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Comparison of Genome Aberrations Between Early-Onset and Late-Onset Breast Cancer

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1. Introduction

Breast cancer is the most common cancer and the second leading cause of cancer deaths in women worldwide. Breast cancer statistics in the US shows a bimodal distribution consisting of early-onset and late-onset patients. Although the incidence of early-onset breast cancer in western population is low, the survival rate is significantly poorer before 40 years old (Yankaskas, 2005). Bonnier and his colleagues showed that the breast cancer patients under 35 years old also have poorer prognostic and possess the following characteristics: (1) a higher frequency of undifferentiated tumors, (2) histoprognostic grade-III cancer, (3) microscopic lymph-node involvement and (4) negative hormonal receptor status (Bonnier et al., 1995).

Although incidence rate of breast cancer has been decreasing in the US, this happens only in the late-onset age group (Benz, 2008). Asian women have significant lower incidence rate of breast cancer (about 25/100000 in Eastern Asia) than the western countries (about 90/100000 in Western Europe) but the rate of incidence is increasing steadily with the improvement of economics in the area. In Taiwan, the incidence of breast cancer has dramatically increased from about 13/100000 in 1980 to 49/100000 in 2005 (Chang et al., 2008). The increase in breast cancer in Asia is different from that of western countries in that the incidence of premenopausal breast cancer is proportionally higher in the Asian women. Similar trend of early-onset breast cancer is found in Africa (Kruger et al., 2007).

According to clinical statistics, breast cancer patients in Taiwan are mainly identified 10 years younger than their counterparts in the western countries. Compared with the late-onset group, the early-onset breast cancer (age < or = 40) has a more aggressive clinical behavior, and its five-year survival rate for each stage is much poorer. One unique feature in

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Taiwan is the large proportion of early-onset breast cancer (Cheng et al., 2000). Compared with the late-onset group, the early-onset breast cancer (age < or = 40) has a more aggressive clinical behavior, and its five-year survival rate for each stage is much poorer. The early-onset breast cancer has poorer prognostic features. Standard pathologic factors are not good predictors of their outcome. Several studies have correlated the breast cancer subtypes with early-onset breast cancer recently(Anders et al., 2008; Lin et al., 2009; Sorlie et al., 2003; Sotiriou et al., 2003). The classification of subtypes has been shown to provide prognostic information and etiologic mechanisms of breast cancer. In Taiwan, the young women breast cancer tends to be more luminal A type with higher ER and PR expression and less basal-like subtype than that of the older women (Cheng et al., 2000; Lin et al., 2009), but with higher risk of second primary malignancy and worse prognosis (Lee et al., 2008; Mellemkjaer et al., 2006; Yu et al., 2006). This feature is quite distinct from that of western developed countries with high prevalence of more aggressive basal-like breast cancer in young women. In western populations, younger women are more likely to have biologically aggressive breast cancer as shown by higher proportions of ER-negative and histologic grade III tumors compared with older patients (Anderson et al., 2002; Anderson et al., 2001; Colleoni et al., 2002). Anders and the colleagues also reported that more aggressive subtypes, such as basal-like subtype, would be over-represented among breast cancer arising in early-onset patients, whereas older women would more commonly be diagnosed with luminal tumors in the USA (Anders et al., 2011). The increasing incidence of breast cancer in the young women population is worrisome since they constitute a major labor force and are also potential mothers who need to take care of young children. It is therefore important to understand the epidemiological as well as genetic origin of the rising incidence of early-onset breast cancer with possible implications in prevention as well as diagnostic/prognostic applications.

