lymphovascular invasion, nuclear grade, and the interval from primary operation to IBTR were significantly associated with DM. Short DFI was reported to be highly correlated with subsequent DM.[21,25,26,31,41–44] These risk factors appear to reflect the inherent aggressive characteristics of primary tumors.[38,39] Thus the risk of developing DM would be predetermined before treatment, with local recurrence being a manifestation of this risk.

The time distribution of annual rates of DM among patients with IBTR showed a noteworthy pattern. Two peaks in the incidence of DM were observed; 4 to 5 years and 12 to 13 years after primary operation. In patients without IBTR, a peak of incidence was seen 3 to 4 years after primary operation, with a gradual decrease thereafter. Our results agreed with the long-term results of NSABP B-06 and some other studies.[32,33] Some groups have presumed that the second peak of DM was due to IBTR.[28,29] Considering that late distant metastases are not likely to develop so frequently after mastectomy, IBTR may be a cause of DM in such cases. Up to now, many investigators thought that IBTR was only a marker for DM[19,20,23,24] because many cases of IBTR that subsequently developed DM had more aggressive primary tumor characteristics. Recently, however, it appears that additional radiation may lead to a survival benefit, suggesting IBTR may, in part, be a cause of DM, especially in cases of IBTR who develop late DM.[45]

Classifying IBTR into true recurrence (TR) or new primary tumor (NP) is one of the concerns. The finding that cumulative incidence of IBTR is linear to 7 years and flattens slightly thereafter (Table 1. line graph) suggests that not a few cases of late recurrence may be NP recurrence. In the current study, we did not distinguish a second primary breast cancer from true recurrence because it is difficult to correctly diagnose. Some studies suggest the prognostic significance of IBTR from this viewpoint. True recurrence is generally thought to have worse prognosis than a new primary tumor.[46–48] Haffty and colleagues speculated that a certain portion of IBTR contained new primary tumor and biologic behaviors were quite different.[48,49] So it is noteworthy that IBTR represent two distinct entities, and classifying IBTR may help our understanding of the complicated behavior of IBTR.

In summary, young age, positive surgical margin, and omission of radiation therapy are independent risk factors for IBTR, and IBTR was certainly correlated with subsequent DM. Initial nodal status and the interval to IBTR were significantly associated with DM after IBTR. It remains unclear whether IBTR is an indicator of DM or a cause of it. Further study is needed to solve this question.

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原著

2007.3.5受付

Intracystic papillary carcinoma (ICPC) の診断と臨床的特徴
—自験例14例からの検討—

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Clinical and Pathological Features of Intracystic Papillary Carcinoma (ICPC) of The Breast：Akagi T[*1], Kinoshita T[*1], Shien T[*1], Hojo T[*1] and Akashi S[*1] ([*1]Breast surgery division, National cancer center hospital)

Background：Intracystic papillary carcinoma (ICPC) of the breast is rare and preoperative diagnosis is difficult. Materials and Methods：This study investigated the clinical and pathological features of ICPC. Fourteen ICPC were included in this study. We reviewed their clinicopathological findings and treatments. Results：In 9 cases, diagnoses of ICPC were obtained using fine needle aspiration and core needle biopsy. In 5 cases, a diagnosis could not be obtained preoperatively. MRI in addition to sonography helped to establish the differential diagnosis from benign tumor and maintain disease-free surgical margins. Conclusion：Preoperative diagnosis of ICPC is difficult and excisoinal biopsy was necessary unless fine needle aspiration and core needle biopsy can obtain the diagnosis. MRI is available to diagnose the invasiveness of this disease.

Key words：Intracystic papillary carcinoma, Preoperative diagnosis
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はじめに

Intracystic papillary carcinoma (ICPC) は乳癌全体の約2％弱[1]とまれな疾患である．現在の乳癌取扱い規約では非浸潤性乳管癌ductal carcinoma *in situ* (DCIS) に含まれ，線維性の壁に囲まれた内腔へ乳頭状に突出し発育する乳癌で，通常周囲間質に高度の浸潤を伴わないとされる[2]．しかし，組織学的に嚢胞壁外や乳管内での高度の進展を示す例[3]や，同時性肝転移例[4]などの報告もある．また良性嚢胞腫瘍との鑑別が困難である．今回われわれは，ICPCの14例を経験したので臨床病理学的検討とともに若干の文献的考察を加えて報告する．

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1. 対象と方法

2000年10月から2006年12月まで当科で経験した原発性乳癌は約2,700症例，そのうちICPCと診断されたのは14例0.51％であった．この14例において臨床病理学的特徴，予後を検討し，さらに免疫組織染色によりホルモンレセプター，HER2，p53を評価した．

2. 結　果

1) 臨床的特徴（表1）

年齢は中央値72.5歳（36～82歳）で，14人のうち1人が男性，女性13人のうち3例が閉経前，10例は閉経後であった．主訴は全例乳房腫瘤で，自己発見が13例，検診発見が1例で，腫瘍径の中央値は25.5mm（11～220mm）であった．占拠部位はA領域に7例，B領域に1例，C領域に2例，D

表1　Intracystic papillary carcinomaの臨床的特徴および診断

症例	年齢・性	病悩期間（月）	部位	US最大径（囊胞mm）	US最大径（充実内腫瘤mm）	US充実腫瘤形状	MMG腫瘤陰影	MMG石灰化	MRI	FNA	CNB	術前病理診断
1	84・F	2	右A	22	5	不整型	辺縁不整	なし	／	／	／	なし
2	83・F	2	左D	11	6	整型	辺縁平滑	なし	／	class 5	／	DC
3	75・F	3	右A	22	7	不整型	辺縁不整	A	／	class 3	+	なし
4	60・F	4	右B	36	10	整型	辺縁平滑	なし	／	class 2	+	なし
5	43・F	3	左A	15	3	整型	辺縁平滑	なし	／	／	+	なし
6	36・F	9	左C	34	17	不整型	はっきりせず	なし	／	／	+	ICPC
7	57・F	4	左E	10	4	整型	辺縁平滑	なし	／	class 5	／	DC
8	70・M	6	左E	50	15	不整型	辺縁不整	なし	／	／	+	ICPC
9	75・F	2	右A	28	20	整型	辺縁平滑	A	／	class 5	／	DC
10	48・F	3	左A	23	5	整型	辺縁平滑	P	／	class 2	+	なし
11	74・F	8	左A	14	14	整型	／	／	／	／	+	ICPC
12	82・F	24	右C	200	30	整型	／	／	BCP	class 2	+	ICPC
13	81・F	2	右A	170	52	不整型	辺縁不整	なし	BCP	class 2	+	ICPC
14	71・F	2	左E	60	21	不整型	辺縁平滑	なし	BCP	／	+	ICPC

＊US：乳腺超音波検査．A：amorphous集簇．P：pleomrphic集簇．BCP：乳癌造影パターン
FNA：Fine needle aspiration．CNB：Core needle biopsy．DC：ductal carcinoma．

