Pathological aspects of breast cancer in Indonesian females, applying a modified WHO classification. A joint study between Indonesia and Japan

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Abstrak

Dari aspek patologi diteliti kembali varian histologik karsinoma payudara dan dibandingkan dengan kasus-kasus dari Jepang. Dipakai klasifikasi yang dianjurkan oleh Japanese Breast Cancer Society, yang membagi lagi karsinoma mammae duktal invasif menjadi 3 subtipe, yaitu: tipe papilotubuler, solid-tubuler dan skirus. Dari Indonesia ada 515 kasus yang ditangani oleh Rumah Sakit Umum Pusat Nasional Dr. Cipto Mangunkusumo (RSCM), berasal dari penelitian ke-1 dan ke-2, sedangkan dari Jepang ada 445 kasus yang ditangani oleh Cancer Institute Hospital (CIH). Di RSCM ditemukan sebanyak 0.97% karsinoma noninvasif, 89.14% karsinoma duktal invasif dan 9.50% tipe khusus. Di CIH ditemukan sebanyak 7.4% karsinoma non-invasif, 80.4% karsinoma duktal invasif dan 11.3% tipe khusus. Insiden karsinoma duktal noninvasif di RSCM lebih rendah daripada CIH dengan perbedaan 6.43%. Di antara subtipe karsinoma duktal invasif, tipe skirus-lah yang paling banyak ditemukan pada kedua kelompok (RSCM dan CIH), dengan insiden 50.49% (RSCM) dan 43.6% (CIH). Subtipe yang paling sedikit di RSCM ialah tipe papilotubuler, sedangkan di CIH ialah tipe solid-tubuler. Tipe khusus ditemukan sebanyak 5 varian di RSCM, sedangkan di CIH 7 varian. Insiden karsinoma musinosum dan karsinoma lobuler invasif di RSCM lebih rendah daripada di CIH, sedangkan karsinoma moduler lebih tinggi. Insiden penyakit Paget juga lebih rendah di RSCM.

Abstract

From the pathological aspect, we analyzed again the histological variants of breast cancer and compare them with cases from Japan. We used the classification recommended by the Japanese Breast Cancer Society, which divided the invasive ductal carcinoma of NOS (no otherwise specified) of the WHO classification into 3 subtypes, namely papillotubular, solid-tubular and scirrhous carcinoma. We had 515 cases from Indonesia (1st batch and 2nd batch) treated at the Dr. Cipto Mangunkusumo National Central General Hospital (RSCM) and 445 cases from Japan, treated at the Cancer Institute Hospital (CIH). The RSCM cases had 0.97% noninvasive carcinoma, 89.14% invasive ductal carcinoma and 9.50% of the specialtypes. The CIH cases had 7.4% noninvasive carcinoma, 80.4% invasive ductal carcinoma and 11.3% of the special types. The incidence of noninvasive ductal carcinoma was lower at RSCM, with a 6.43% difference. Among the subtypes of invasive ductal carcinoma, the scirhous carcinoma was the most common in both groups (RSCM and CIH), with an incidence of 50.49% (RSCM) and 43.6% (CIH). The least common at RSCM was the papillotubular type, while at the CIH it was the solid-tubular type. Among the special types, only 5 variants were encountered at RSCM and 7 at CIH. The incidences of mucinous carcinoma and invasive lobular carcinoma were lower at RSCM, while the medullary carcinoma was higher. The incidence of Paget's disease was also lower at RSCM.

Keywords: *Pathological, breast cancer, WHO-classification, Japan-Indonesia study.*

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INTRODUCTION

Breast cancer is a worldwide and serious disease, which create a major public health problem. There are geographic differences in their incidence rate, being higher in Northern America and Europe than in Asian countries and Japan. Its frequency is increasing during the last 15 years, especially among women with a high socioeconomic status, namely from 12.1-16.6 to 21 per 100,000 females in Japan and from 71.7 to 91 per 100,000 females in Northern America. In Singapore the incidence of all ethnic groups almost doubling over the last 20 years. In Indonesian,

the data collected from 13 Pathology Laboratories spread throughout Indonesia, showed that breast cancer ranked the second among females, with 18.03% relative frequency (ASCAR = age standardized cancer ratio 17.84%) in 1988 and 18.44% (ASCAR 17.46%) in 1989.

These differences have attracted investigators to look upon several aspects of breast cancer, including epidemiological, clinical, pathological, and nutritional aspects. A Joint Study on etiology and Clinicopathology of breast cancer has been conducted since 1988, between Indonesia and Japan.