Etiological factors of breast cancer are complex. Reproductive history, diet, alcohol, and body size among others have been implicated (Jevtic et al., 2010; McTiernan et al., 2010; Phipps et al., 2011). Among these factors reproductive history has been found to be strongly correlated with breast cancer is reproductive history. Since the early observation of high incidence of breast cancer among nuns in eighteenth century nulliparity and older age at first birth have been strongly associated with incidence of breast cancer (Butt et al., 2009; Muti, 2005; Trichopoulos et al., 2008; Wu et al., 2011; Yaghjyan and Colditz, 2011). Both nulliparity and older age pregnancy and child birth are characteristics of developed countries and countries with rapid economic growth as in Taiwan. This may partly explain the rapid rise of this disease here.

The association of reproductive history and breast cancer might be understood from hormone target theory (Adami et al., 1995; Adami et al., 1998; Cerliani et al., 2011; Trepp et al., 2010). Mammary gland formation consists of three stages: *organogenesis,* which grows from terminal end bud (TEB) to non-pregnant primary ductal system with cuboidal epithelial cells and is stimulated by prolactin; mature gland formation, with highly branched ducts and lobular buds; pregnancy gland formation, through the stimulation of several hormones with differentiation of lobular buds into fully differentiated type III lobules with milk secreting columnal cells. These complicated differentiation processes involve temporal controls from hormones, cytokines, specific transcription factors, growth factors as well as contribution from stromal elements including myoepithelial cells, base membrane and a collection of integrins (Ahmad and Kumar, 2011; Chen and Capecchi, 1999; Chodosh et al., 1999; Flucke et al., 2010; Howell and Evans, 2011; Li et al., 2010; Okoh et al.,

2011; Tamimi et al., 2011). As a major organ involved in pregnancy the major player in mammary gland development is hormone. Induction of cell differentiation by hormone during pregnancy provides protection against tumorigenesis because the epithelial cells become fully differentiated and are not susceptible to carcinogens. This explains the role of parity in breast cancer. The better protection for earlier pregnancy can be explained by the smaller hormone targets and the less chance to accumulate deranged cells.

According to the hormone target theory, stimulation of cell growth of undifferentiated epithelial cells in immature mammary gland may provide a mechanism for early-onset breast cancer. The predominance of immature epithelial cells in embryo provides the target for the initiation of tumorigenesis when intrauterine hormone concentration is high. Indeed, animal studies showed that undifferentiated TEB is the most susceptible to carcinogen for the formation of tumor (Bai and Rohrschneider, 2010; Roussos et al., 2010; Russo and Russo, 1994). Recent evidence even points to the immature gland in utero as the target for the initiation of breast cancer (Brisken and O'Malley, 2010; Hardy et al., 2010; Hilakivi-Clarke and Clarke, 1998; Sanderson et al., 1998; Torres-Arzayus et al., 2010).

Although there is intensive study of the genetic pathways involved in breast tumorigenesis, the genetic basis of the breast cancer in young women and the differences between early-onset and late-onset tumors remain largely unknown. The different pathological features of the two types of cancer suggest that they have different genetic origin. In order to explore the genetic basis of early-onset and late-onset breast cancer, we analyzed the candidate genes associated with the chromosomal aberrations in these two types of cancer from data in the public domain as well as from our own array-CGH data from the patients in Taiwan through literature search of involvement of genes in the aberration regions. Furthermore, the differential gene expression of these two types of cancer is analyzed by SAGE technique to deduce the genes that may be specifically related to early-onset cancer.

2. Comparison of genomic aberrations between early- and late-onset breast cancer

Breast cancer frequently contains amplification in several regions of chromosomes. Recent advances in high resolution array-CGH analysis and the availability of human genome sequence enabled finding candidate genes involved in breast cancer from these chromosomal aberration regions. We are interested in studying genes associated with early-onset (age <40) breast cancer which has become a major health concern in Taiwan. Early-onset breast cancer has poor prognosis compared with late-onset (age >70) breast cancer and genomics analysis indicated that they have different chromosomal and genetic aberration profiles, suggesting they have different origins. In this article we summarized the current candidate genes involved in breast cancer from genomic data and presented data on genetic differences between the two types of breast cancer. The possible implication in the genetic differences is discussed.