表2　手術・病理所見

症例	術式	囊胞壁外浸潤	周囲DCIS	リンパ節転移	各種レセプター	p53	G	NG
1	Bp	なし	なし	郭清なし	ER 2 PgR 2 HER 2+	−	1	1
2	Bp	なし	なし	郭清なし	ER 2 PgR 0 HER 2−	−	1	1
3	Bt+sampling	なし	なし	0/2	ER 2 PgR 2 HER 2−	+	2	2
4	Bq	なし	なし	郭清なし	ER 2 PgR 1 HER 2−	−	2	2
5	Bp+Ax	なし	なし	0/11	ER 2 PgR 2 HER 2−	−	2	2
6	Bp+Ax	なし	あり	0/22	ER 2 PgR 2 HER 2−	−	1	1
7	Bt+Ax	なし	なし	0/20	ER 2 PgR 2 HER 2+	−	2	2
8	Bp	なし	なし	郭清なし	ER 2 PgR 2 HER 2+	2+	2	2
9	Bt+Ax	なし	なし	0/18	ER 1 PgR 1 HER 2−	−	2	3
10	Bq+SLN	なし	なし	0/4	ER 1 PgR 2 HER 2−	−	1	1
11	Bp	あり	なし	郭清なし	ER 2 PgR 2 HER 2−	−	1	1
12	Bt+SLN	なし	なし	1/5	ER 3 PgR 3 HER 2−	−	1	1
13	Bt+SLN	なし	あり	0/5	ER 3 PgR 3 HER 2−	−	1	1
14	Bt+SLN	あり	あり	0/3	ER 3 PgR 2 HER 2−	−	1	1

領域に1例で，E領域に3例に存在した．病悩期間は中央値5.2カ月（2～24カ月）であった．

2) 診断

超音波検査では1例は多房性の囊胞であったが，他13例はすべて単房性の囊胞であり，いずれの症例も内部に充実性成分を認めた．腫瘍径は中央値25.5mm（11～220mm）で，充実成分径は中央値12mm（3～52mm）であった．内部の充実成分の形状は整，不整とさまざまであった．

マンモグラフィー（MMG）は12例に施行，7例が辺縁平滑で，4例は辺縁不整の腫瘤陰影として描出され，1例はMMG上腫瘤陰影を認めなかった．amorphousおよびpleomorphicな集簇する石灰化を3例にみとめた．MRIは3例に施行，囊胞内容液はいずれも血性所見を呈した．ダイナミックスタディーでは3例（100%）ともに乳癌の造影パターンを示した．また囊胞壁外進展を1例（症例14）に認めた．8例にFine needle aspiration施行，class5が3例，class3が1例，class2が4例であった．class5であった3例はいずれもductal carcinoma疑いという結果であった．Fine needle aspirationの細胞診陽性率は8例中3例（37.5%）であった．class3以下の5例にはCore needle biopsy 追加施行した．また5例はFine needle biopsy施行せずに，はじめからCore needle biopsyを施行．計10例のCore needle biopsyを施行，

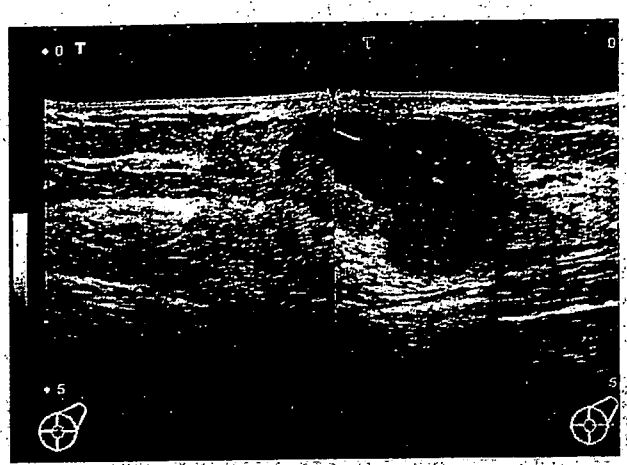

図1　超音波所見
後方エコーの増強を伴った50×43×26 mmの嚢胞と，嚢胞壁の一部から内腔に突出する21×18×7 mm大の乳頭状腫瘍を認めた．

図2　マンモグラフィー所見
medio-lateral viewでE領域に辺縁平滑で，ほぼ均一な腫瘤陰影を認めた．石灰化は認めなかった．

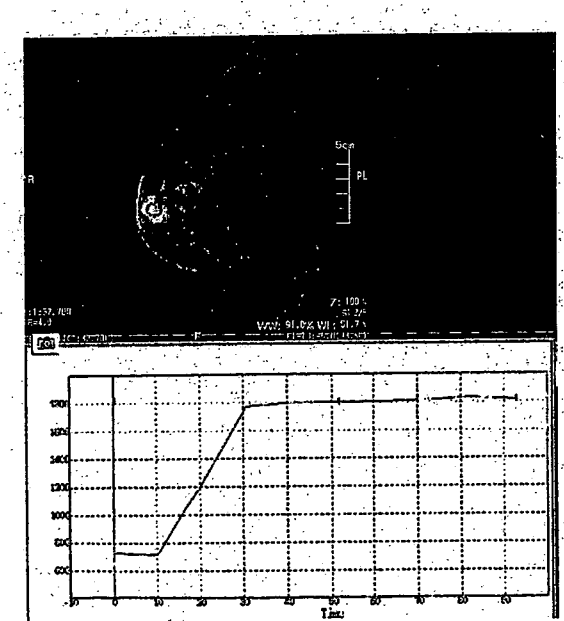

図3　MRI
ダイナミックスタディーにて乳癌の造影パターンを示した．

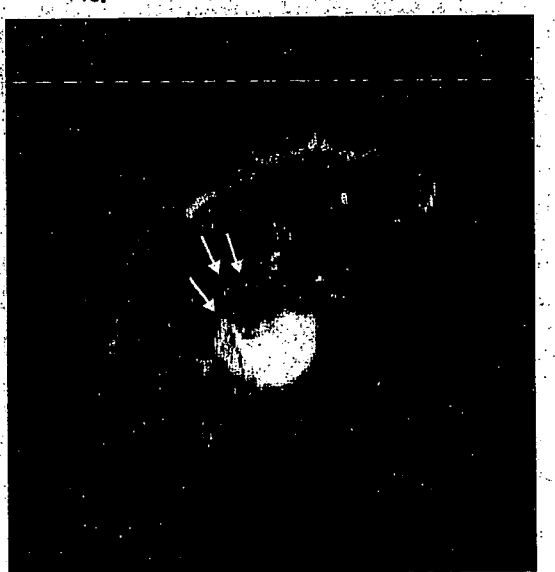

図4　MRI
T2W1において嚢胞壁と考えられる低信号域の断裂が認められ，MRI上，腫瘍の嚢胞壁外進展がみられた．

ICPCの術前病理学的診断を得た症例は計6例(60%)であり，残りの4例はCore needle biopsyでも確定できず切除生検にて乳癌の診断を得た．なお1例はFine needle aspirationおよびCore needle biopsyをともに施行せずに切除生検を行った．

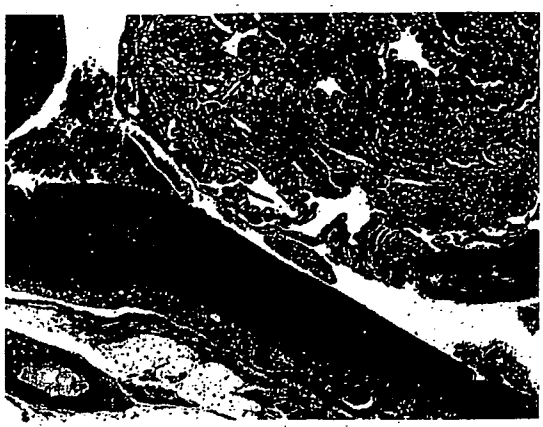

図5　病理組織所見
径5cm大の嚢胞内に2cm大の乳頭状隆起性病変を認め，嚢胞液は暗赤色であった．この隆起性病変は中等度の核異型，核分裂像を有する腫瘍細胞が乳頭状，cribriform patternを呈して増殖．

