Molecular Subtypes of Breast Cancer Emerging in Young Women in Taiwan: Evidence for More Than Just Westernization as a Reason for the Disease in Asia

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Abstract

Background: **In the past two decades, the incidence of breast cancer in young Taiwanese females has been rapidly increasing, approaching the risk level of western countries. As a first step to investigate the possible etiology, we examined the molecular subtypes of female breast cancer in Taiwan.**

Methods: **This study included 1,028 consecutive patients with breast cancer diagnosed in National Taiwan University Hospital between 2004 and 2006. Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2, cytokeratin 5/6, and epidermal growth factor receptor expression and/or gene amplification were analyzed.**

Results: **Younger (≤50 years) breast cancer patients had a higher prevalence of luminal A (67% versus 57%; $P < 0.001$) and a lower prevalence of basal-like subtype (9% versus 17%; $P < 0.001$) compared with older (>50 years) patients. The higher prevalence of luminal A subtype was mainly attributed to a higher ER (75% versus 63%; $P < 0.001$) and PR (47% versus 33%; $P < 0.001$) expression rate in younger patients than older patients. Tumors with histologic grade 3 were less prevalent in younger patients than in older patients (23% versus 30%; $P = 0.01$). For very young (<35 years) patients, the molecular subtype distribution, ER and/or PR expression rate, and histologic grade were not significantly different from those of less young (35-50 years) patients.**

Conclusions: **Young breast cancer patients in Taiwan are characterized by a high prevalence of luminal A subtype and low prevalence of histologic grade 3 tumor and/or basal-like subtype. These features are distinct from young breast cancer patients in western countries.**

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Introduction

Although the incidence of invasive breast cancer in women is lower in Asian countries than in western countries, it has been rapidly increasing in parts of Asia, including Singapore, Korea, Japan, and Taiwan (1-4). Similar to findings in Japan (3), our previous age-period-cohort analysis showed a significantly stronger birth cohort effect on the incidence trend of breast cancer in Taiwanese than in Caucasian Americans. The increase in breast cancer incidence was striking in women born after the 1960s. For women born from 1961 to 1969, the incidence rate of breast cancer from age 30 to 35 years (23.03 of 100,000) was quite close to that of Caucasian Americans (24.08 of 100,000; refs. 4, 5). This strong birth cohort effect suggests that a change in environmental exposure might have had a great effect on the pathogenesis of breast cancer in these countries. The most widely cited environmental factor responsible for increasing the incidence of breast cancer in developing countries is the westernized lifestyle (6). However, evidence for this hypothesis remained to be explored. A reasonable first step to test this hypothesis is to compare the molecular subtypes between the two populations. If the westernized lifestyle is the only reason for the rapid increase in breast cancer in young women in Asia, it can be expected that the characteristics of these tumors should be similar to their age counterpart of those in Occidental populations.

In Occidental populations, younger (<50 years) women are more likely to have biologically aggressive breast cancer as shown by higher proportions of estrogen receptor (ER)-negative and histologic grade 3 tumors compared with older (≥50 years) women (7, 8). The very young (<35 years) patients have even higher proportion of aggressive breast tumors compared with less young patients (35-50 years; refs. 7, 9). Among patients with the same age groups, Surveillance, Epidemiology, and End Results database showed that African American had higher proportions of aggressive breast tumors compared with non-African American (10, 11).

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Since the year 2000, several gene expression profiling studies have led to the classification of breast carcinomas as luminal A, luminal B, human epidermal growth factor receptor-2 (HER-2)-overexpressing, basal-like, and normal breast subtypes, which differ markedly in prognosis (12-15). However, these gene expression studies examined relatively small samples from frozen tumor banks. Immunohistochemistry is a more feasible surrogate method for systematically evaluating the incidence of these molecular subtypes in a large population-based study. Several studies have successfully classified the breast cancer subtypes using immunohistochemistry to analyze ER, progesterone receptor (PR), HER-2, cytokeratin (CK) 5/6, and epidermal growth factor receptor (EGFR) expression in sections of formalin-fixed, paraffin-embedded tumors. The classification of molecular subtypes has been shown to provide prognostic information (16-18) and aid in delineating etiologic and pathogenetic mechanisms of breast cancer (19).