2.1 Review of chromosome aberrations in early- and late-onset breast cancer and candidate genes associated with tumorigenesis

To explore the genes differentially associated with early-onset and late-onset breast cancers, we first collected the aCGH data in the Progenetix database (www.progenetix.net) (Baudis and Cleary, 2001; Boldt et al., 2010; Fridlyand et al., 2006; Reis-Filho et al., 2005) and reanalyzed the data. All the samples were regrouped based on the age of patients: younger

and elder groups were defined as less than 46 and more than 70 years old respectively. Then the frequency of copy number gains or losses (y axis) were plotted with the probes along with the chromosome order (x axis). As the frequency lower than 10% may reflect the randomly change dues to the genomic instability of tumor, we define gain or loss more than 30% as significant aberrations. Early or late onset-specific aberrations were defined as gain or loss more than 30% and higher than the other group at least 15%. When these data are lined up chromosome-by-chromosome (Fig. 1), regions of chromosome aberrations common to both groups as well as specific to each group can be discerned (Table 1). Genes within each regions identified are then examined through literature search to identify candidate genes involved in breast carcinogenesis (Table 2, and 3). Genes that are either down-related or suppress tumorigenesis are in italic.

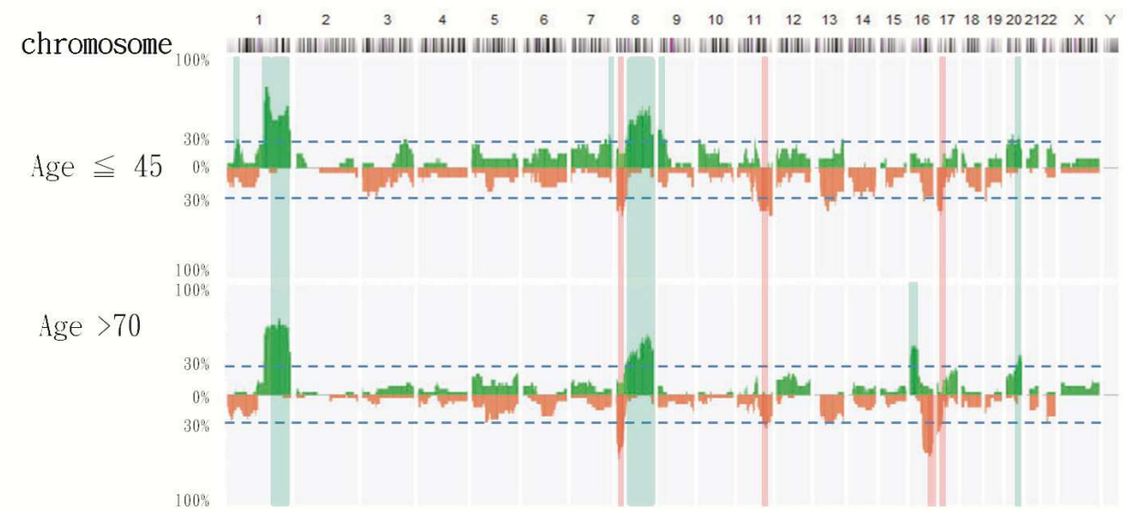


Fig. 1. Chromosome aberrations in early- and late-onset breast cancer.

	Gains		Losses	
Early onset	Ch1	41~42Mb	-	-
	Ch1	148~157Mb	-	-
	Ch3	161~172Mb	-	-
	Ch7	150~151Mb	-	-
	Ch9	0~14Mb	-	-
	Ch13	103~112Mb	-	-
Late onset	Ch16	7~25Mb	Ch16	74~81Mb
Common	Ch1	175~247Mb	Ch8	3~32Mb
	Ch8	48~114Mb	Ch11	108~114Mb
	Ch20	50~51Mb	Ch17	0~9Mb

Table 1. Aberrant chromosomal regions in Breast Cancer Patients.