図6　病理組織所見
腫瘍細胞の間質への浸潤が認められた．

3) 手術・病理（表2）

5例に腋窩郭清を伴う乳房切除術および乳房部分切除術を施行，4例は腋窩郭清を伴わない乳房部分切除術を施行した．さらに2004年以降の4例はセンチネルリンパ節生検を伴う乳房切除術および乳房部分切除術を施行した．嚢胞内容液の性状はいずれもきわめて淡い血性から濃い暗赤色を呈し，14例のうち2例（14.2%）に間質浸潤を認めた．また3例に嚢胞壁外にDCISを認め，1例に腋窩リンパ節転移を認めた．G1とG2がそれぞれ8例（57%）6例（43%），NG1とNG2とNG3がそれぞれ8例（57%）5例（36%）1例（7%）であった．またホルモンレセプターはERが全例（100%），PgRは13例が陽性（92.8%）で，HER2は3例（21.4%），p53は2例（14.2%）が陽性であった．

4) リンパ節転移症例

ICPC14例のうち1例に腋窩リンパ節転移を認めた．本症例は82歳女性，病悩期間が24カ月，腫瘍径が20cmであった．Core needle biopsyでICPCの診断を得，乳房切除術およびセンチネルリンパ節生検を施行，術中迅速病理診断にてセンチネルリンパ節転移はなかったが，永久標本にてリンパ節1個にmicrometastasisを認めた．ER，PgRはともに陽性，HER2，p53はいずれも発現していなかった．作成標本上，嚢胞壁外への浸潤はみとめていない．

5) 補助療法・予後

13例にTAM投与，温存術8例中3例に残存乳房に対する術後照射を行った．男性症例の1例の他因死を除き，13例すべて再発の所見なく生存中である．次に代表的な1例（症例14）を提示する．

症　例：71歳，女性．

家族歴：特記事項なし．

既往歴：特記事項なし．

現病歴：2006年10月，左乳房腫瘤に気づき前医受診し，当科紹介となる．

入院時血液検査所見：末梢血，生化学検査ともに正常範囲内で，腫瘍マーカー（CEA 0.9ng/ml，CA15-3 14U/ml，ST439<1.0）の上昇もみられなかった．

入院時現症：左乳房E領域を中心にBD領域に及ぶ60mm大のやや弾性硬の腫瘤を認めた．胸筋，皮膚への固定は認めなかった．乳頭分泌なく，腋窩リンパ節も触知しなかった．

超音波所見（図1）：後方エコーの増強を伴った60×43×26mmの嚢胞と，嚢胞壁の一部から内腔に突出する21×18×7mm大の乳頭状腫瘍を認めた．

MMG所見（図2）：E領域に辺縁平滑で，ほぼ均一な腫瘤陰影を認めた．石灰化は認めなかった．

MRI：ダイナミックスタディーにて乳癌の造影パターンを示した（図3）．また，T2W1において嚢胞壁と考えられる低信号域の断裂が認められ，

MRI上，腫瘍の嚢胞壁外進展がみられた（図4）．

経　過：以上の所見より，2006年11月Core needle biopsy施行し，ICPCの診断を得て，乳房切除術＋センチネルリンパ節生検を施行した．術中迅速病理診断にてセンチネルリンパ節に転移は認めなかった．

病理組織所見：径5.cm大の嚢胞内に2cm大の乳頭状隆起性病変を認め，嚢胞液は暗赤色であった．この隆起性病変は中等度の核異型，核分裂像を有する腫瘍細胞が乳頭状，cribriform patternを呈して増殖（図5），一部間質への浸潤が認められた（図6）．リンパ節転移は認めず(0/3)，G2，NG2および免疫組織学的検索にてER，PgRはともに陽性，HER2，p53はいずれも発現していなかった．

3. 考　察

ICPCは嚢胞内腔へ乳頭状に突出し発育する乳癌で，乳癌全体の約2％弱[1]といわれている．一般的にductal carcinoma *in situ*の範疇で浸潤を伴うことはほとんどなく，現在の乳癌取扱い規約によれば，病巣が嚢胞内に限局し，非浸潤性嚢胞内乳癌とすることが記載されている．しかし，組織学的にも嚢胞壁外への浸潤や乳管内で広く進展を示す例[3]や，同時性肝転移例[4]などの報告もあり，定義についてはいまだコンセンサスを得られていない．したがって今回われわれは，浸潤の有無を問わず病理学的検索にて，ICPCと診断された14例を検討した．通常の乳癌と比較すると，平均年齢65歳（範囲34～92歳）[1]と高齢者に多いとされ，今回の14例でも中央値72.5歳（36～82歳）であり通常乳癌より高齢であった．また病悩期間も長いことも報告[2,5]されており，今回も中央値5カ月（1～24カ月）であった．腫瘍の性質として通常乳癌より発育が緩徐で，潰瘍を形成せずにGradeが低いため，放置されやすいと考えられる．良悪性の鑑別として，嚢胞内乳頭腫と鑑別は困難である．鑑別点としては嚢胞内乳頭腫の平均年齢は40.7～47歳で低く，60歳以上の嚢胞内腫瘍では，癌は81％に認めたという報告がある[7,8,9]．また腫瘍径は悪性であれば良性より大きい傾向にあるが，良悪性鑑別において診断的価値は低い[7,8]と報告されている．超音波検査は良悪性の鑑別検査としてあげられるが，嚢胞内腫瘤部分の辺縁など良悪性とも不整なものが多く鑑別にあまり有用でないといわれている[8,9]．通常乳癌における良悪性の鑑別としてMRIは有用であり，MRI所見が乳癌病理組織像を反映するという報告もある[10]．われわれは症例12以降の3例においてMRIを施行しいずれもダイナミックスタディーにて悪性を示す造影パターンを呈した．ICPCにおいても良悪性鑑別のため画像診断の1つとしてMRIは重要であると考えられる．またさらに，症例14においてMRIで腫瘍の嚢胞壁外浸潤を認めたように，MRIは進展度診断にも有用であり，嚢胞壁進展の評価にもきわめて有効である．以上より，少しでも悪性が疑われる場合はFine needle aspirationを行い，さらにCore needle biopsyをエコーガイド下に充実性部分を確実に穿刺することが必要である．しかし本検討症例においてもそうであるが，嚢胞内充実成分への針生検は難しく，Fine needle aspirationおよびCore needle biopsyにても診断の得られない症例では積極的に切除生検を考慮するべきと思われる．治療は原則として非浸潤性乳管癌(DCIS)治療に沿って行うことが可能である．しかし，嚢胞壁外浸潤を示す例[3]や，同時性肝転移例[4]などの報告もあることを把握しておく必要がある．報告によると浸潤癌はまれではなく，乳管内進展についても嚢胞壁より2cm以上超えて乳管内を進展するものも報告されている[6]．今回の14例中2例に浸潤部分を認め，さらに別の1例に作成標本には浸潤部は認めなかったが，リンパ節転移を認め，標本作成外に浸潤部分が存在したことが推察された．このように切除範囲決定には，MRIによる進展度評価を参考にし，広範な腫瘍進展を念頭において断端陰性となることが重要である．術前化学療法，術後化学療法の報告はなく，統一された指針はないが，第一選択治療は切除療法と考える．リンパ節転移に関しては0～25％と報告に幅があるが，通常の乳癌より頻度は低いとされている[8,9]．われわれは2004年以降よりセンチネルリンパ節生検を開始し，4例にセンチネルリンパ節生検を伴う乳房切除，乳房部分切除術を施行した．通常乳癌と同様，郭清省略には慎重であるべきで，センチネルリンパ節生検はよい適応と思われる．

