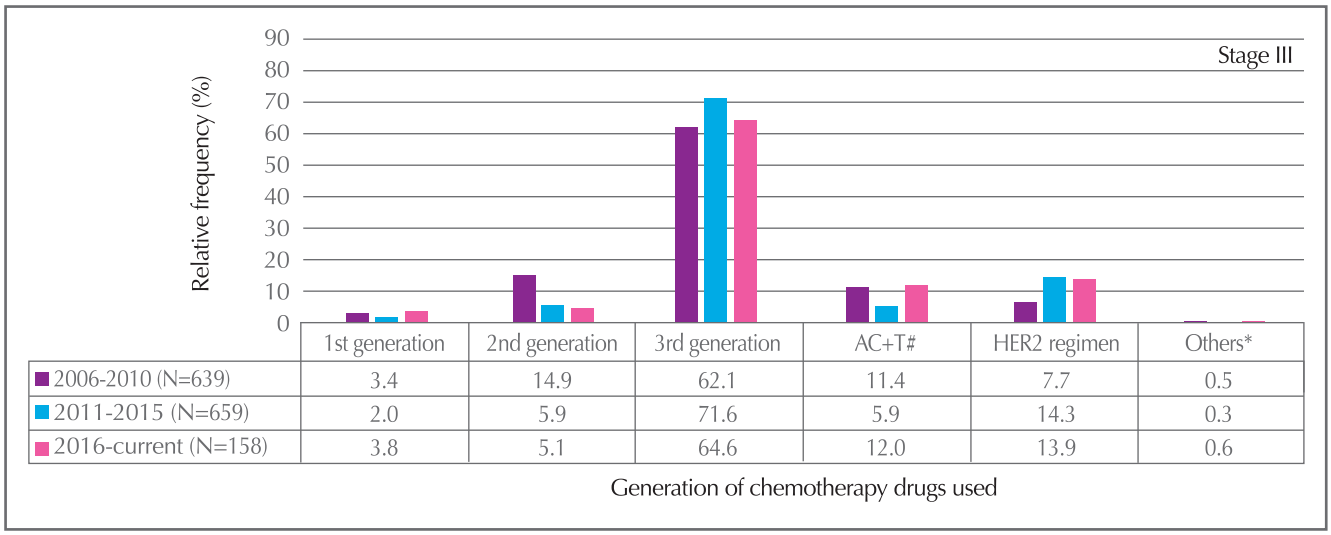
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=1,343)	34.9	31.3	22.3	7.0	4.2	0.4
2011-2015 (N=1,329)	22.6	32.1	30.2	5.7	9.2	0.1
2016-current (N=328)	15.5	37.8	22.6	8.2	15.9	0.0



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=670)	7.8	30.3	46.7	8.5	6.7	0.0
2011-2015 (N=733)	3.8	14.5	63.0	6.3	12.4	0.0
2016-current (N=168)	3.0	10.7	61.9	11.9	12.5	0.0

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

Figure 2.21: Generation of chemotherapy drugs used by cancer stage in adjuvant setting (N=7,899) (cont'd)



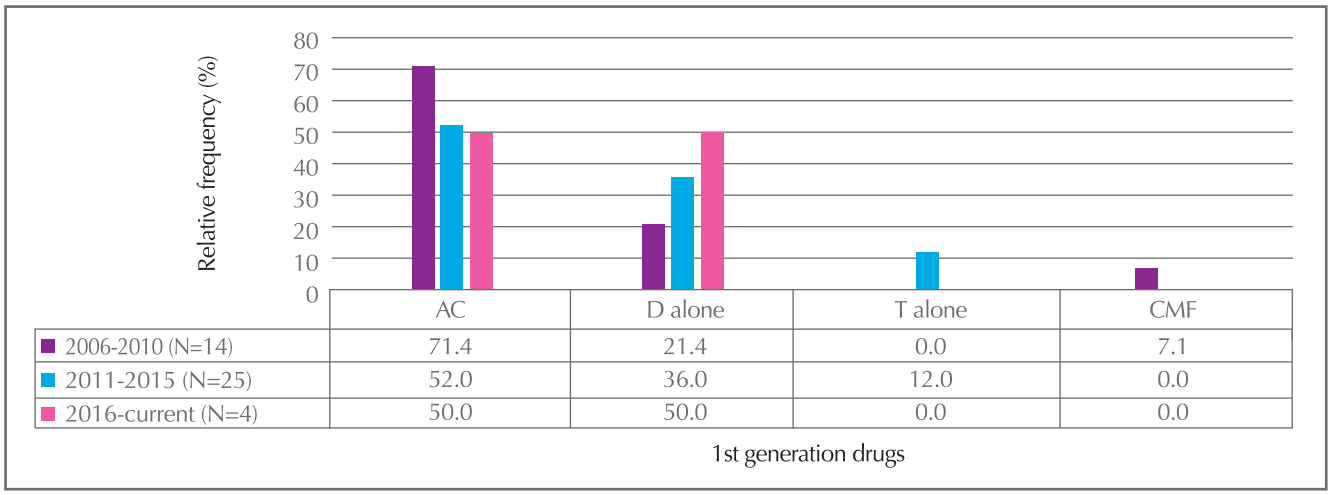
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=639)	3.4	14.9	62.1	11.4	7.7	0.5
2011-2015 (N=659)	2.0	5.9	71.6	5.9	14.3	0.3
2016-current (N=158)	3.8	5.1	64.6	12.0	13.9	0.6