To investigate the possible etiologies for the increasing young breast cancer rate in Taiwan, this study employed immunohistochemical techniques to identify their clinicopathologic features and molecular subtypes.

Materials and Methods

Patients and Tumor Samples. This study included consecutive patients with invasive breast carcinoma, newly diagnosed at National Taiwan University Hospital (NTUH) between January 2004 and December 2006. Data on demographic and tumor characteristics were obtained from a prospectively collected database maintained by the Cancer Registry and the Office of Medical Records at NTUH. Patients with carcinoma *in situ* with microinvasion <2 mm were excluded. The Research Ethics Committee of NTUH approved this study protocol.

Evaluation of ER, PR, HER-2, CK5/6, and EGFR Status. The status of ER, PR, and HER-2 in tumors was determined by immunohistochemistry and prospectively recorded. Immunohistochemistry was done on formalin-fixed, paraffin-embedded tissue sections (thickness 4 μm) in the Central Pathology Laboratory at NTUH. ER and PR were determined using the Ventana Benchmark system (Ventana Medical Systems) and prediluted antibodies (anti-ER clone 6F11 and anti-PR clone 16). An ordinal score was assigned for each case based on the percentage of positive-staining tumor cells (0, none; 1, 1-9%; 2, 10-29%; 3, 30-49%, 4, 50-69%; and 5, 70-100%). Consistent with the clinically established cutoff points used for ER and PR positivity, tumors with ≥10% positively stained nuclei (immunohistochemistry score ≥2) were considered positive (20).

HER-2 expression was measured using the universal iView-Dab detection kit (Ventana Medical System) and anti-HER-2 (polyclonal, 1:1200; DAKOCytomation) as the primary antibody. The DAKO classification system was used to interpret HER-2 expression. Scores of 0 and 1+ were considered negative, and 3+ was considered positive. Cases with a score of 2+ were tested for gene amplification by fluorescence *in situ* hybridization (FISH) using the U.S. Food and Drug Administration-approved PathVysion assay (Vysis). A ratio of *HER-2* gene/chromosome 17 ≥2.0 was considered positive. All FISH analysis was centrally done at the National Health Research Institutes in Taipei. Specimens were considered HER-2 positive if they had an immunohistochemistry score of either 3+ or 2+ with gene amplification identified by FISH (21).

For triple-negative (ER-/PR-/HER-2-) breast tumors, immunohistochemical studies for CK5/6 and EGFR were done to identify the basal-like subtype. The primary antibody for CK5/6 was D5/16 B4 (DAKOCytomation). Preputial epithelium was used as a positive control and omission of the primary antibody incubation step was used as a negative control. CK5/6 was scored positive if any cytoplasmic and/or membranous staining was seen in the tumor cells (22). EGFR was stained using the EGFR pharmDX immunohistochemistry assay (DAKO code K1494) with the DAKO autostainer. The cell lines HT-29 and CAMA-1 supplied by the manufacturer were used as positive and negative controls, respectively. The intensity of EGFR staining was scored as follows: 0 (no staining observed), 1+ (faint brown membranous staining), 2+ (intermediate brown membranous staining), and 3+ (dark brown or black membranous staining). EGFR was considered positive if any membranous staining in tumor cells was observed (22).

Tumor Histology and Definition of Breast Cancer Immunohistochemistry Subtypes. All histological slides were reviewed by one pathologist (J-Y.L.) and tumors were classified according to the Nottingham modification of the Scarff-Bloom-Richardson criteria (23), except for invasive lobular and mucinous carcinomas. Based on histology, tumors were classified into the following five groups: A (invasive ductal carcinomas not otherwise specified; medullary, apocrine, and neuroendocrine carcinomas), B (tubular, mucinous, papillary carcinoma, and cribriform carcinomas), C (metaplastic, anaplastic, and undifferentiated high-grade carcinomas), D (invasive lobular carcinomas), and E (mixed ductal and lobular carcinomas; ref. 16).

According to the definitions used in prior studies, the immunohistochemistry subtypes were as follows: luminal A (ER+ and/or PR+, HER-2-), luminal B (ER+ and/or PR+, HER-2+), HER-2+/ER- (ER-, PR-, and HER-2+), basal-like (ER-, PR-, HER-2-, CK5/6+, and/or EGFR+), and unclassified (negative for all five markers; refs. 16, 22).