今回14例すべてホルモン感受性を認め，乳房部分切除は8例に施行した．補助療法としては，明確な指針はないがDCIS治療にしたがって，症例を選びホルモン療法，残存乳房放射線照射などを考慮する必要があると思われる．

4. 結　語

ICPCの14例につき臨床病理学的検討を加え報告した．良悪性の鑑別は困難であり，Fine needle aspiration, Core needle biopsyに加え切除生検が必要である．切除範囲決定には，MRIによる進展度評価を参考に，広範な腫瘍進展を念頭において断端陰性となることが重要である．また，腋窩リンパ節の評価は病変の大きさに関わらず必要であり，現在広く施行されているセンチネルリンパ節生検は腋窩リンパ節転移の少ないICPCによい適応と考えられる．

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ORIGINAL ARTICLE

Favorable outcome in patients with breast cancer in the presence of pathological response after neoadjuvant endocrine therapy ☆

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Summary Neoadjuvant endocrine therapy (NAET) can expand the number of breast cancer patients who can be treated with breast-conserving surgery and can predict benefit from adjuvant endocrine therapy. Because no validated surrogate markers for long-term outcome have been established, we conducted prospective trials to evaluate pathological response and Ki-67 index following treatment with tamoxifen or anastrozole. The study population included postmenopausal women with operable breast tumors that were both estrogen and progesterone receptor-positive and larger than 3 cm. Response was classified as pathological response (minimal response or better) and non-response. Non-responding (25.5%, vs. response 85.9%, $p = 0.002$), axillary node-positive (58.4% vs. node negative 100%, $p = 0.045$), and high pretreatment Ki-67 index (41.4% vs. low Ki-67 87.1%, $p = 0.03$) patients were significantly associated with poor 5-year relapse-free survival. Multivariate analysis of relapse-free survival indicated that pathological response was independent. Therefore, pathological response may be a favorable prognostic factor after NAET.

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Introduction

With the recent development of aromatase inhibitors, neoadjuvant endocrine therapy (NAET) has attracted attention as a potentially effective therapy that might allow breast conservation even in women with large breast tumors[1–4]. In addition, NAET offers the possibility of testing therapeutic efficacy *in vivo*, which is of great importance for optimal adjuvant treatment. However, the short history of NAET leaves several questions to be answered. First, short-term surrogate markers of subsequent risk of relapse and death from breast cancer have not been established for NAET[5]. Recently, early changes in Ki-67 have been reported to be possible predictors of long-term outcome[6–8]. The short-term reduction in Ki-67 levels in NAET (in the IMPACT trial) paralleled that observed in patients who received the same endocrine therapy in the adjuvant setting (ATAC); this suggested that the changes in Ki-67 in NAET might be predictive of long-term outcome[7]. However, these data were not obtained in direct long-term follow-up studies of NAET. Second, classifications of pathological therapeutic response, which have been mainly produced based on pathological changes following chemotherapy or radiotherapy, have not been validated for tumors treated by NAET. We conducted a small study to clarify the significance of the classification of pathological therapeutic response and the Ki-67 index as prognostic factors of long-term outcome in response to NAET.

Patients and methods

This analysis includes 45 postmenopausal women with operable estrogen and progesterone receptor (ER and PgR)-positive breast tumors that were larger than 3 cm as confirmed by core needle biopsy. These women were enrolled in two-phase II studies on NAET at the National Cancer Center Hospital (NCCH), Tokyo. Between February 1999 and July 2002, 31 patients were enrolled in a neoadjuvant tamoxifen study (neo TAM), in which they received tamoxifen for 4 months preoperatively. Between November 2002 and 2004, 17 patients were enrolled in a neoadjuvant anastrozole study (neo ANZ), in which they received anastrozole for 5 months preoperatively. Three patients in the neo TAM group were excluded from this analysis because they received preoperative chemotherapy following NAET and their tumors could not be evaluated for pathological response to endocrine therapy; two of these patients rejected mastectomy when there was no reduction of their tumors by NAET. These patients received chemotherapy with the hope that their tumors might shrink enough to allow breast-conserving surgery. Unfortunately, their tumors remained widespread in a mosaic pattern and they finally agreed to mastectomies. The third patient showed progressive disease, which led to skin invasion, and received chemotherapy before surgery. All patients provided written informed consent for study participation as approved by the institutional review board of the NCCH. Patients who responded to NAET continued the same endocrine therapy postoperatively for 5 years. Patients who showed clinically progressive disease or stable disease and pathological lymph node involvement after NAET received adjuvant chemotherapy, if tolerable, with a regimen containing anthracycline or classical CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) following surgery. All patients who underwent breast-conserving surgery received postoperative radiotherapy to the ipsilateral breast.

Tumor response

Primary tumors were clinically assessed every month. Clinical complete response (cCR) was defined as the clinical disappearance of the tumor at the end of NAET, and clinical partial response (cPR) was defined as a $\geqslant$70% decrease from baseline of the largest diameter[9]. Clinical progressive disease was defined as a $\geqslant$20% increase from the most reduced size of the largest diameter. If progressive disease was observed, patients immediately underwent radical mastectomy.

Outcome measures

Relapse-free survival (RFS) was defined as the time from the initiation of treatment to local, regional, or distant treatment failure.

Histological examination

Evaluation of ER and PgR status was by immunohistochemical studies using antibodies 1D5 and PgR636 (DAKO, Glostrup, Denmark), and tumors with more than 10% strongly stained nuclei were described as ER- or PgR-positive. Tumors obtained by core needle biopsy judged as positive for both receptors before treatment were eligible for this study. HER2 status was evaluated immunohistochemically using HercepTest (Dako), and 3+: strong complete membrane staining in $>$10% of tumor cells was defined as positive.

Ki-67 was stained using the MIB-1 antibody (DAKO) according to previously described methodology[10]. Ki-67 was scored as the percentage of positively stained cells among 1000 malignant cells in specimens obtained by either core needle biopsy before treatment (baseline) or by surgery after NAET. The cut-off value for Ki-67 positivity was defined as the median value of the Ki-67 index in this study population. The proportional change in Ki-67 expression from baseline was calculated as (residual Ki-67 index—pretreatment Ki-67 index) × 1/pretreatment Ki-67 index[7].

Histopathological therapeutic response was classified according to the General Rules for the Clinical and Pathological Recording of Breast Cancer 2005[11]. For Grade 0, no response was observed; Grade 1a comprised those tumors with mild changes in cancer cells regardless of the area, or marked changes seen in less than one-third of cancer cells; Grade 1b comprised tumors with marked changes seen in more than one-third but less than two-thirds of tumor cells; Grade 2 tumors contained marked changes in more than two-thirds of tumor cells; and Grade 3 tumors demonstrated a complete response, with no cancerous cells remaining. Mild changes include slight degenerative changes in cancer cells not suggestive of cancer cell death (including cancer cells with vacuolation of the cytoplasm, eosinophilic cytoplasm, swelling of the nucleus, etc). Marked changes include marked degenerative changes in cancer cells suggestive of cancer cell death (including liquefaction, necrosis, and disappearance of cancer cells). The pathological response group was defined as tumors with Grade1a, 1b, and 2 responses. The non-response group was defined as tumors with Grade 0 response.