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

iii. Palliative chemotherapy

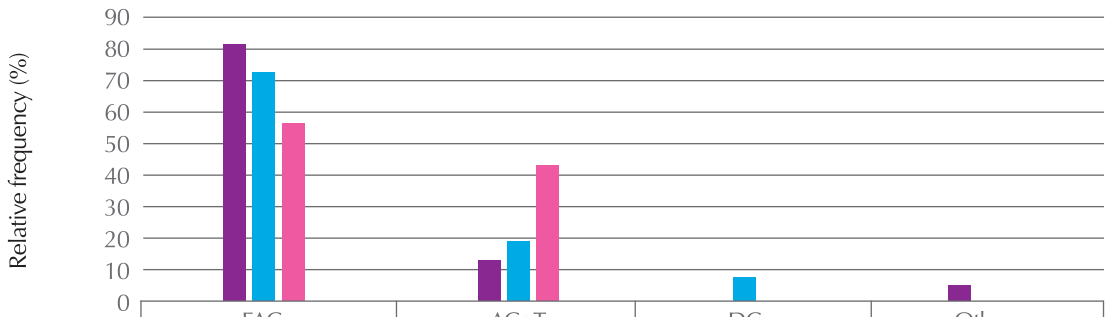
2.56 Of the patients who underwent chemotherapy, 3.0%-4.7% (2006-2010: 3.0%; 2011-2015: 4.7%; 2016-current: 3.8%) received it as palliative (stage IV) treatment. Figures 2.22, 2.23 and 2.24 show the use of chemotherapy drugs of the three generations in palliative setting in the three cohorts. The use of HER2 regimens in palliative chemotherapy is shown in Figure 2.25. Figure 2.26 shows the relative frequency for different generations of drugs used by biological subtype.

Figure 2.22: Type of first generation chemotherapy drugs (non-HER2 regimen) used in palliative setting (N=43)



	AC	D alone	T alone	CMF
2006-2010 (N=14)	71.4	21.4	0.0	7.1
2011-2015 (N=25)	52.0	36.0	12.0	0.0
2016-current (N=4)	50.0	50.0	0.0	0.0

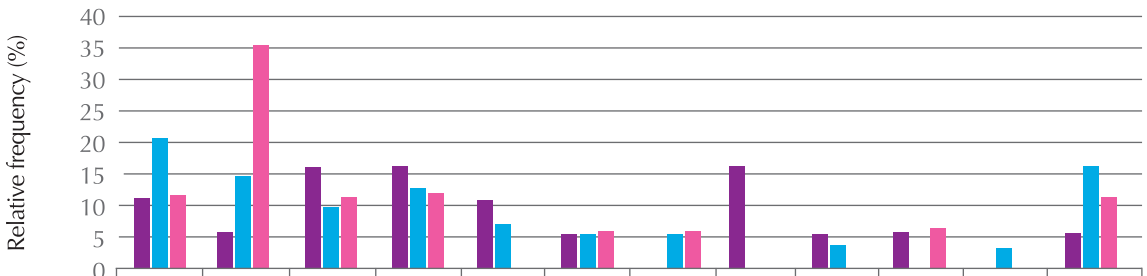
Figure 2.23: Type of second generation chemotherapy drugs (non-HER2 regimen) used in palliative setting (N=75)



	FAC	AC+T	DC	Others
2006-2010 (N=31)	80.6	12.9	0.0	6.5
2011-2015 (N=37)	73.0	18.9	8.1	0.0
2016-current (N=7)	57.1	42.9	0.0	0.0

2nd generation drugs

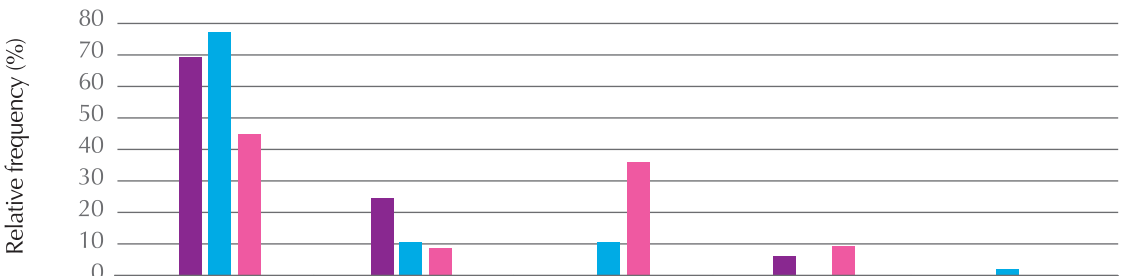
Figure 2.24: Type of third generation chemotherapy drugs (non-HER2 regimen) used in palliative setting (N=89)



	AC+D	AC+T	FAC+TC	TC	TAC	FEC+D	TEC	FAC+D	TC+AC	FAC+T	FEC+T	Others
2006-2010 (N=18)	11.1	5.6	16.7	16.7	11.1	5.6	0.0	16.7	5.6	5.6	0.0	5.3
2011-2015 (N=54)	20.4	14.8	9.3	13.0	7.4	5.6	5.6	0.0	3.7	0.0	3.7	16.5
2016-current (N=17)	11.8	35.3	11.8	11.8	0.0	5.9	5.9	0.0	0.0	5.9	0.0	11.6

3rd generation drugs

Figure 2.25: Type of HER2 regimens used in palliative setting (N=76)