In the first batch of a three years study we encountered dissimilar pathological finding. The Cipto Mangunkusumo National Central General Hospital (RSCM) cases had lower incidences of noninvasive ductal carcinoma, mucinous carcinoma and invasive lobular carcinoma than cases from CIH (Cancer Institute Hospital, Tokyo). Medullary carcinoma was more frequent at the RSCM. An extended study was done to include nutritional analysis. From the pathological aspects we analyzed again the histological variants of breast cancer and compare with the cases from Japan.

MATERIALS AND METHODS

Table 1. Histological classification of breast tumors (Japanese Breast Cancer Society, 1984)

Malignant (Carcinoma)
1. Noninvasive carcinoma
   a. Noninvasive ductal carcinoma
   b. Lobular carcinoma in situ
2. Invasive carcinoma
   a. Invasive ductal carcinoma
      a1. Papillotubular carcinoma
      a2. Solid-tubular carcinoma
      a3. Scirrhous carcinoma
   b. Special types
      b1. Mucinous carcinoma
      b2. Medullary carcinoma
      b3. Invasive lobular carcinoma
      b4. Adenoid cystic carcinoma
      b5. Squamous cell carcinoma
      b6. Spindel cell carcinoma
      b7. Apocrine carcinoma
      b8. Carcinoma with cartilaginous and or osseous metaplasia
      b9. Tubular carcinoma
      b10. Secretory carcinoma
      b11. Others
3. Paget's disease

Note: See Appendix for the principles and details of the classification.

Two hundred and twenty six cases of breast cancer were available. Some of these cases the diagnosis of breast cancer were performed at another Hospital without mentioning the subtypes. This occurred in 11 cases, so for histopathological analysis we had 215 cases. The classification used that recommended by the Japanese Breast Cancer Society, which divided the invasive ductal carcinoma of N.O.S (no otherwise specified) of the WHO classification into subtypes, papillotubular, solid tubular and scirrhous carcinoma.

RESULTS

The case distribution by histological type is shown in Table 2.

Table 2. Case distribution of histological types of breast cancer (1992-1995)

Histological types	Number of cases	%
Noninvasive carcinoma		
a. Noninvasive ductal carcinoma	1	0.46
b. Lobular carcinoma in situ		
Invasive carcinoma		
a. Invasive ductal carcinoma		
a1. Papillotubular	15	6.98
a2. Solid-tubular	66	30.70
a3. Scirrhous	113	52.86
b. Special types		
b1. Mucinous carcinoma	4	1.86
b2. Medullary carcinoma	10	4.65
b3. Invasive lobular carcinoma	5	2.33
b4. Squamous cell carcinoma	1	0.46
Total	215	100.00

The invasive ductal carcinoma accounted for 90.24% of the cases, followed by the special types with 9,3%. Only 1 case of noninvasive ductal carcinoma was found (0.46%). In one case of papillotubular carcinoma a coincidental finding with a lobular carcinoma in situ was seen. When we compiled the 1st batch and the 2nd batch of the study, the results is shown in Table 3.

Table 3. Histological types and case distribution of breast cancer of the whole study (1988-1995)

Histological types	Number of cases	%
Noninvasive carcinoma		
a. Noninvasive ductal carcinoma	5	0.97
b. Lobular carcinoma in situ		
Invasive carcinoma		
a. Invasive ductal carcinoma		
a1. Papillotubular	54	10.49
a2. Solid-tubular	145	28.6
a3. Scirrhous	260	50.49
b. Special types		
b1. Mucinous carcinoma	8	1.55
b2. Medullary carcinoma	27	5.24
b3. Invasive lobular carcinoma	12	2.33
b4. Adenoid cystic carcinoma	1	0.19
b5. Squamous cell carcinoma	1	0.19
Paget's disease	2	0.39
Total	515	100.00

The most common was the invasive ductal carcinoma with 89.14%. The special types with 9.50%. Only 5 cases of noninvasive ductal carcinoma were found, comprised only 0.97%. Among the special types, the medullary carcinoma was the most common, with 5.24% incidence rate. When we compare the whole cases with cases from Japan, the result is seen in Table 4.

The RSCM cases had 0.97% noninvasive carcinoma, 89.14% invasive ductal carcinoma, and 9.50% of the special types. The CIH cases had 7.4% noninvasive carcinoma, 80.4% invasive ductal carcinoma, and 11.3% of the special types. The incidence of noninvasive ductal carcinoma is lower at the RSCM, with a 6.43% difference.