Statistical Analysis. Data on clinicopathologic features among the three age groups (<35, 35-50, and >50 years) were compared by χ^2 test. Differences in clinicopathologic characteristics among the breast cancer subtypes were examined using one-way ANOVA for age and χ^2 tests for the remaining variables. Fisher's exact test with the Monte Carlo method was used when expected cell counts were <5. These analyses were done using SPSS for Windows version 13.0 software.

Results

Clinicopathologic Characteristics by Age Groups. After excluding 17 patients with carcinoma *in situ* with microinvasion and 3 patients with triple-negative infiltrating ductal carcinoma with unavailable archival tissues, a total of 1,028 patients with a median age of 50 years (range, 23-88 years) were included in the analysis. Among the 48 patients who received neoadjuvant chemotherapy, axillary lymph node status was not available in 16 patients and stage could not be categorized into I, II, III, or IV according to the American

Joint Committee on Cancer (6th edition) criteria in 13 patients. Histologic grade was not evaluated in 41 invasive lobular carcinomas, 24 mucinous carcinomas, and 7 papillary carcinomas and could not be identified in 7 invasive ductal carcinomas and 2 mixed ductal and lobular carcinomas.

Table 1 summarizes the demographic and tumor characteristics of patients by age group. There was no significant difference among age groups in American Joint Committee on Cancer stage, axillary lymph node status, histology type, and HER-2 status. The frequencies of ER+ tumor, PR+ tumor, and ER+/PR+ subtype were significantly higher in younger (≤50 years) than in older (>50 years) patients ($P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively). There was a significant heterogeneity of histologic grade between younger (≤50 years) and old (>50 years) patients ($P = 0.02$). Tumors with histologic grade 3 were less prevalent in younger (≤50 years) than in older (>50 years) patients (23% versus 30%; $P = 0.01$). Moreover, comparisons of very young (<35 years) and less young (35-50 years) patients revealed that the frequencies of ER+ tumor, PR+ tumor, ER/PR subtype, and histologic grade were not significantly different ($P = 0.80$, 0.24, 0.60, and 0.40, respectively).

Molecular Subtypes and Expression of Markers by Age Groups. The 1,028 tumors were classified as luminal A in 635 (62%), luminal B in 90 (9%), HER-2+/ER- in 121 (12%), basal-like in 132 (13%), and unclassified subtype in 50 (5%) tumors. Younger (≤50 years) patients had a significantly higher prevalence of luminal A (67% versus 57%; $P < 0.001$) and a significantly lower prevalence of basal-like subtype (9% versus 17%; $P < 0.001$) when compared with older (>50 years) patients. There was a trend toward lower prevalence of HER-2+/ER- in younger (≤50 years) than in older (>50 years) patients (10% versus 14%; $P = 0.06$). The prevalence of luminal B and unclassified subtypes, however, was not significantly different between these two groups. In the very young (<35 years) age group, the distribution of molecular subtypes was not significantly different from those in the less young (35-50 years) age group ($P = 0.56$).

Table 1. Clinicopathologic characteristics and molecular subtypes of the three age groups (<35, 35-50, and >50 y)