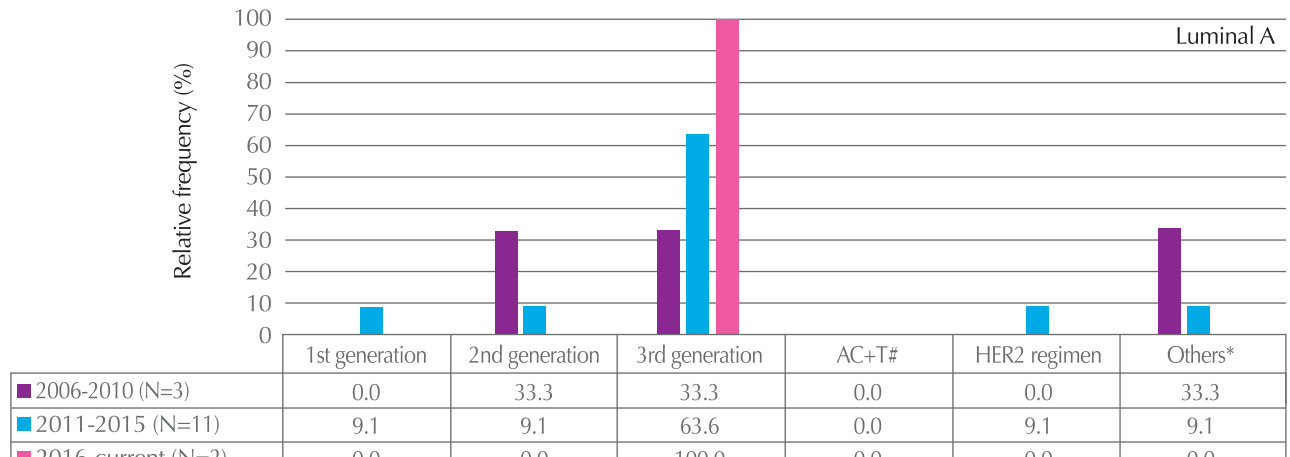


	T+C+H	T+H	T+C+P+H	ACy/ECy+T+H	T+P+H
2006-2010 (N=16)	68.8	25.0	0.0	6.3	0.0
2011-2015 (N=49)	77.6	10.2	10.2	0.0	2.0
2016-current (N=11)	45.5	9.1	36.4	9.1	0.0

HER2 regimens

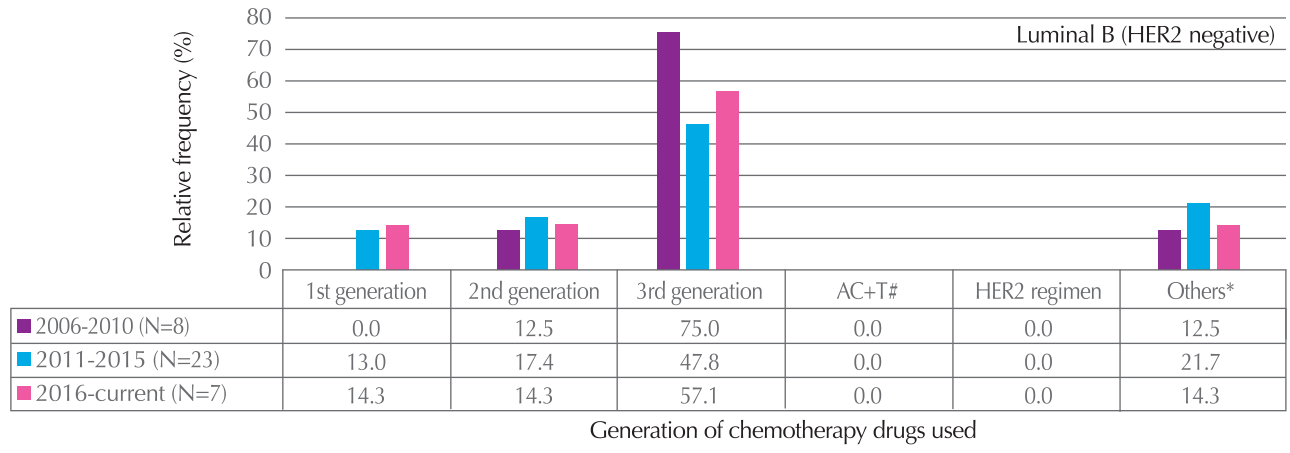
A: Anthracycline; C: Carboplatin; T: Taxane; H: Trastuzumab; Cy: Cyclophosphamide; P: Pertuzumab

Figure 2.26: Generation of chemotherapy drugs used by biological subtype in palliative setting (N=190)