Among the special types at the RSCM only 5 variants were encountered, while at the CIH, there were 7 variants. The incidences of mucinous carcinoma and invasive lobular carcinoma were lower at the RSCM, while the medullary carcinoma was higher. The incidence of Paget's disease was also lower at the RSCM. The age incidences of the 226 cases of the 2nd batch of the study are presented in Table 5.

Table 4. Case distribution of histological types of breast cancer

Histological Types	RSCM (1988-1995)		CIH (1989)	
	Number of cases	%	Number of cases	%
Noninvasive carcinoma				
a. Noninvasive ductal carcinoma	5	0.97	33	7.4
b. Lobular carcinoma in situ				
Invasive carcinoma				
a. Invasive ductal carcinoma				
a.1. Papilotubular	54	10.49	86	19.3
a.2. Solid-tubular	145	28.16	78	17.5
a.3. Scirrhous	260	50.49	194	43.6
b. Special types				
b1. Mucinous carcinoma	8	1.55	16	3.6
b2. Medullary carcinoma	27	5.24	6	1.3
b3. Invasive lobular carcinoma	12	2.33	20	4.5
b4. Adenoid cystic carcinoma	1	0.19	-	-
b5. Squamous cell carcinoma	1	0.19	1	0.2
b6. Spindle cell carcinoma	-	-	1	0.2
b7. Apocrine carcinoma	-	-	2	0.4
b8. Tubular carcinoma		-	-5	1.1
Paget's disease	2	0.39	3	0.7
Total	515	100.00	445	100.00

Table 5. Case distribution by age at operation/biopsy (RSCM, 1988-1995)

Age	Number of Cases	%
20-	3	1.33
30-	63	27.87
40-	68	30.09
50-	66	29.20
60-	23	10.18
70-	3	1.33
Total	226	100.00

In Table 6 is shown the case distribution of the whole cases by age.

Table 6. Case distribution by age of the whole cases (RSCM, 1988-1995)

Age	Number of cases	%
20-	16	3.04
30-	135	25.67
40-	161	30.61
50-	121	23.00
60-	81	15.40
70-	12	2.28
Total	526	100.00

The youngest was 22 years old and the oldest 75 years old. The peak incidence was in the 5th decade (30.61%), followed by the 4th decade with 25.67%. Under 40 years of age there were 28.71% of the cases. Compare to cases from CIH, the case distribution of breast cancer by age is seen in Table 7.

Table 7. Case distribution of breast cancer cases by age

Age	RSCM (1988-1995)		CIH (1989)	
	No. of cases	%	No. of cases	%
20 -	16	3.04	2	0.4
30 -	135	25.67	59	13.2
40 -	161	30.61	171	38.8
50 -	121	23.00	120	26.9
60 -	81	15.40	74	16.6
70 -	12	2.28	17	3.8
80 -	-	-	3	0.7
Total	526	100%	446	100%

Both groups have the same peak incidence in the 5th decade, with an incidence of 30.61% at RSCM and 38.3% at CIH. In the 4th decade, the incidence was almost twice compare to the CIH cases (25.67%) against 13.2%). Also in the 3rd decade the RSCM had more number of cases, with a 3% difference. The case distribution by size of tumor of the 2nd batch and compare to the cases from CIH is shown in Table 8. The data were available in only 199 cases.

Table 8. Cases distribution by size of tumor

Size of Tumor	RSCM (1992-1995)		CIH (1989)	
	No. of cases	%	No. of cases	%
T0	-	-	22	4.9
T1	3	1.50	182	40.8
T2	36	18.09	191	42.8
T3	36	18.09	21	4.7
T4	124	62.31	30	6.7
Total	199	100%	446	100%

The RSCM T1 + T2 accounted for 19.59%, while at CIH it was 83.6%. The reserved occurred for T3 and T4. At RSCM it was 80.4%, at CIH only 11.4%.

DISCUSSION

In this study we used the classification proposed by the Japanese Breast Cancer Society, which is essentially the same as the WHO classification with a minor modification. The invasive ductal carcinoma (WHO NOS/NST) = No otherwise specified/No special type) which in reality has different pattern of infiltration is further sub-classified into 3 sub-types, namely papillotubular, solid-tubular and scirrhous carcinoma, which have prognostic significance. They also reflect the degree of differentiation, which from poor to well is in an order of scirrhous ca, solid ca and papillotubular ca. The scirrhous carcinoma has the poorest prognosis. This subclassification can be used instead of the grading system. There were several grading systems proposed,[8,9] but we are still looking for an Internationally recognized breast cancer grading system. Using this classification we could avoid the universal problem of the grading of breast cancer.