Characteristics	Total	No. (%)		*P*	No. (%)		*P*
		<35 y	35-50 y		<50 y	>50 y	
Case no.	1,028	65	450		515	513	
American Joint Committee on Cancer stage							
I	316	22 (35)	152 (34)	0.98	174 (34)	142 (28)	0.17
II	471	29 (46)	194 (44)		223 (44)	248 (49)	
III	176	9 (14)	75 (17)		84 (17)	92 (18)	
IV	52	3 (5)	22 (5)		25 (5)	27 (5)	
NA	13	2	7		9	4	
Lymph node status							
+	458	26 (41)	200 (45)	0.53	226 (45)	232 (46)	0.84
–	554	37 (59)	240 (55)		277 (55)	277 (54)	
NA	16	2	10		12	4	
Histology group							
A	943	61 (94)	414 (92)	0.40	475 (92)	469 (91)	0.27
B	34	4 (6)	16 (4)		20 (4)	14 (3)	
C	3	0	1 (0)		1 (0)	2 (0)	
D	43	0	15 (3)		15 (3)	26 (5)	
E	5	0	4 (1)		4 (1)	2 (0)	
Histologic grade							
1	188	12 (20)	93 (22)	0.85	105 (22)	83 (18)	0.02
2	511	32 (54)	231 (56)		263 (55)	248 (53)	
3	248	15 (25)	92 (22)		107 (23)	141 (30)	
NA	81	6	34		40	41	
ER status							
+	708	48 (74)	339 (75)	0.80	238 (75)	321 (63)	<0.001
–	320	17 (26)	111 (25)		128 (25)	192 (37)	
PR status							
+	440	30 (44)	243 (54)	0.24	273 (47)	167 (33)	<0.001
–	588	35 (56)	207 (46)		242 (53)	346 (67)	
Combined ER/PR status							
+/+	423	29 (45)	235 (52)	0.60	264 (51)	159 (31)	<0.001
+/–	285	19 (29)	104 (23)		123 (24)	162 (32)	
–/+	17	1 (2)	8 (2)		9 (2)	8 (2)	
–/–	303	16 (25)	103 (23)		119 (23)	184 (36)	
HER-2 status							
+	211	13 (20)	89 (20)	0.97	102 (20)	109 (21)	0.57
–	817	52 (80)	361 (80)		413 (80)	404 (79)	
Molecular subtype							
Luminal A	635	41 (63)	304 (68)	0.56	345 (67)	290 (57)	<0.001
Luminal B	90	8 (12)	43 (10)		51 (10)	39 (8)	
HER-2+/ER–	121	5 (8)	46 (10)		51 (10)	70 (14)	
Basal-like	132	9 (14)	38 (9)		47 (9)	85 (17)	
Unclassified	50	2 (3)	19 (4)		21 (4)	29 (6)	

Abbreviation: NA, not available.

Because of the heterogeneity of molecular subtypes among the different age groups, we analyzed the association of each age group with each of the expression markers and summarize the findings in Table 2. The immunohistochemistry scores for ER and PR differed significantly among the three age groups ($P < 0.001$ and $P < 0.001$, respectively). Younger (≤50 years) patients had a higher prevalence of tumors with high ER or PR expression (immunohistochemistry score 4/5) compared with older (>50 years) patients (ER, 70% versus 60%; $P < 0.001$ and PR, 32% versus 18%; $P < 0.001$). The prevalence of tumors with high ER or PR expression (immunohistochemistry score 4/5) was not significantly different between very young (<35 years) and less young (35-50 years) groups. These results indicated that younger (≤50 years) patients had a higher prevalence of ER+ or PR+ tumors even when only high immunohistochemistry scores were considered positive. Immunohistochemistry scores for HER-2 did not vary significantly among the three age groups. The prevalence of HER-2 3+ tumors also did not vary significantly among the three age groups (14% versus 16% versus 16%; $P = 0.89$). Among the 147 HER-2 2+ tumors, 49 (33%) were confirmed to have *HER-2* gene amplification by FISH. As defined by the results of immunohistochemistry and FISH, the prevalence of HER-2 positivity did not differ significantly among the three age groups. Among the 182 triple-negative (ER-/PR-/HER-2-) tumors, 124 (68%) were CK5/6 positive and 138 (76%) were EGFR positive. Representative CK5/6 and EGFR immunohistochemistry results for triple-negative tumors are shown in Fig. 1. The prevalence of CK5/6 positivity and EGFR intensity did not differ significantly among the three age groups (Table 2). These results indicate that the high prevalence of luminal A and low prevalence of basal-like subtype in younger (≤50 years) patients were mainly attributable to the high prevalence of ER and/or PR expression.