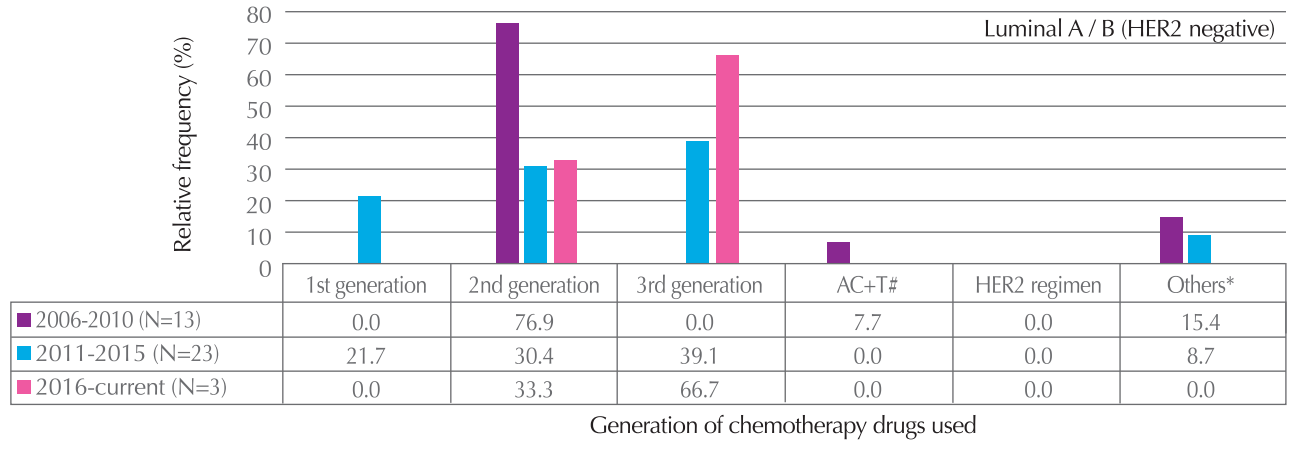
	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=3)	0.0	33.3	33.3	0.0	0.0	33.3
2011-2015 (N=11)	9.1	9.1	63.6	0.0	9.1	9.1
2016-current (N=2)	0.0	0.0	100.0	0.0	0.0	0.0

Generation of chemotherapy drugs used



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=8)	0.0	12.5	75.0	0.0	0.0	12.5
2011-2015 (N=23)	13.0	17.4	47.8	0.0	0.0	21.7
2016-current (N=7)	14.3	14.3	57.1	0.0	0.0	14.3

Generation of chemotherapy drugs used

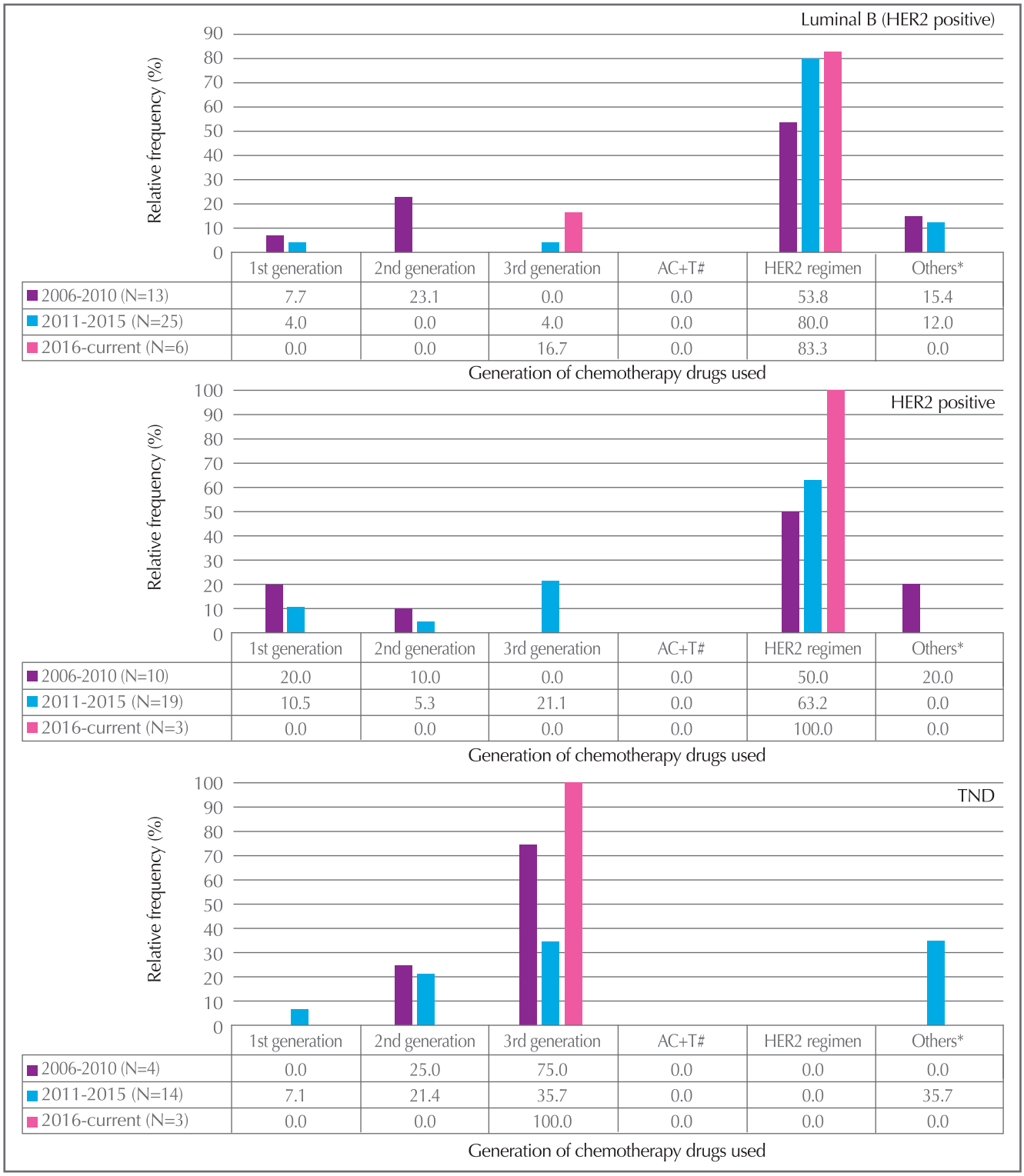


	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=13)	0.0	76.9	0.0	7.7	0.0	15.4
2011-2015 (N=23)	21.7	30.4	39.1	0.0	0.0	8.7
2016-current (N=3)	0.0	33.3	66.7	0.0	0.0	0.0