Early-onset	**GAINS**	Chr1 ***41~42Mb***	MIRN30E
		Chr1 ***148~157Mb***	ECM1, HORMAD1, CTSS, CTSK, ARNT, PRUNE, S100A10, S100A11, FLG, HAX1, PYGO2, CKS1B, ADAM15, MUC1, NES, NTRK1
		Chr3 ***161~172Mb***	PRKCI, SKIL
		Chr7 ***150~151Mb***	ABCF2, RHEB *KCNH2*
		Chr9 ***0-14Mb***	VLDLR
Late-onset	**GAINS**	***Chr16*** ***7~25Mb***	CIITA, SOCS1 *MIRN193B, PALB2*
	LOSSES	***Chr16*** ***74~81Mb***	CNTNAP4, ADAMTS18, WWOX, HSD17B2

Table 2. Aberrations in early-and late-onset breast cancer.

Totally, there are 6 early-onset specific gains on the chromosomes 1 (41-42Mb; 148-157Mb), 3 (161-172Mb), 7 (150-151), 9 (0-14Mb) and 13 (103-112Mb), one late-onset specific gain on chromosome 16(7-25Mb), three common gains on chromosomes 1 (175-247Mb), 8 (48-114Mb) and 20 (50-51Mb). There is a late-onset specific loss in chromosome 16 (74-81Mb) and common loss on chromosomes 8 (3-32Mb), 11 (108-114Mb) and 17 (0-9Mb). Genes that have been shown to be involved in breast carcinogenesis in these regions through literature search are listed in Table 2 and 3.

Interestingly, the early onset-specific aberrations contain more IGF-1 and ER signaling associated genes than the late onset. Candidate genes present in the IGF-1, ER and TGF-beta pathways in both groups of breast cancer patients are listed in Table 4.

The association of ER genes with early-onset cancer is expected since these patients are premenopausal. Since IGF-1 pathway plays an important role in breast tumorigenesis, the genes specific for the late and early-onset cancer are depicted in Fig. 2 to illustrate their positions in the pathway.

2.2 Clustering of breast cancer related genes in chromosome regions

A striking feature of the analysis of genes associated with gain or loss in breast cancer chromosomes is that the regions often harbor breast cancer related genes in a cluster fashion and demarked by the presence of genes down-regulated or are anti-tumorigenic in breast cancer.

GAINS	***Chr1 175~247Mb***	PTGS2, PLA2G4A, RGS2, KIF14, LAD1, TIMM17A, ELF3, UBE2T, JARID1B, ADIPOR1, ADORA1, PCTK3, IKBKE, MAPKAPK2, CD55, CD46, NEK2, DTL, ATF3, ESRRG, GPATCH2, TGFB2, DUSP10, ENAH, EPHX1, PARP1, WNT9A, WNT3A, ARF1, EXO1, AKT3, SMYD3 *RGSL1, RNASEL, RGS16, BTG2, KISS1, RASSF5, IL10, LAMB3, IRF6, PROX1, PTPN14, TLR5, T53BP2, FH, CHM*
	Chr8 48~144Mb	SNAI2, LYN, SDCBP, ASPH, COPS5, PRDM14, NCOA2, TPD52, FABP5, E2F5, WWP1, CPNE3, MMP16, CCNE2 TSPYL5, MTDH, LAPTM4B, YWHAZ, CTHRC1, ANGPT1, EIF3E, EBAG9, TRPS1, RAD21, TNFRSF11B, HAS2, ATAD2, TRMT12, TATDN1, SQLE, MYC, PVT1, DDEF1, WISP1, PTP4A3 *CEBPD, PRKDC, RB1CC1, SOX17, CRH, VCPIP1, SGK3, SULF1, DECR1, TP53INP1, STK3, UBR5, DPYS, NOV, MTSS1, NDRG1*
LOSSES	***Chr8 3~32Mb***	ANGPT2, CTSB, EGR3, LOXL2, NKX3-1, STC1, CLU, PBK *CSMD1, MCPH1, MSRA, GATA4, DLC1, MTUS1, ASAH1, NAT1, PSD3, LZTS1, PDLIM2, RHOBTB2, BNIP3L, EPHX2, DUSP4, PPP2CB, WRN, NRG1*
	Chr11 108-114Mb	- *PPP2R1B*
	Chr17 0~9Mb	MYBBP1A, PELP1, PLD2, NUP88, *MIRN22, SMYD4, HIC1, MNT, ALOX15, CXCL16, PFN1, XAF1, MIRN195, MIRN497, CLDN7, GPS2, SHBG, ATP1B2, TP53*