Statistical analysis

The χ^2 test was used for comparisons of tumor characteristics and responses among groups. The Kaplan–Meier methods were used to generate RFS curves. The log rank test was used for the comparison of RFS between two groups. Differences with $p<0.05$ were considered to be significant.

Table 1 Characteristics of patients and tumors treated with tamoxifen (neo TAM group) and anastrozole (neo ANZ group).

	Neo TAM group ($n=28$)	Neo ANZ group ($n=17$)	
Age	60 (51–75)	61 (54–87)	
Tumor before NAET			
T2	18	11	
T3	7	4	NS
T4	3	2	
Clinical response			
CR	1	3	
PR	12	10	
NC	15	4	$p=0.05$
PD	0	0	
Surgery			
Mastectomy	17	13	
BCS	11	4	NS
Pathological response			
Grade 2	3	3	
Grade 1b	4	2	
Grade 1a	11	11	$p=0.02$
Grade 0	10	1	
Axillary nodal status			
Negative	7	6	
1–3	12	7	NS
4–9	7	3	
>10	2	1	

NAET: neoadjuvant endocrine treatment; CR: complete response; PR: partial response; NC: no change; PD: progressive disease; NS: not significant; BCS: breast-conserving surgery.

Results

Tumor and patient characteristics in the neo TAM and neo ANZ groups are shown in Table 1. The clinical response rates (cCR+cPR) for the neo TAM and neo ANZ groups were 46.4 and 76.5%, respectively. Of the neo ANZ group, only four patients underwent breast-conserving surgery, because some patients with good clinical responses chose mastectomies and refused postoperative radiotherapy. Patients treated with neo ANZ showed a statistically significantly higher rate of pathological

Table 2 Tumor characteristics and responses to NAET stratified by patients with events and those without events.

	Non-response group ($n = 11$)	Pathological response group ($n = 34$)	
Age	57 (51–73)	61 (52–87)	
Tumor before NAET			
T2	9	20	
T3	1	10	
T4	1	4	NS
Histological grade before NAET			
Grade 1	1	8	
Grade 2	6	15	
Grade 3	4	9	NS
Not available	0	2	
HER2 status before NAET			
Negative	11	34	
Positive	0	1	NS
NAET			
Tamoxifen	10	18	
Anastrozole	1	16	NS
Clinical response			
CR	0	4	
PR	4	18	
NC	7	12	NS
PD	0	0	
Ki-67 index before NAET			
High	6	17	
Low	5	17	NS
Residual Ki-67 index			
High	7	16	
Low	4	18	NS
Proportional reduction of Ki-67 index			
Median(Q_1–Q_3)	−0.05 (−0.67–0.37)	−0.46 (−0.85–0.83)	NS
Lymphovascular invasion			
Negative	9	28	
Positive	2	6	NS
Axillary nodal status			
Negative	2	11	
1–3	6	13	
4–9	1	9	
>10	2	1	NS
Adjuvant therapy			
Endocrine only	5	20	
Chemotherapy added	6	14	NS

Q_1: first quartile; Q_3: third quartile.

response (Grades 1+2) than those treated with neo TAM ($p = 0.02$).

Tumor characteristics stratified by patients with pathological response or non-response are shown in Table 2. There were no statistically significant differences in tumor size, histological grade, HER2 status, clinical response, lymphovascular invasion, pathological nodal status, or addition of adjuvant chemotherapy between these groups. Reduction of Ki-67 was not significantly associated with either pathological or clinical response.

The median follow-up time after NAET was 44.7 months. There were 11 locoregional and/or metastatic events during this time. No ipsilateral breast tumor recurrence was observed after breast-conserving surgery. Patients with pathological non-response (25.5%, vs. response group 85.9%, $p = 0.002$; Fig. 1), axillary node positivity (58.4% vs. node negative 100%, $p = 0.045$), addition of adjuvant chemotherapy (41.2% vs. only endocrine therapy 77.5%, $p = 0.01$), and high pretreatment Ki-67 index (41.4% vs. low Ki-67 index 87.1%, $p = 0.03$; Fig. 2) were significantly associated with poor 5-year RFS. Initial T category, histological grade, clinical response, type of endocrine therapy, presence of reduction in Ki-67 values, and lymphovascular invasion was not associated with survival.

The median follow-up time for the neo TAM group was 65.8 months. In this group, patients with pathological non-response (28.0%, vs. response group 88.2%, $p = 0.006$; Fig. 3), axillary node positivity (59.9% vs. node-negative 100%), addition of adjuvant chemotherapy (43.2%, vs. only endocrine therapy 77.8%, $p = 0.03$), and high residual Ki-67 index (44.0%, vs. low Ki-67 index 100%, $p = 0.01$) were significantly associated with poor 5-year RFS.

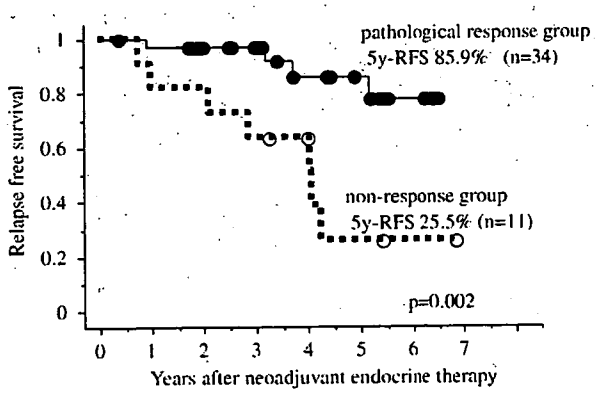

Figure 1 Relapse-free survival curves following neoadjuvant endocrine therapy stratified into a pathological response group (—) and a non-response group (- - -). A statistically significant difference was observed between the groups ($p = 0.002$).

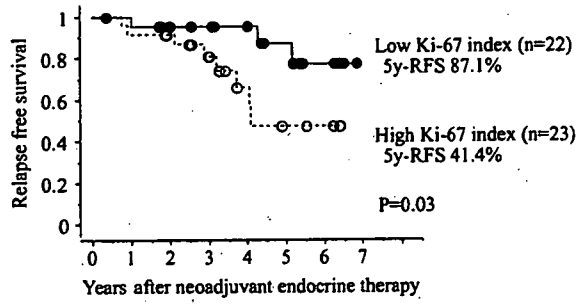

Figure 2 Relapse-free survival curves following neoadjuvant endocrine therapy stratified into a low pretreatment Ki-67 index group (—) and a high Ki-67 index group (- - -). A statistically significant difference was observed between the groups ($p = 0.03$).