Generation of chemotherapy drugs used

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

Figure 2.26: Generation of chemotherapy drugs used by biological subtype in palliative setting (N=190) (cont'd)



	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=13)	7.7	23.1	0.0	0.0	53.8	15.4
2011-2015 (N=25)	4.0	0.0	4.0	0.0	80.0	12.0
2016-current (N=6)	0.0	0.0	16.7	0.0	83.3	0.0

	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=10)	20.0	10.0	0.0	0.0	50.0	20.0
2011-2015 (N=19)	10.5	5.3	21.1	0.0	63.2	0.0
2016-current (N=3)	0.0	0.0	0.0	0.0	100.0	0.0

	1st generation	2nd generation	3rd generation	AC+T#	HER2 regimen	Others*
2006-2010 (N=4)	0.0	25.0	75.0	0.0	0.0	0.0
2011-2015 (N=14)	7.1	21.4	35.7	0.0	0.0	35.7
2016-current (N=3)	0.0	0.0	100.0	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

D. Endocrine therapy

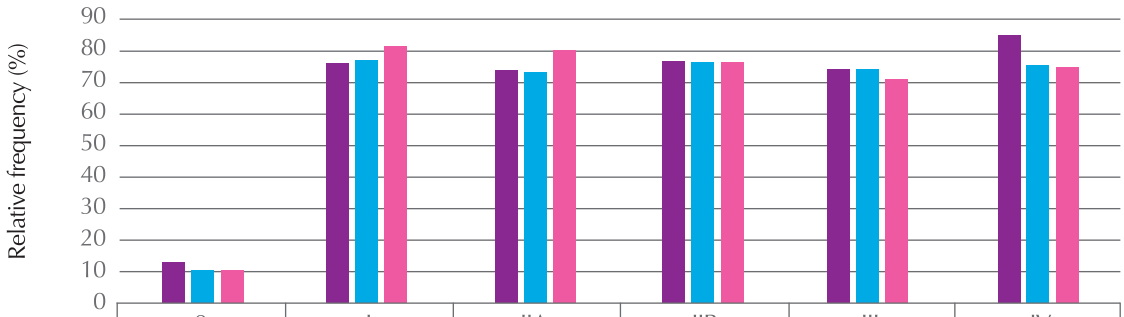
2.57 Endocrine therapy plays an important role in all stages of the treatment and prevention strategy for hormone receptor-positive invasive or in situ breast cancer. Breast cancer develops from abnormal breast cells that are often sensitive to sex hormones, such as estrogen and progesterone. Endocrine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

2.58 In the cohorts, about two-thirds (2006-2010: 67.6%; 2011-2015: 67.9%; 2016-current: 69.1%) of the patients were treated with endocrine therapy, over 96% (2006-2010: 97.3%; 2011-2015: 96.4%; 2016-current: 96.9%) being adjuvant, while neoadjuvant (2006-2010: 0.2%; 2011-2015: 0.6%; 2016-current: 1.0%) and palliative (2006-2010: 2.5%; 2011-2015: 3.1%; 2016-current: 2.1%) accounted for small proportions. In addition, about 90% (2006-2010: 88.8%; 2011-2015: 92.6%; 2016-current: 88.0%) of the patients received endocrine therapy at public medical facilities, while the remainder (2006-2010: 11.2%; 2011-2015: 7.4%; 2016-current: 12.0%) at private medical facilities.

2.59 For the patients with invasive breast cancer, high proportions received endocrine therapy (74.0%-85.0%), while for in situ breast cancer, only about one-tenth (10.3%-12.8%) received endocrine therapy (Figure 2.27).

2.60 Two types of drugs are commonly used for reducing the level of female hormones: anti-estrogens and aromatase inhibitors. Anti-estrogen drugs slow down breast cancer growth by sticking 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 decrease 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 2.27: Use of endocrine therapy by cancer stage (N=17,774)



	0	I	IIA	IIB	III	IV
2006-2010 (N=6,756)	12.8	75.4	74.3	77.6	75.4	85.0
2011-2015 (N=8,460)	10.4	77.9	74.0	77.2	75.0	76.0
2016-current (N=2,558)	10.3	81.8	80.1	75.3	71.5	75.0

Cancer stage

Table 2.33: Forms of endocrine therapy by age group (N=11,295)

	Age group % for 2006-2010, % for 2011-2015, % for 2016-current								
	<45			45-55			≥55		
Tamoxifen	94.1	97.5	95.8	75.0	87.3	78.7	42.2	52.7	34.7
Tamoxifen-> Aromatase inhibitors	4.8	1.2	1.0	14.8	4.2	1.2	22.6	8.4	4.1
Aromatase inhibitors	1.0	1.3	3.2	10.2	8.6	20.1	35.3	38.9	61.1

Total number of patients in each group:

<45: 1,094 (for 2006-2010), 1,074 (for 2011-2015), 310 (for 2016-current)