In the second batch of the study we found only 1 cases of noninvasive ductal carcinoma (0.46%) among 215 cases of breast cancer, while in the batch

of the study, we encountered 4 cases (1.33%) among 300 cases of breast cancer. When we combined the cases (Batch 1 & 2, RSCM) and compared with the cases from Japan (CIH), we found that the incidence of noninvasive ductal carcinoma was lower at the RSCM, with a 6.43% difference. The earlier detection of breast cancer could be responsible for the difference, especially with mammography screening which has led to increase detection of ductal carcinoma in situ (noninvasive ductal carcinoma).[11]

All our cases of noninvasive ductal carcinoma/ductal carcinoma in situ (DCIS) were of the comedo type. In our previous study, other subtypes were also encountered, such as the micropapillary, cribriform and the solid variety.[12] The increased prevalence of ductal carcinoma in situ (DCIS) has produced a growing awareness of the importance of its diverse pattern and have become clinically significant as predictive indicators of success for planned local excisions of small DCIS lessions.[13]

Bellamy et al[14] in a review of 130 cases of noninvasive ductal carcinoma of the breast concluded that the comedo carcinoma DCIS had an occult presentation significantly more likely than other patterns to involve multiple quadrants of breast, irrespective of nuclear grade or necrosis. Our cases of DCIS were detected at early stages (I and II).

In the second batch, the invasive ductal carcinoma accounted for 90.24% of the cases, followed by the special types with 9.3%. In the first batch of the study we found 88.33% of invasive ductal carcinoma and 9.67% of the special types. The CIH cases accounted for 80.4% and 11.3% respectively. The invasive ductal carcinoma was the most common, accounting for at least 80% of breast cancer.

Among the subtypes of invasive ductal carcinoma, the RSCM cases had 50.49% of the scirrhous type (Table 4), followed by the solid-tubular type of 28.16% and the papilotubular type of 10.49%.

While the CIH cases had 43.6% scirrhous type, followed by the papilotubular type of 19.3% and the solid-tubular type was the least common. The subclassification of invasive ductal carcinoma into 3 sub-types has prognosis significance. The scirrhous carcinoma shows the worst prognosis, with a ten-year survival rate of 61.2%. The papilotubular carcinoma shows the most favorable prognosis, with a ten-year survival rate of 77.4%. The ten-year survival rate for solid-tubular carcinoma is 64.9%.

The RSCM cases had 9.50% of the special types, while at the CIH it was 11.3% (Table 4). Among the special types at the RSCM, only 5 variants were encountered, while at the CIH, there were 7 variants, including spindle cell carcinoma, apocrine carcinoma and tubular carcinoma. We had one case of adenoid cystic carcinoma, which was found at the CIH. The incidence rates of mucinous and invasive lobular carcinoma at the RSCM were lower than at the CIH, while the medullary carcinoma was higher (5.24% at the RSCM, against 1.3% at the CIH). In the literature, the medullary carcinoma constitutes approximately about 5 to 8% of invasive mammary cancer.[15] Histologically, they are very poorly differentiated or high-grade cancer, but has a less aggressive behavior. They are usually large (4 cm or more in diameter). These features were consistent with our cases, which were presented with stage III disease at initial diagnosis.

Using the strict definition of medullary carcinoma, Ridolfi et al[16] found a significantly higher overall survival rate at 10 years of 84%, even when nodal metastases were present. The smaller medullary carcinoma had a better prognosis than the larger ones, but the most important prognostic feature within the group of medullary carcinoma was the density of lymphoplasmacytic infiltrate. Those patients with a relatively sparse infiltrate had a relatively poor prognosis.

We had one case of adenoid cystic carcinoma in a 52-year old woman in this study, presenting with a circumscribed lesion of 6 cm in diameter. It has been stated that this tumor is usually small, but may become as large as 8 cm in diameter, and grossly well demarcated and has a good prognosis.[15]

The two cases of Paget's disease in our study were 55 years and 60 years old respectively, similar to the findings reported in the literature, that Paget's disease of the nipple tend to occur in an older age group. One case was associated with an in situ ductal carcinoma. Both cases were of stage I.

If we compared the case distribution of breast cancer by age among both groups (RSCM and CIH), then we found that both groups have the same peak incidence in the 5th decade, with an incidence of 30.61% at the RSCM and 38.3% at the CIH. In the 4th decade, the incidence was almost twice/doubled compare to

the CIH cases (25.67% against 13.2%). Also in the 3rd decade, the RSCM had more number of cases, with a 3% difference. At the younger age group, breast cancer occurred more frequently in the Indonesian females as compared to the Japanese females. Table 8 showed the case distribution by tumor size of the 2nd batch of the study. At the RSCM T1+T2 accounted for 19.59%, and in the 1st batch T1+T2 accounted for 19%, while at the CIH, it was 83.6%. The reversed occurred for T3 and T4. At RSCM it was 80.4% (batch 2), or 81% (batch 1), while at the CIH only 11.4%. At RSCM, the majority (more than 80%), were of T3+T4 size, while at CIH the majority (more than 80%) were of T1+T2 size. At their presentation, the tumor size of breast cancer among Indonesian females was larger than that among Japanese females.