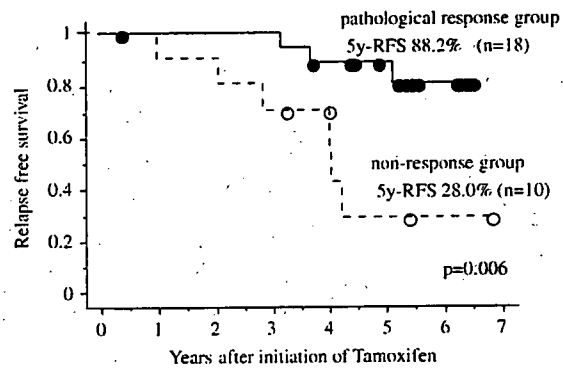

Figure 3 Relapse-free survival curves following neoadjuvant endocrine therapy using tamoxifen stratified into a pathological response group (—) and a non-response group (- - -). A statistically significant difference was observed between the groups ($p = 0.006$).

The median follow-up time for the neo ANZ group was 30.0 months. The pathological response group achieved statistically better 3-year RFS than the non-response group (93.3% vs. 0%, $p < 0.0001$).

Multivariate regression analyses using a logistic regression model were conducted to identify independent prognostic factors for RFS (Table 3). These analyses indicated that pathological response ($p = 0.007$) was significantly related to RFS.

Discussion

Although the sample sizes in this study are small, the pathological response group showed significantly more favorable outcomes than the non-pathological response group following NAET. This result is supported by all of the analyses conducted in this study and suggests that the pathological therapeutic response may be a prognostic factor for

Table 3 Multivariate analysis for RFS after NAET.

		Hazard ratio (95%CI)	p-value
Pathological response	Non-response/response	6.3 (1.6–23.8)	0.0067
Pretreatment Ki-67	Low/high	0.26 (0.055–1.17)	0.079
Residual Ki-67	Low/high	0.65 (0.14–2.98)	0.58

RFS: relapse-free survival; CI: confidence interval.

long-term outcome following NAET. The response necessary for a favorable prognosis seems to differ between neoadjuvant chemotherapy and NAET. In the neoadjuvant cytotoxic chemotherapy setting, where response (pCR or not) is a clinically significant predictor of outcome[12], long-term outcome following treatment with cytostatic agents can be predicted based on the achievement of minimal pathological change. Using chemotherapy, total killing of cancer cells is necessary to improve prognosis; therefore, physicians should pursue regimens that will reach the highest pCR rates possible. On the other hand, only a few patients have been reported to achieve pCR following NAET[3]. This is one reason for hesitation in using endocrine agents in a neoadjuvant setting. However, with endocrine therapy, minimal pathological changes may have the same power to improve prognosis.

In this study, low Ki-67 index before NAET in all cases and low residual Ki-67 index in the neo TAM group were significant favorable prognostic factors. Ki-67 has been reported to carry modest prognostic significance and the residual (after treatment) level of Ki-67 may be a better predictor of response and/or absolute long-term outcome than the proportional reduction in Ki-67 because it is more likely to relate to the growth rate of the persistent disease[13]. The results of this study are concordant with these results. The results of the IMPACT trial supported the hypothesis that a reduction of Ki-67 in NAET might be predictive of long-term outcome, but this was not demonstrated in this study. As Urruticoechea has reported that a change in Ki-67 score of at least 32–50% between two determinations using core needle biopsies is required to consider the difference statistically different for an individual patient and attributable to treatment effects[13], the problem with the reproducibility of Ki-67 measurements must be overcome.

Patients who underwent additional adjuvant chemotherapy showed a statistically significant reduction in RFS compared with those who underwent only endocrine therapy. Selection bias must be considered, as most of the patients with positive lymph nodes were treated with chemotherapy. However, whether or not the chemotherapy was efficacious remains controversial because hormone-sensitive breast cancer is less responsive to chemotherapy[14,15]. Further investigations are required to determine the best treatment plan for such cases.

Neoadjuvant chemotherapy has now been established as one of the standard treatments for operable breast cancer. On the other hand, there is less evidence on NAET than on neoadjuvant chemotherapy, including long-term outcome. In this situation, NAET should be used to treat selected patients who will obtain great benefit from endocrine therapy and will not respond to chemotherapy and/or do not need chemotherapy. Without a doubt, hormone receptor status is the first eligibility criterion. Many studies on neoadjuvant chemotherapy have confirmed that hormone-sensitive tumors show worse responses to chemotherapy than hormone-resistant tumors[14,15]. However, not all hormone-sensitive tumors respond to endocrine therapy, underscoring the need for additional predictive tests. Gene analysis can be used as a second eligibility criterion. A multigene assay (Oncotype DX)™ succeeded in predicting that approximately half of the women with node-negative, hormone receptor-positive breast cancer who were treated with local therapy and tamoxifen have an excellent prognosis, with more than 90% having 10-year relapse-free survival; these patients are unlikely to benefit from chemotherapy[16,17]. A more favorable response and long-term outcome without severe adverse events may be achieved with only hormone therapy using gene expression profiles to select patients who are good candidates for NAET.

This study suggests that pathological response is a favorable prognostic factor following NAET. We await validation of these results in large studies such as the IMPACT trial or Letrozole P024 to establish the surrogate markers that predict the risk of recurrence.

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Original Article

The prevalence of intrinsic subtypes and prognosis in breast cancer patients of different races

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Abstract

A recent report indicated that a high prevalence of basal-like breast tumors (estrogen receptor [ER]-negative, progesterone receptor [PR]-negative, human epidermal growth factor receptor [HER] 2-negative, and cytokeratin 5/6-positive and/or HER1-positive) could contribute to a poor prognosis in African American women with breast cancer. It has been reported that Japanese women with breast cancer have a significantly better survival rate than other races in the USA. These findings suggest that breast cancers in Japanese women have favorable biological characteristics. To clarify this hypothesis, we conducted a cohort study to investigate the prevalence of intrinsic subtypes and prognosis for each subtype in 793 Japanese patients. This study revealed a very low prevalence (only 8%) of basal-like breast tumors with aggressive biological characteristics in Japanese patients. Survival analysis showed a significantly poorer prognosis in patients with basal-like tumors than in those with luminal A tumors (ER- and/or PR-positive, and HER2-negative) with favorable biological characteristics. These findings support the hypothesis that breast cancers in Japanese women have more favorable biological characteristics and a better prognosis than those in other races. In conclusion, the prevalence of basal-like breast tumors could influence the prognosis of breast cancer patients of different races. The prevalence of intrinsic subtypes should be taken into account when analyzing survival data in a multi-racial/international clinical study.

Keywords: Breast cancer; Intrinsic subtype; Triple-negative tumor; Prevalence; Japanese; Prognosis

Introduction

Although breast cancer survival has improved over the past 20 years in some developed countries,[1] significant differences in breast cancer stage, treatments, and mortality rates still exist in the world with regard to race and ethnicity.[2] The causes of survival difference are likely to be multifactorial including socio-economical factors, differences in access to insurance, screening and treatments, and biological differences among breast cancers themselves. These biological differences may reflect genetic influences and differences in lifestyle, nutrition or environmental exposure.