Table 2. Immunohistochemistry (ER, PR, HER-2, CK5/6, and EGFR) and FISH (HER-2/*neu*) results among the three age groups (<35, 35-50, and >50 y)

Marker	Total	No. (%)			*P*
		<35 y	35-50 y	>50 y	
Case no.	1,028	65	450	513	
ER					
5	575	42 (64)	258 (57)	275 (54)	<0.001
4	91	5 (9)	56 (13)	30 (6)	
3	31	0 (0)	21 (5)	10 (2)	
2	11	1 (2)	4 (1)	6 (1)	
1	8	0 (0)	4 (1)	4 (1)	
0	312	17 (26)	107 (24)	188 (37)	
PR					
5	152	11 (17)	87 (19)	54 (11)	<0.001
4	106	8 (12)	61 (14)	37 (7)	
3	107	4 (6)	59 (13)	44 (9)	
2	75	7 (11)	36 (8)	32 (6)	
1	75	2 (3)	30 (7)	43 (8)	
0	513	33 (51)	177 (40)	303 (59)	
HER-2					
3+	161	8 (12)	70 (16)	83 (16)	0.88
2+ with FISH+	50	5 (8)	19 (4)	26 (5)	
2+ with FISH-	100	8 (12)	46 (10)	46 (9)	
1	285	19 (29)	129 (29)	137 (27)	
0	432	25 (38)	186 (41)	221 (43)	
CK5/6					
+	124	9 (82)	36 (63)	79 (69)	0.45
0	58	2 (18)	21 (37)	35 (31)	
EGFR					
3+	16	0 (0)	4 (7)	12 (11)	0.09
2+	38	6 (55)	7 (12)	25 (22)	
1+	84	3 (27)	28 (49)	53 (46)	
0	44	2 (18)	18 (32)	24 (21)	

Correlation of Clinicopathologic Characteristics with Molecular Subtypes. The correlation of clinicopathologic characteristics with molecular subtypes is shown in Table 3. Among the molecular subtypes, significant differences were found in age ($P = 0.006$), American Joint Committee on Cancer stage ($P = 0.02$), axillary lymph node status ($P < 0.001$), histology group ($P = 0.002$), and histologic grade ($P < 0.001$). Patients with basal-like or unclassified subtype were older than those with other subtypes. Patients with HER-2+/ER- subtype were most likely to have positive axillary lymph nodes. Basal-like, HER-2+/ER-, and unclassified subtypes were associated with a higher prevalence of histologic grade 3 tumors. Luminal A subtype was associated with a higher prevalence of histology group B and group D, which were highly correlated with ER expression.

Discussion

In this study, we analyzed the molecular subtypes of breast cancer in women and their prevalence in different age groups in Taiwan using immunohistochemical surrogates for breast cancer subtypes. In contrast to previous data for Caucasians and African Americans (16, 19), younger (≤50 years) Taiwanese patients with breast cancer had a higher prevalence of luminal A, a lower prevalence of basal-like subtype, and a lower prevalence of histologic grade 3 tumors compared with older (>50 years) patients. The higher prevalence of luminal A subtype was mainly attributed to a higher ER and/or PR expression rate in younger patients than older patients.

In the present study, the fractionated ER score was shown to display a bimodal distribution, with substantial proportions at score 5 (56%) and score 0 (30%; Table 2). The bimodal distribution was consistent in the three age groups and quite close to recent reports (24, 25). As previous reports (25, 26), we also observed some patients whose tumors expressed PR but not ER albeit at a low frequency (2%). These indicate that the variation of ER assessment in different pathology laboratories may not affect the result.

Furthermore, to avoid the risk of bias due to data collected from a single institute, we compared differences in age distribution and hormone receptor expression in different age groups between the present study and that from Taiwan Cancer Database. Taiwan Cancer Database was initiated in 2003 by the Bureau of Health Promotion, Department of Health, Taiwan. A joint breast cancer treatment committee at each participant hospital had established a prospectively collected database (27). Thirty-two hospitals including NTUH had participated in this program by 2006. A total of 6,339 patients were included by Taiwan Cancer Database between January 1 and December 31, 2005. The age-related (<35, 35-50, and >50 years) prevalence rates of breast cancer used in the present study (6%, 44%, and 50%) and those in the Taiwan Cancer Database (5%, 44%, and 52%) were similar. The data from Taiwan Cancer Database consistently showed that younger patients (≤50 years) had higher prevalence of ER (66% versus 57%; $P < 0.001$) and PR (62% versus 49%; $P < 0.001$)