45-55: 1,776 (for 2006-2010), 1,903 (for 2011-2015), 492 (for 2016-current)

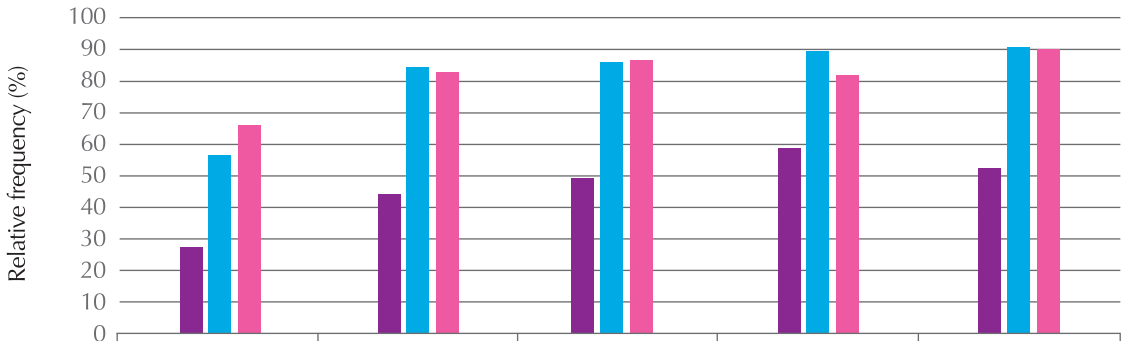
≥55: 1,449 (for 2006-2010), 2,425 (for 2011-2015), 772 (for 2016-current)

E. Anti-HER2 targeted therapy

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

2.62 Of the patients with invasive HER2 positive breast cancer in the three cohorts, 43.1%-79.5% (2006-2010: 43.1%; 2011-2015: 78.1%; 2016-current: 79.5%) underwent anti-HER2 targeted therapy. Among them, 88.4%-94.5% (2006-2010: 94.5%; 2011-2015: 93.1%; 2016-current: 88.4%) were adjuvant, 3.4%-10.5% (2006-2010: 3.4%; 2011-2015: 4.3%; 2016-current: 10.5%) were neoadjuvant and 1.0%-2.6% (2006-2010: 2.1%; 2011-2015: 2.6%; 2016-current: 1.0%) were palliative. In addition, the majority (2006-2010: 87.0%; 2011-2015: 90.3%; 2016-current: 89.1%) of the patients received anti-HER2 targeted therapy at public medical facilities, while the remainder (2006-2010: 13.0%; 2011-2015: 9.7%; 2016-current: 10.9%) 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 roughly the same for the 2011-2015 and 2016-current cohorts (Figure 2.28).

Figure 2.28: Use of anti-HER2 targeted therapy in HER2 positive patients by cancer stage (N=3,215)



	I	IIA	IIB	III	IV
2006-2010 (N=1,377)	28.2	44.1	49.5	58.4	53.3
2011-2015 (N=1,499)	57.5	85.2	86.4	89.4	90.6
2016-current (N=339)	66.1	83.0	87.0	82.4	90.0

Cancer stage

F. Multimodality treatment

2.63 Combinations of treatment modalities, including surgery, radiotherapy, chemotherapy, endocrine therapy and anti-HER2 targeted therapy, are usually used for treating breast cancer effectively. Table 2.34 shows the multimodality treatment pattern of the patients. In general, the number of modalities increased with increasing cancer stage. In the three cohorts, the majority (92.7%-94.6%) of the stage 0 patients received two or less modalities. On the other hand, more than three-quarters of the patients with stage IIA (78.5%-81.5%), stage IIB (88.4%-93.7%) or stage III (94.3%-97.3%) breast cancer received three or more modalities.

G. Complementary and alternative therapies

2.64 Apart from the standard medical treatments and care of breast cancer described in the previous sections of this chapter, some patients may seek different kinds of complementary and alternative therapies, such as taking traditional Chinese medicines, health foods and supplements. A total of 6,827 (2006-2010: 41.6%; 2011-2015: 37.6%; 2016-current: 24.5%) patients in the three cohorts sought complementary and alternative therapies as part of their treatment. Among them, over 95% (2006-2010: 95.6%; 2011-2015: 95.5%; 2016-current: 96.7%) were adjuvant, while neoadjuvant (2006-2010: 3.7%; 2011-2015: 3.2%; 2016-current: 0.9%) and palliative (2006-2010: 0.7%; 2011-2015: 1.3%; 2016-current: 2.4%) accounted for only small proportions. In addition, about two-thirds (64.1%-67.7%) of the patients used traditional Chinese medicines (Figure 2.29).