A number of studies have investigated the causative factors leading to racial disparity in breast cancer survival

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between African American (AA) and white American patients in the USA. Possible explanations include aggressive phenotypes of breast tumors,[3–5] such as high-grade and estrogen receptor (ER)-negative (ER−), patient characteristics,[6,7] such as obesity and a higher rate of co-morbidity, inadequate mammmographic screening,[8,9] delay of diagnosis leading to advanced stage,[10,11] and inadequate treatment,[12–14] such as not meeting treatment guidelines in AA women; however, these factors are unable to totally elucidate the disparity. Interestingly, a recent report indicated that a higher prevalence of basal-like breast tumors (ER−, progesterone receptor negative [PR−], human epidermal growth factor receptor 2-negative [HER2−], cytokeratin [CK] 5/6-positive, and/or HER1-positive [HER1+]), which have aggressive biological phenotypes and a poor outcome, and a lower prevalence of luminal A tumors (ER+ and/or PR+, and HER2−), which have an estrogen-responsive phenotype and a favorable outcome, could contribute to a poorer prognosis in young AA women with breast cancer.[15]

In contrast to AA patients, according to the Hawaii Tumor Registry of the Surveillance, Epidemiology, and End Results Program in the USA, Japanese patients with breast cancer have a significantly better survival rate than patients of other races after controlling for age, stage, and ER/PR status. There are no differences, however, in the survival rates of Chinese, Filipino, and Caucasian women.[16] These findings suggest that breast cancers in Japanese women have favorable biological characteristics, such as a lower prevalence of basal-like breast tumors. To clarify this hypothesis, we conducted a retrospective cohort study to investigate the prevalence of intrinsic subtypes of breast tumors and prognosis for each subtype in Japanese breast cancer patients.

Patients and methods

Study patients

The goal of the present study was to estimate the prevalence of breast cancer subtypes in Japanese breast cancer patients, and to examine correlations between clinico-pathologic variables and survival. Clinico-pathologic data of a cohort of consecutive Japanese patients with invasive breast cancer treated between January 2000 and December 2003 were collected from three different institutes, Kawasaki Medical School Hospital, Tohoku University Hospital, and Tohoku Kousai Hospital in Japan. The study procedures were approved by the institutional review board of each hospital.

Based on the histologic records, tumors were classified into two categories: invasive ductal carcinomas not otherwise specified (NOS) and others. The American Joint Committee on Cancer (AJCC, 5th edition) stage and lymph node status were collected from the medical records. Histologic grading was according to the modified Bloom and Richardson method by Elston and Ellis (Nottingham's grading system).[17] Lymph vessel invasion (LVI) was assessed using hematoxylin–eosin-stained glass slides. Vascular channels lined by thin endothelial cells, especially close to the small arteries and veins, were considered as lymph vessels, and tumor emboli were floating in the lumen in LVI-positive cases. Most LVI were seen at the periphery of the invasive tumors.[18] Blood vessel invasion (BVI) was evaluated using elastica Masson stain or immunostaining for CD34. Tumor cell nests surrounded by elastic fibers and the wall of smooth muscle, next to the small arteries (but not mammary ducts with multilayered elastic fibers) were considered as positive.[18]

Immunohistochemical (IHC) subtypes

ER and PR status were determined by IHC performed at each institute. The cutoffs for receptor positivity were 10%. The HER2 status was also determined by IHC at each institute. According to the criteria of the HecepTest, scores 0 and 1 were considered negative, and scores 2 and 3 were considered positive.[19] Triple-negative (ER−, PR−, and HER2−) breast cancer samples were examined by IHC for CK 5/6 and HER1. CK 5/6 and HER1 were considered positive when more than 10% of the tumor cells were labeled. First antibodies and IHC procedures are presented in Table 1.

According to Carey et al.,[15] IHC intrinsic subtypes were defined as follows: luminal A (ER+ and/or PR+, HER2−), luminal B (ER+ and/or PR+, HER2+), basal-like (ER−, PR−, HER2−, CK 5/6-positive, and/or HER1+), HER2+/ER−, and unclassified (negative for all five markers).

Statistical analysis

Differences between breast cancer subtypes with regard to clinico-pathologic characteristics were examined using analysis of variance, χ^2 tests or Fisher's exact test. Survival curves were generated using the Kaplan–Meier method, and the log-rank test was used to compare mean survival across IHC subtypes. StatView statistical software was used to manage and analyze data. Statistical differences were considered significant at $P \leqslant 0.05$.

Results

IHC subtypes and characteristics of patients

Clinico-pathologic data on 793 Japanese patients with invasive breast cancer were collected from three hospitals in Japan. The characteristics of the patients with IHC data, overall and according to IHC subtypes, are presented in Table 2. IHC subtypes differed significantly by age ($P = 0.025$), AJCC stage ($P < 0.001$), histologic grade ($P < 0.001$), LVI ($P = 0.018$), and BVI ($P = 0.026$). Patients with the basal-like subtype were younger than patients with the HER2+/ER− subtype. Patients with basal-like tumors were more likely to be in the more advanced stage, and to have tumors with a higher histologic grade or BVI than patients with luminal A tumors.

Table 1
Source, dilution, pretreatment and cutoff values of antibodies used

Antibody, clone	Dilution	Source	Pretreatment	Cutoff values
ER [1D5]	1:400	IMMUNOTECH	Autoclaved	⩾10% (positive)
PR [636]	1:2000	DAKO	Autoclaved	⩾10% (positive)
HER2 [HercepTest]	NA*	DAKO	None	NA
HER1 [2-18C9]	NA	DAKO	Proteinase K	⩾10% (positive)
CK 5/6 [D5/16134]	1:100	DAKO	Autoclaved	⩾10% (positive)

*Not assessable.

Table 2
Prevalence of intrinsic subtypes and clinico-pathological characteristics in Japanese breast cancer patients

	All cases	Luminal A	Luminal B	HER2+/ER−	Basal-like	Unclassified	*P* value*
No. of cases	793	502 (63)†	155 (20)	55 (7)	67 (8)	14 (2)	
Age, median (range), years-old	54 (19–88)	53 (27–88)	53 (19–85)	60 (31–84)	54 (30–79)	50 (36–66)	0.025
AJCC stage							<0.001
I	289	213	48	4	18	6	
II	360	208	70	39	38	5	
III	68	36	17	4	8	3	
IV	40	19	15	4	2	0	
Missing	36	26	5	4	1	0	
Histology							0.142
Invasive ductal carcinoma NOS	721	447	149	53	60	12	
Specific types	70	54	5	2	7	2	
Missing	2	1	1	0	0	0	
Histologic grade							<0.001
I	156	131	23	0	1	1	
II	320	235	56	15	11	3	
III	197	61	48	33	49	6	
Missing	120	75	28	7	6	4	
LVI							0.018
Positive	345	212	69	32	27	5	
Negative	373	249	62	20	36	6	
Missing	75	41	24	3	4	3	
BVI							0.026
Positive	126	82	18	10	14	2	
Negative	570	267	105	40	49	9	
Missing	97	53	32	5	4	3	
Nodal status							0.572
Positive	303	184	62	25	27	5	
Negative	437	286	78	25	29	9	
Not applicable or missing	53	32	15	5	1	0	
Outcome							
Follow-up, median (range), months	46.5 (1–84)						
5-year DFS	85.5%	90.3%	82.9%	62.1%	77.1%	81.8%	<0.001‡
5-year OS	92.8%	96.9%	86.6%	86.9%	86.2%	83.3%	<0.001‡

*Comparing five subtypes using χ^2 test or Fisher's exact test.
†In %.
‡Log-rank test.

Survival by IHC subtypes

Survival data on 786 of 793 patients with invasive breast cancer were available from three hospitals. The duration of follow-up was 1–84 months (median, 46.5). During this period, recurrence was observed in 91 patients, and 48 patients died of any causes.