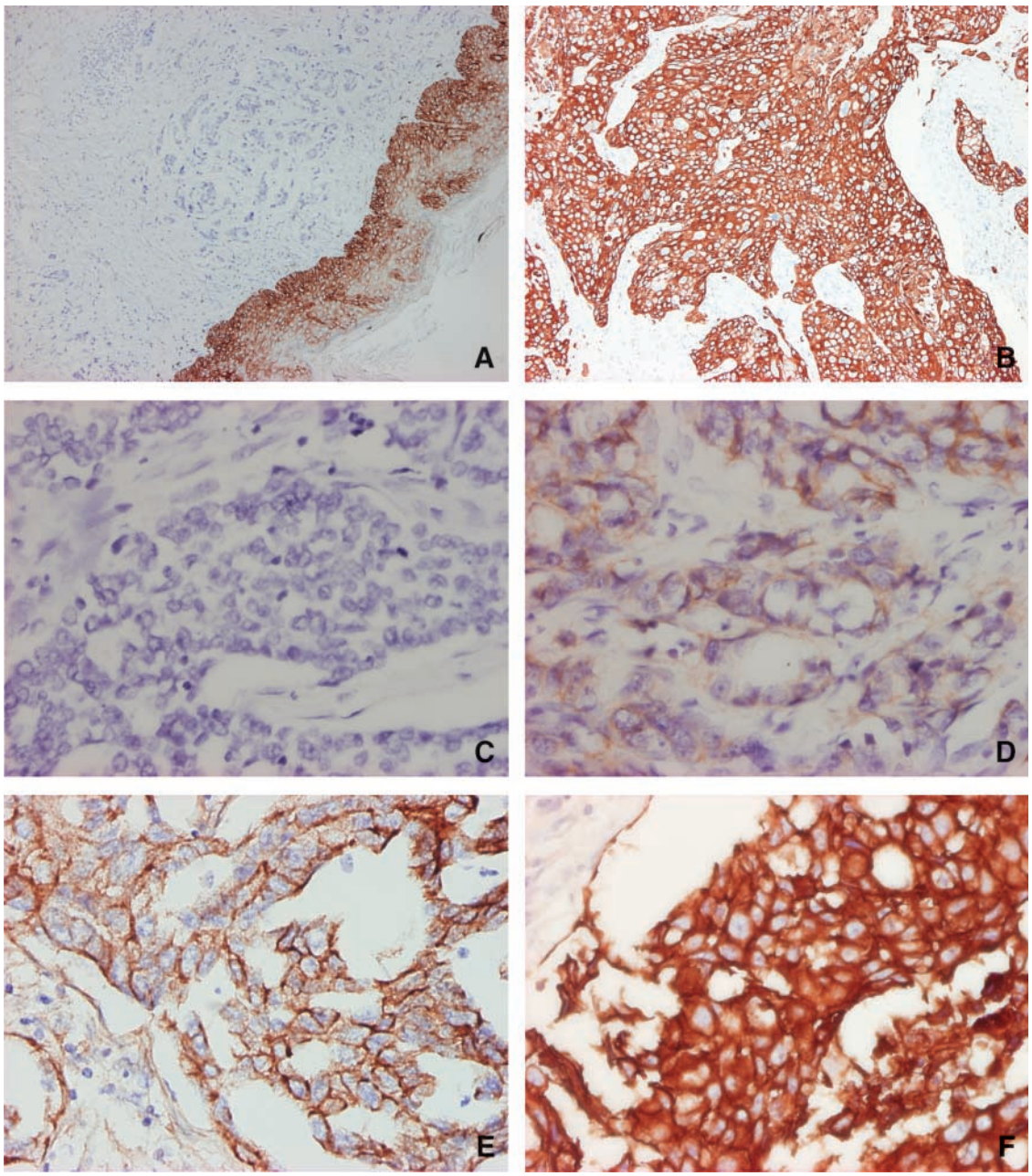

Figure 1. Immunohistochemical analysis of CK5/6 and EGFR in triple-negative tumors. **A.** Absence of CK5/6 in tumor cells but positive in the surrounding skin tissue. **B.** Diffuse strong expression of CK5/6 in tumor cells. EGFR expression in four tumors with scores of 0 (**C**), 1+ (**D**), 2+ (**E**), and 3+ (**F**), respectively. Original magnifications, ×40 (**A** and **B**) and ×200 (**C-F**).

expression compared with older patients (>50 years; ref. 28). This finding confirmed that the subjects in the present study were representative of the population in Taiwan and the use of different methods and criteria of positivity for ER and PR evaluation at different hospitals did not affect the unique finding that prevalence of hormone receptor expression was higher in younger patients in Taiwan.