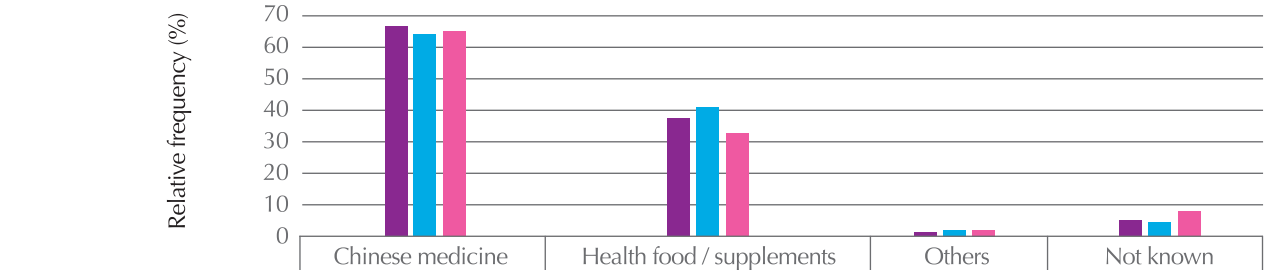
Table 2.34: Number of treatment modalities by cancer stage (N=17,379)

	Cancer stage % for 2006-2010, % for 2011-2015, % for 2016-current																	
	0			I			IIA			IIB			III			IV		
0	0.4	0.5	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.3	0.0	0.2	0.0	0.0	0.8	0.0
1	41.9	42.9	39.7	6.2	6.7	4.7	1.9	1.9	3.1	0.7	1.1	1.7	0.4	0.6	1.6	6.8	8.0	17.2
2	52.3	50.6	52.4	32.0	32.9	32.1	16.6	19.2	18.4	6.6	5.2	9.6	2.3	2.4	4.1	19.6	13.6	14.1
3	5.5	5.8	7.0	42.5	41.1	45.2	38.4	35.6	35.9	28.9	27.1	24.5	18.7	17.7	18.3	35.1	31.2	21.9
4	0.0	0.1	0.3	17.8	15.4	14.3	39.3	37.4	35.7	56.9	54.7	54.6	67.3	62.5	62.8	33.1	34.8	32.8
5	0.0	0.1	0.0	1.6	3.9	3.7	3.8	5.8	6.9	6.9	11.9	9.3	11.3	16.6	13.2	5.4	11.6	14.1

Total number of patients in each group:

0: 842 (for 2006-2010), 1,007 (for 2011-2015), 330 (for 2016-current)
I: 2,089 (for 2006-2010), 2,679 (for 2011-2015), 810 (for 2016-current)
IIA: 1,764 (for 2006-2010), 2,021 (for 2011-2015), 619 (for 2016-current)
IIB: 844 (for 2006-2010), 1,096 (for 2011-2015), 302 (for 2016-current)
III: 950 (for 2006-2010), 1,247 (for 2011-2015), 317 (for 2016-current)
IV: 148 (for 2006-2010), 250 (for 2011-2015), 64 (for 2016-current)

Figure 2.29: Type of complementary and alternative therapies used (N=6,827)



	Chinese medicine	Health food / supplements	Others	Not known
2006-2010 (N=2,864)	67.7	38.2	1.8	5.9
2011-2015 (N=3,297)	64.1	41.2	2.1	5.4
2016-current (N=666)	65.0	33.0	2.1	8.3

Complementary and alternative therapies

Others include: Tai Chi, Qigong, Naturopathy, acupuncture and moxibustion, massage and yoga

VI. Patient status

2.65 Once treatment is completed, the Hong Kong Breast Cancer Registry will follow up with the registered patients annually to ascertain the efficacy of the treatment. To date, a total of 16,603 patients in the three cohorts completed at least one follow-up. About two-fifths (43.8%) of them had the last follow-up within the past two years and about one-third (36.8%) have been followed up for five or more years (Table 2.35). The mean and median follow-up period were 4.2 and 3.5 years respectively.

2.66 Of the patients who have been followed up, 1.4% experienced only locoregional recurrence (LR), 1.9% experienced only distant recurrence (DR), and 1.4% experienced both locoregional and distant recurrence concurrently or sequentially. The mean and median time to recurrence are shown in Table 2.35.

2.67 Table 2.36 shows the number of invasive breast cancer patients with LR in different groups specified by surgery type received 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 (Table 2.36). Overall, the patients who received mastectomy had lower LR rates than those who received breast-conserving surgery without radiotherapy. The common sites for LR were chest wall (32.8%) and breast (29.9%) (Table 2.37).

Table 2.35: Follow-up of 16,603 patients

	Number	%
Follow-up period		
< 1 year	2,295	13.8
1-2 years	2,972	17.9
2-5 years	5,220	31.4
5-10 years	5,574	33.6
10+ years	536	3.2
Mean follow-up period		4.2 years
Median follow-up period		3.5 years
Locoregional recurrence		
No. of locoregional recurrences	237	1.4
Mean time to locoregional recurrence		3.3 years
Median time to locoregional recurrence		2.6 years
Distant recurrence		
No. of distant recurrences	313	1.9
Mean time to distant recurrence		3.4 years
Median time to distant recurrence		2.7 years
Locoregional and distant recurrence		
No. of locoregional and distant recurrences	238	1.4
Mean time to locoregional and distant recurrence		3.3 years
Median time to locoregional and distant recurrence		2.6 years
Mortality*		
No. of deaths from breast cancer	196	1.2
No. of deaths from unrelated causes	100	0.6
No. of deaths with causes not known	69	0.4

*Data as of Feb 2019 with traceable medical records only.