Breast cancer subtypes significantly differed in 5-year disease-free survival (DFS, $P<0.001$): luminal A (90.3%), luminal B (82.9%), HER2+/ER− (62.1%), basal-like

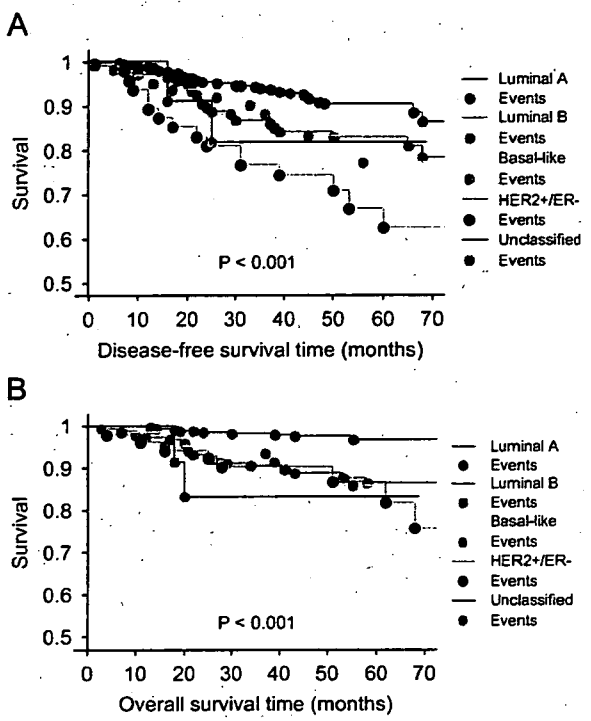

Fig. 1. DFS (A) and OS (B) curves in breast cancer patient groups divided by IHC intrinsic subtypes.

subtype (77.1%), and unclassified (81.8%). They also differed in 5-year overall survival (OS, $P<0.001$): luminal A (96.9%), luminal B (86.6%), HER2+/ER− (86.9%), basal-like subtype (86.2%), and unclassified (83.3%). Kaplan–Meier survival curves are presented in Fig. 1. Both DFS and OS were significantly worse among basal-like and HER2+/ER− breast cancer patients compared with luminal A patients.

Differences in DFS and OS by IHC subtypes were seen among lymph node-positive patients ($P = 0.006$ for DFS and $P<0.001$ for OS) but not lymph node-negative patients; however, the number of patients after stratifying by lymph node status was limited and these data should be interpreted with caution. Five-year DFS within lymph node-positive patients by subtype was as follows: luminal A (79.3%), luminal B (71.2%), HER2+/ER− (35.2%), basal-like subtype (68.1%), and unclassified (50.0%). Five-year OS within lymph node-positive patients was as follows: luminal A (96.3%), luminal B (75.6%), HER2+/ER− (84.1%), basal-like subtype (83.9%), and unclassified (60.0%).

Discussion

Carey et al. have recently reported for the first time the population-based prevalence of intrinsic subtypes of breast tumors. They refined an IHC-based assay to identify breast tumor intrinsic subtypes instead of gene expression profiling.[15] This IHC-based assay has been verified against gene expression profiles to estimate the prevalence of intrinsic subtypes.[15,20] Additionally, large-scale subtyping using gene expression profiling from formalin-fixed, paraffin-embedded samples is not currently feasible; therefore, we conducted this cohort study to investigate the prevalence of intrinsic subtypes using the IHC-based assay in Japanese breast cancer patients.

According to Carey et al.,[15] the prevalence of basal-like and luminal A tumors in the Carolina Breast Cancer Study was 27% and 47% in AA patients and 16% and 54% in non-AA patients, respectively. Since breast cancer-specific survival was significantly worse in patients with basal-like tumors than with luminal A tumors, the higher prevalence of a basal-like subtype could contribute to a worse prognosis in AA patients. Moreover, the prevalence of basal-like and luminal A tumors was 39% and 36% in premenopausal AA patients, respectively. In contrast, the prevalence of basal-like and luminal A tumors was 8% and 63% in Japanese breast cancer patients, respectively, in the present study. The prevalence of basal-like tumors was 2–3 times lower in Japanese patients than in non-AA patients or AA patients. In addition, the prevalence of luminal A tumors was 9–16% higher in Japanese patients than in non-AA patients or AA patients. Breast cancer patients with basal-like tumors had a poorer prognosis in terms of DFS and OS than those with luminal A tumors in the present study (Fig. 1) as previously indicated in the report by Carey et al.[15] These findings have suggested that the lower prevalence of basal-like tumors and higher prevalence of luminal A tumors in Japanese patients could contribute to their better prognosis.

A limited number of studies have investigated the prevalence of intrinsic subtypes by the IHC-based assay in different races. On the other hand, the prevalence of triple-negative breast tumors has recently become available. Triple-negative tumors include both basal-like and unclassified tumors. The prevalence of basal-like tumors was reported to be approximately 70% in triple-negative tumors[15]; it was 78% in the present study. The prevalence of triple-negative tumors was 22% in the Carolina Breast Cancer Study,[15] 16% in a large series of patients in the UK,[21] 26% in conservatively managed patients in the USA,[22] and 31% in consecutive patients in Korea.[23] In the present study, the prevalence of triple-negative tumors was only 10%, 1.6–3 times lower in Japanese patients than in patients of other races. These findings also support the lower prevalence of basal-like tumors in Japanese patients.

Differences in genetic influences or lifestyle may explain the prevalence of intrinsic subtypes among different races. Differences in the distribution of breast cancer risk factors, such as breast cancer family history, age at menarch, age at first birth, body mass index, and hormone replacement therapy, have been extensively investigated, and these differences may explain differences in breast caner incidence rates among different races.[5] However, the investigation of causative factors leading to differences in the prevalence of intrinsic subtypes in different races remains

to be investigated. Because of a close correlation between the prevalence of intrinsic subtypes and the prognosis of breast cancer patients indicated by us and others,[15,20] nutritional or environmental factors influencing the prevalence may provide hints for developing new intervention strategies to reduce breast cancer mortality rates. It has been indicated that the intake of green tea or soy beans relates to a reduction in breast cancer incidence rates.[24,25] Furthermore, the consumption of green tea was suggested to correlate with not only a reduction in breast cancer incidence but also improved outcome of breast cancer patients in Japanese women.[26] In addition, it is suggested that breast cancer patients with a high intake of green tea tend to have less aggressive and hormone-responsive breast tumors.[27] Interestingly, recent experimental studies have revealed that green tea extracts such as (−)-epigallocatechin gallate have significant anti-tumor activity in breast cancer cells with basal-like phenotypes.[28–30] These findings suggest that green tea intake may modify the biological characteristics of breast tumors and the prevalence of intrinsic subtypes. Further epidemiologic and experimental studies are warranted to investigate the role of green tea intake in breast cancer development and progression.

In conclusion, the present study suggests for the first time that a lower prevalence of basal-like breast tumors and a higher prevalence of luminal A breast tumors could contribute to a favorable prognosis of Japanese breast cancer patients. Taken together with the worse prognosis of AA patients having a higher prevalence of basal-like tumors and a lower prevalence of luminal A tumors, it could be concluded that the prevalence of intrinsic subtypes differs among different races and such a difference may explain differences in the prognosis of breast cancer patients of different races. From the clinical point of view, the prevalence of intrinsic subtypes should be taken into account when analyzing survival data in a multi-racial/international clinical study. In addition, causative factors influencing the prevalence of intrinsic subtypes should be explored to develop intervention strategies to reduce breast cancer incidence and the mortality rate.

Conflict of Interest Statement

None declared.

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