Table 3. Aberrations in both early- and late-onset breast cancer.

	IGF-1 Signaling	Estrogen Receptor Signaling	TGF-Beta Signaling
Early onset specific aberrations	IRS2, JAK2, PRKAG2, PRKCI, SHC1	SHC1, HIST2H3C	
Late onset specific aberrations	SOCS1		
Common aberrations	AKT3, NOV, PIK3C2B, PIK3R5, PTK, YWHAE, YWHAZ	H3F3A/H3F3B, HIST3H3, MED30, MED31, NCOA2, PELP1, POLR2A, POLR2K, PRKDC, TAF2, TAF5L	TGFb2

Table 4. The relationship of aberrant genes and IGF-1, ER, and TGF- signal pathways.

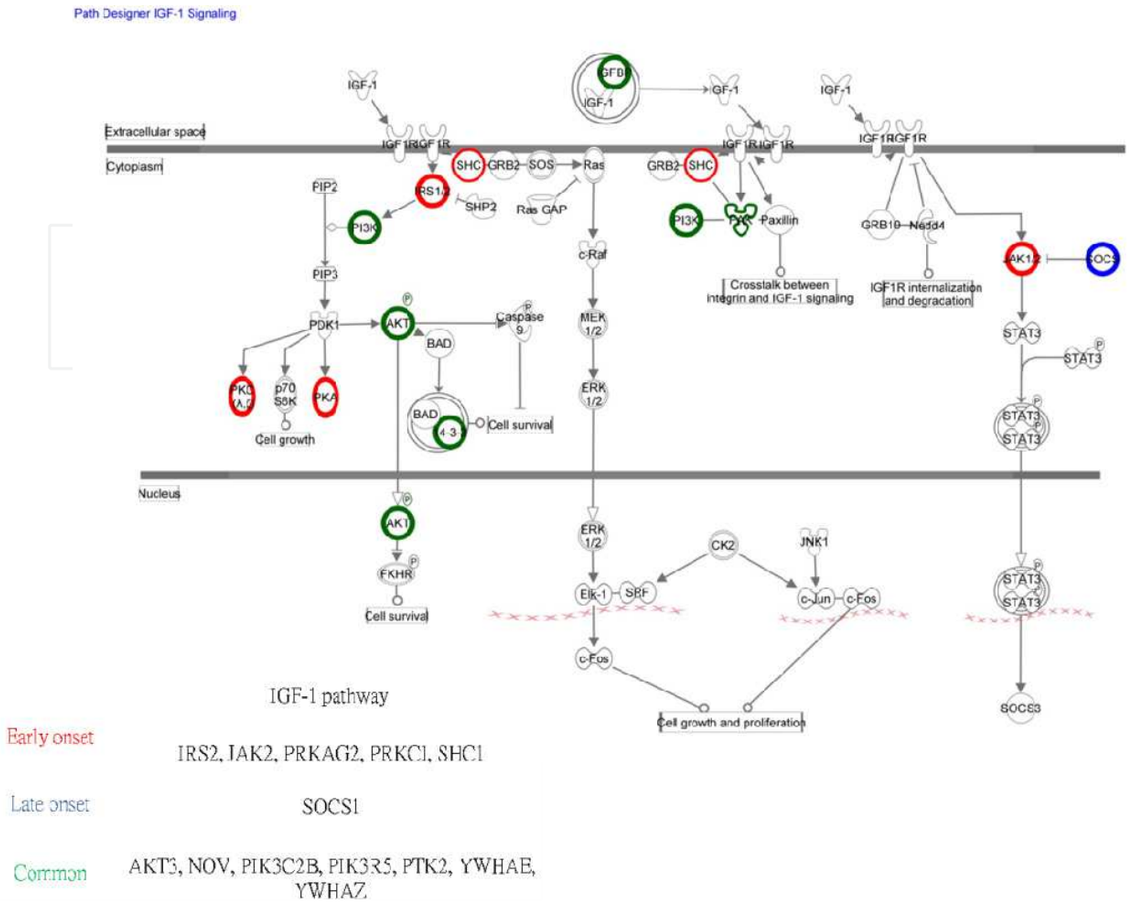


Fig. 2. IGF-1 signal pathway.

For example, 198-201Mb in 1q32.1 contains eight genes related to breast tumorigenesis, KLF14, LAD1, TIMM17A, ELF3, UBE2T, JARID1B, ADIPOR1 and ADORA1 as well as a gene CARP1 that is over-expressed in cancers (Fig. 3 shows the distribution of genes positively correlated with breast cancer as red line and negatively correlated with breast cancer as green). We also observed the clustering of the genes that inhibits breast tumorigenesis or are down-regulated in breast cancer in chr17 0-9Mb region that is often deleted in breast cancer. These are mir-22, SMYD4, HIC1, MNT, ALOX15, CLCX16, PFN1, XAF1, mir-195, mir-497, CLDN7, GPS2, SHBG, ATP1B2, and TP53. The pro- and anti-tumorigenesis genes are often found clustered together in a region of the chromosome.

2.3 Comparison of chromosome aberrations between early-onset and late-onset breast cancers in Taiwan

To investigate the gene aberrations between early-onset and late-onset breast cancer in Taiwan, we have used Vysis GenoSensor ™ Array 300 microarray chip, containing 378 target clone DNA (P1, BAC or PAC clones) representing regions that are important in cytogenetics and oncology, to analyze 15 early-onset and 15 late-onset breast cancer samples. The tissue samples of primary breast cancers were obtained by either biopsies or surgical excision from Koo Foundation Sun Yat- Sen Cancer Center (KF-SYSCC), Taipei, Taiwan. Instead of metaphase chromosome in conventional CGH, BAC or PAC DNAs are

used as hybridization template in array- CGH, which can increase resolution up to approximate 100 kb.