Four population-based studies, which used the same immunohistochemistry markers, have been previously reported and summarized in Table 4 (16-19). The Carolina Breast Cancer Study conducted in the United States showed that premenopausal African Americans had a significantly lower prevalence of luminal A (36% versus 59%; $P < 0.001$) and a higher prevalence of basal-like subtype (39% versus 14%; $P < 0.001$) compared with postmenopausal African Americans. The higher prevalence of basal-like subtype could contribute to the poor prognosis of premenopausal African Americans with breast cancer. In non-African Americans, the frequencies of luminal A (51% versus 58%; $P = 0.20$) and basal-like (16% versus 16%; $P = 0.94$) subtypes did not differ significantly between premenopausal and postmenopausal patients

Table 3. Correlation of molecular subtypes and clinicopathologic characteristics

Characteristics	Total	No. (%)					*P*
		Luminal A	Luminal B	HER-2+/ER-	Basal-like	Unclassified	
Case no.	1,028	635	90	121	132	50	
Age, mean (SD), y	51	51 (11)	50 (12)	52 (9)	54 (13)	54 (11)	0.006
American Joint Committee on Cancer stage							
I	316	196 (31)	29 (33)	33 (27)	36 (27)	22 (44)	0.02
II	471	295 (47)	36 (40)	52 (43)	72 (55)	16 (32)	
III	176	105 (16)	21 (24)	22 (18)	19 (15)	9 (18)	
IV	52	28 (4)	3 (3)	14 (12)	4 (3)	3 (6)	
NA	13	11	1	0	1	0	
Lymph node status							
+	458	291 (47)	45 (51)	66 (55)	40 (31)	16 (32)	<0.001
–	554	331 (53)	44 (49)	54 (45)	91 (69)	34 (68)	
NA	16	13	1	1	1	0	
Histology group							
A	994	562 (89)	85 (94)	120 (99)	128 (97)	49 (98)	0.002
B	34	31 (5)	1 (1)	0 (0)	2 (2)	0 (0)	
C	3	1 (0)	1 (1)	0 (0)	0 (0)	1 (1)	
D	41	35 (6)	3 (3)	1 (1)	2 (2)	0 (0)	
E	6	6 (1)	0 (0)	0 (0)	0 (0)	0 (0)	
Histologic grade							
1	188	160 (28)	12 (14)	3 (3)	9 (7)	4 (8)	<0.001
2	511	332 (59)	48 (56)	55 (47)	54 (42)	22 (44)	
3	248	73 (13)	25 (29)	60 (51)	66 (51)	24 (48)	
NA	81	70	5	3	3	0	

(16). A study from Poland showed that premenopausal patients had a higher prevalence of basal-like subtype (17% versus 10%; $P = 0.02$) but a similar prevalence of other subtypes compared with postmenopausal patients (19). Although this study was limited by its consideration of age instead of menopausal status, the implications of findings based on such a design are supported by the Carolina Breast Cancer Study, which showed that analysis based on age <50 and ≥50 years rather than menopausal status did not affect the results (16). In addition, the definition of HER-2 positivity varied among these four previous population-based studies. In the present study, HER-2 positivity was defined as either immunohistochemistry 3+ or 2+ staining intensity with gene amplification detected by FISH. These criteria have been universally adopted in clinical practice and trials for HER-2-targeted therapy (29).