Table 2.36: Locoregional recurrence by type of surgery received and cancer stage at diagnosis

	Cancer stage, Number (% in the overall patient cohort with surgeries)				
	I	IIA	IIB	III	Total
BCS with RT	26/2,583	45/1,525	9/518	13/339	93/4,965
	(1.0)	(3.0)	(1.7)	(3.8)	(1.9)
BCS without RT	6/107	5/67	1/16	0/7	12/197
	(5.6)	(7.5)	(6.3)	(0.0)	(6.1)
MTX	48/2,915	69/2,918	49/1,734	112/2,187	278/9,754
	(1.6)	(2.4)	(2.8)	(5.1)	(2.9)

BCS: Breast-conserving surgery; MTX: Mastectomy; RT: Radiotherapy

Table 2.37: Sites involved in locoregional recurrence (N=475)

	Number	%
Chest wall	156	32.8
Breast	142	29.9
Axilla	149	31.4
Supraclavicular fossa	93	19.6
Internal mammary node	34	7.2
Infraclavicular fossa	4	0.8
Others	35	7.4

Note: Recurrence may involve multiple sites simultaneously, so the total percentages for recurrence sites may exceed 100.

2.68 In the cohort, 551 (3.3%) patients experienced distant recurrence. Among them, the top four organs involved were bone (57.4%), lung (48.8%), liver (40.8%) and brian (17.1%) (Table 2.38). 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 2.39.

Table 2.38: Organs involved in distant recurrence (N=551)

	Number	%
Bone	316	57.4
Lung	269	48.8
Liver	225	40.8
Brain	94	17.1
Mediastinal nodes	92	16.7
Neck nodes	43	7.8
Distant lymph nodes	42	7.6
Pleural cavity	27	4.9
Adrenal	12	2.2
Peritoneal	11	2.0
Contralateral axillary nodes	5	0.9
Ovary	5	0.9
Spleen	4	0.7
Thyroid glands	2	0.4
Pancreas	1	0.2
Kidney	1	0.2
Uterus	1	0.2
Unspecified	34	6.2

Note: Recurrence may involve multiple sites simultaneously, so the total percentages for recurrence sites may exceed 100.

Table 2.39: Time for organ specific metastasis and distribution of the biological subtypes of patients

	Bone (N=316)	Lung (N=269)	Liver (N=225)	Brain (N=94)
Time for metastasis, median years (range)	3.4 (0.3-11.2)	3.4 (0.2-11.2)	3.1 (0.2-9.8)	3.3 (0.2-10.0)
Biological subtypes				
Luminal A*	31 (11.1)	16 (6.9)	22 (10.8)	8 (9.4)
Luminal B (HER2-ve)#	63 (22.6)	42 (18.2)	46 (22.7)	13 (15.3)
Luminal A/B (HER2-ve)†	89 (31.9)	66 (28.6)	62 (30.5)	14 (16.5)
Luminal B (HER2+ve)^	48 (17.2)	39 (16.9)	32 (15.8)	16 (18.8)
HER2+ve ❋	20 (7.2)	22 (9.5)	19 (9.4)	15 (17.6)
TND§	28 (10.0)	46 (19.9)	22 (10.8)	19 (22.4)
Not known	37	38	22	9

* 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
§ TND (Triple Negative Disease): ER and PR-, HER2-, and any Ki-67 index

2.69 In the cohort, the proportion of those 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 5.8% of stage III patients. Stage III patients had higher rates of only DR (5.8%) and combination of LR and DR (3.8%) than those with lower cancer stages (Table 2.40).

2.70 In the cohort, 196 (1.2%) patients died from breast cancer. About three-fifths (59.1%) of them were stage III or IV at initial diagnosis. Survival time ranged from 0.6 to 11.2 years. Information on biological subtypes of these patients is shown in Table 2.41.

Table 2.40: Locoregional and distant recurrence among invasive breast cancer patients by cancer stage (N=13,734)

	Cancer stage, Number (%)				
	I (N=5,157)	IIA (N=4,137)	IIB (N=2,100)	III (N=2,340)	Total (N=13,734)
LR only	57 (1.1)	61 (1.5)	18 (0.9)	38 (1.6)	174 (1.3)
DR only	45 (0.9)	60 (1.5)	54 (2.6)	136 (5.8)	295 (2.1)
LR and DR	23 (0.4)	58 (1.4)	41 (2.0)	90 (3.8)	212 (1.5)

LR: Locoregional recurrence; DR: Distant recurrence

Table 2.41: Characteristics of breast cancer-specific deaths (N=196)

	Cancer stage at initial diagnosis						
	0	I	IIA	IIB	III	IV	Unstaged
No. of cases (% of breast cancer death cases)	**4 (2.0)**	**18 (9.2)**	**28 (14.3)**	**18 (9.2)**	**82 (41.8)**	**34 (17.3)**	**12 (6.1)**
Survival time (range in years)	**4.5 – 7.3**	**1.6 – 9.6**	**1.6 – 10.3**	**2.1 – 11.2**	**0.6 – 11.2**	**0.6 – 7.4**	**1.1 – 6.2**
Time from first diagnosis of DM to death (years), mean (range)	**1.0 (0.5-1.5)**	**2.1 (0.7-4.6)**	**1.2 (0.1-5.9)**	**1.7 (0.1-6.2)**	**1.4 (0.0-6.2)**	**3.3 (0.6-7.4)**	**1.5 (0.3-3.2)**
Biological subtypes							
Luminal A*	0	2	2	2	5	0	0
Luminal B(HER2 negative)#	0	4	4	2	10	2	1
Luminal A/B (HER2 negative)†	2	2	9	8	25	12	2
Luminal B (HER2 positive)^	2	2	2	1	14	7	4
HER2 positive ❉	0	3	4	0	11	6	0
TND§	0	5	6	4	12	4	0
Not known	0	0	1	1	5	3	5

* 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

§ TND (Triple Negative Disease): ER and PR-, HER2-, and any Ki-67 index