It is well established that the size of an invasive mammary cancer is an independent prognostic variable.[17,18] In general, the smaller the primary tumor, the lower the chance of axillary lymph node metastases. In an analysis of 200 breast cancers treated by radical mastectomy, Fisher et al[19] found that tumors less than 1cm in diameter had a 22% likelihood of axillary metastases, and tumors with more that 6cm in diameter had a 63% likelihood of axillary node metastases. Sakamoto et al[20] in a study of 936 cases of breast cancer surviving ten years, found that tumors between 2.1-5 cm in size had 51.2% 10-year survival rate, and only 39.4% for tumors with greater than 5.1 cm in size.

CONCLUSIONS

The incidence of invasive ductal carcinoma was lower at the RSCM, with a 6.43% difference. In both groups (RSCM & CIH), the invasive ductal carcinoma was the most common, accounting for at least 80% of breast cancer. Among the special types, the incidence rates of mucinous and invasive lobular carcinoma at the RSCM were lower than at the CIH, while the medullary carcinoma was higher.

At younger age group (20-29 years), breast cancer had already occurred more frequently in the Indonesian females as compared to the Japanese females. At their presentation, the tumor size of breast cancer among Indonesian females was larger than among Japanese females.

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APPENDIX

A. Principles of classification

1. Breast carcinoma is classified into three groups; noninvasive carcinoma, invasive carcinoma and Paget's disease.
2. Noninvasive carcinoma is classified into noninvasive ductal carcinoma and lobular carcinoma in situ; Invasive carcinoma into invasive ductal carcinoma and special types.
3. Invasive ductal carcinoma is further classified into three subgroups; papilotubular carcinoma, solid-tubular carcinoma and scirrhous carcinoma.

B. Definition of histological types

1. Invasive carcinoma

   This group represents a carcinoma with invasion.

2a. Invasive ductal carcinoma

   This is classified into three subgroups; papilotubular carcinoma, solid-tubular carcinoma and scirrhous carcinoma. Classification of invasive carcinoma follows the rule of predominancy when there are two or more histological patterns. In a case where judgement of the predominant type is difficult, the least differentiated type should be chosen as the histological type, with supplementary description of other histological types.

   Remark 1:
   In practice, the predominant histological type should be taken for the principal classification, and the secondary histological type should be added as a supplementary description.

   Remark 2:
   The degree of differentiation from poor to well is in order of scirrhous carcinoma, solid-tubular carcinoma and papilotubular carcinoma.

   Remark 3:
   A lesion with slight extraductal invasion should be so described for easier correspondence with the WHO classification.

2.a1. Papilotubular carcinoma

   This carcinoma is characterized by papillary projection and tubule formation, and may contain a solid pattern inpart. Comedocarcinoma belongs to this type.

   Remark 1:
   Comedocarcinoma should be identified as that.

   Remark 2:
   Papillary carcinoma which is an independent histological type in the WHO classification has been included in papilotubular carcinoma. However, there is still room for further consideration.

2.a2. Solid-tubular carcinoma

   This is a carcinoma characterized by a solid cluster of cancer cells with expansive growth forming sharp borders.

   Note: Since this type is characterized by distinct bounderies, tumors composed of medullary and/or solid nests are also included, even if interstitial components of stromal tissue are present. Central necrosis or fibrosis may also be evident.

2.a3. Scirrhous carcinoma

   Cancer cells of this histologic type show scattered invasion into the stroma in small clusters or in trabecular structures with accompanying desmoplasia of varying degrees. There are two subtypes. One is a pure scirrhous carcinoma which has extremely small amount of intraductal component and extensive stromal invasion. The other derives from papilotubular or solid-tubular carcinoma with a predominance of diffuse stromal invasion.

   Note: The differential diagnosis between scirrhous carcinoma and solid-tubular carcinoma relies on the size of cancer nests and the fashion of filtration at the tumor margin. Scirrhous carcinoma is composed of small nests, grows diffusely and infiltrates into the stromal tissue. On the other hand, solid-tubular carcinoma has large nets, grows expansively and is well circumscribed.