We have reported here the first study showing that, in certain geographic areas, younger patients with breast cancer may have higher prevalence of luminal A and/or hormone receptor expressions than their older counterpart. Reasons for the high prevalence of luminal A subtype and/or hormone receptor expression in emerging young Taiwanese patients remain unclear. As our previous report (4) described, the major environmental difference between younger and older generations in Taiwan seemed to be the increasing westernization of lifestyle. Taiwan has become increasingly industrialized since 1960s. Women born after the 1960s had been exposed to more high-calorie and high-fat diets in their childhood than women of previous generation. In addition, Taiwanese women had earlier menarche, reduced fertility rate, delayed childbearing, and decreased breast-feeding since 1960s (30). These factors have been linked to increasing incidence of breast cancer in Taiwan (31-33) and western countries (34-36). However, if the westernized lifestyle is the only reason for the rapid increase in breast cancer in young women in Asia, the characteristics of their tumors should be similar to those in Occidental populations. Unexpectedly, we found that the frequency of luminal A

Table 4. Summary of four population-based breast cancer subtype studies

Population (study period, y)	No. patients	Luminal A (%)	Luminal B (%)	HER-2+/ER- (%)	Basal-like (%)	Unclassified (%)
United States [Carolina Breast Cancer Study (16), 1993-1996]	496					
African American	196					
Premenopausal	97	36	9	9	39	6
Postmenopausal	99	59	16	7	14	4
Non-African American	300					
Premenopausal	164	51	18	6	16	10
Postmenopausal	136	58	16	6	16	4
Korea [1993-1998 (17)]	776	44	8	17	15	16
Japan [2000-2003 (16-18)]	793	63	20	7	8	2
Poland [2000-2003 (19)]	804					
Premenopausal	217	66	5	5	17	6
Postmenopausal	535	68	7	9	10	6
Taiwan (2004-2006)	1,028					
≤50 y	515	67	10	10	9	4
>50 y	513	57	8	14	17	6

subtype was even more prevalent in younger (≤50 years) Taiwanese patients (66%) than premenopausal African Americans (36%) and non-African Americans (51%). Furthermore, the basal-like breast cancer was less prevalent in younger Taiwanese (9%) than in premenopausal African Americans (39%) and non-African Americans (16%). It is difficult to compare the present study with other three population-based studies, because the studies from Korea and Japan did not report the molecular subtype distribution by age or menopausal status (17, 18) and the study from Poland showed an exceptionally low (10%) prevalence of HER-2 expression related (luminal B plus HER-2+/ER-) subtypes in premenopausal patients (19) compared with others studies and previous reports (37, 38). The low sensitivity of HER-2 detection in the latter study may significantly affect the distribution of all subtypes.

The very young (<35 years) Taiwanese patients were also found to have high frequency of luminal A (63%) subtype and ER expression (74%). The ER expression rate was higher than several previous reports of the same age group from the United States (range, 48-57%; refs. 7, 39) and Europe (range, 51-69%; refs. 9, 40-42). Previous studies from western countries consistently showed that ER expression in very young patients was associated with worse prognosis (40, 41). However, we analyzed 178 very young breast cancer patients diagnosed at NTUH between 1997 and 2006 and found that ER expression was associated with favorable prognosis.[6] In addition, the frequency of histologic grade 3 tumor was lower in very young patients in Taiwan (25%) than in the United States (range, 49-61%; refs. 39, 43) and Europe (range, 48-80%; refs. 9, 40-42). These findings implied that the emerging young breast cancer in Taiwan might not just be a mirror image of their western counterpart.

Genetic factors or interactions of genetic factors with other environmental factors may contribute to the young female breast carcinogenesis in Taiwan and in parts of Asia. For example, the Japanese study also revealed a high prevalence of luminal A subtype (63%) and a low prevalence of basal-like subtype (8%) in breast cancers, although an age-specific variation was not described (18). These observations suggest that ethnic differences in breast carcinogenesis exist among Asian and Occidental populations. Determining how these ethnic factors may interact with environmental factors leading to carcinogenesis in young breast cancer in Taiwan, and possibly some other Asian countries alike, is a challenging but important problem that must be solved if the surge in breast cancer is to be limited in this part of the world.

Disclosure of Potential Conflicts of Interest

The authors have no potential conflicts of interest that are relevant to the research described in this article.

[6] C-H. Lin, C-S. Huang, Y-S. Lu, et al. Avaluation of estrogen receptor expression as a prognostic factor for very young women (below 35 years) with breast cancer in Taiwan. Unpublished data.

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