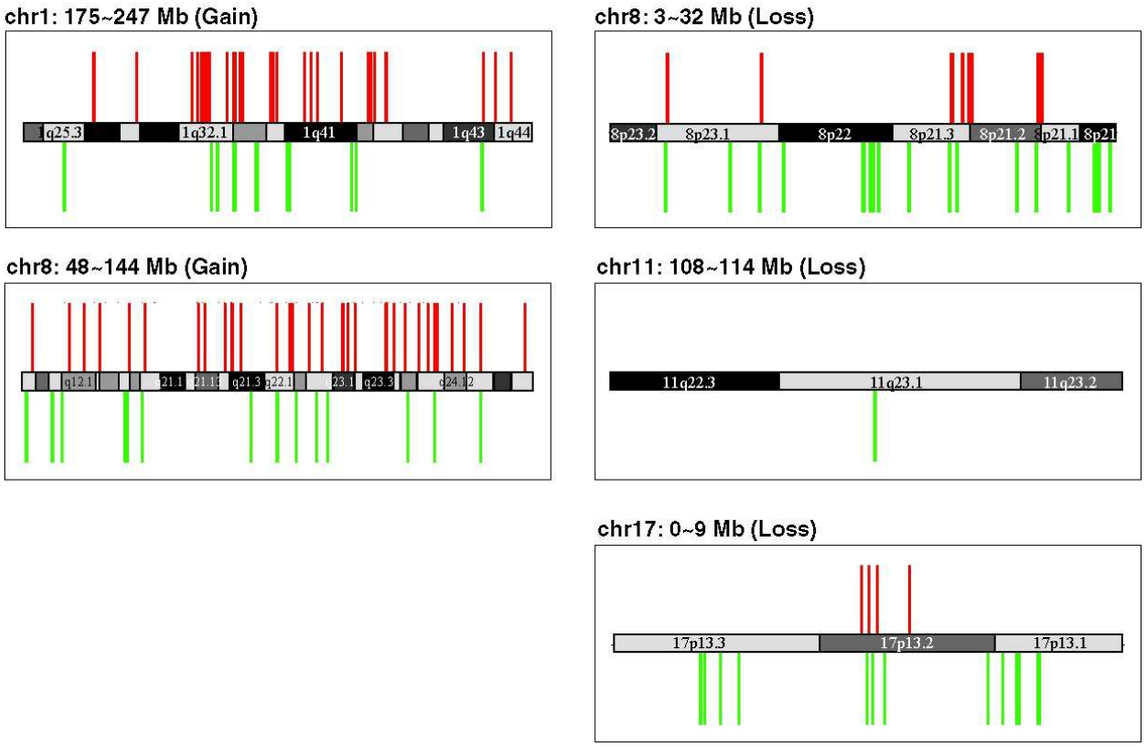


Fig. 3. Common genomic aberration in both early- and late-onset breast cancers. Left panel shows the amplified regions and right panel shows the deleted regions in breast cancers. The red and green lines represent the gene position in the genome. Red lines indicate genes positively correlated with breast cancer and green lines indicate negatively correlated with breast cancer.

The genes present in the most frequent gain or loss regions of early-onset and late-onset breast cancer in Taiwan were analyzed by array-CGH. The genes related to breast cancer in these regions are shown in Table 5. There are two regions differentially gained or loss in late-onset and three regions differentially gained or loss in early-onset. As in the results above, the regions are marked by the presence of both pro- and anti-tumor genes (in *italic*) except 17q23 which is amplified in a subset of early-onset cancer but in none of the late-onset cancer. We analyzed the genes of this region flanking our array-CGH BAC probes. It contains seven genes involved in breast tumorigenesis and represents a region of interest for early diagnosis of breast cancer in young women.

2.4 SAGE analysis of gene expression in early- and late-onset breast cancer in Taiwan

We analyzed 10325 SAGE Taq sequences, and classified SAGE data into two groups (evaluated significance by monte-carol algorthim). There are 460 genes related to the early-onset group, and 214 genes involved in late-onset breast cancer.

SAGE analysis found 12 breast cancer related genes highly prevalent in early-onset than late-onset. Among these genes, cytokeratin 5 and 17 are basal cell markers and are often found in

basal-like and triple-negative breast cancer subtypes. Luminal specific cytokeratin KRT8 and KRT19 was also found to be enriched in early-onset cancer. This result suggests that there are two different subtypes, basal-like and luminal groups, of breast cancer in the early-onset samples we analyzed. Both tumor promoting and inhibiting genes are found expressed in the SAGE data. For example, KLK6 inhibits EMT and its expression is negatively correlated with breast cancer metastasis (Pampalakis et al., 2009) and FLNA (filamin A) is known to suppress breast cancer migration and invasion (Xu et al., 2010). The expression of the tumor suppressive CDH1, CDH13, CTNNB1, SFN, NDRG1 and PFN1 in early-onset tumor also suggests the less invasive nature. IGFBP4 is positively correlated with ER and PR but negatively correlated with Her2 and has better disease outcome (Mita et al., 2007). On the other hand, S100P and LCN2 promote breast cancer progression. Whether the expression of tumor suppressive genes reflects the more benign nature of the early-onset breast cancer or due to mutations in these genes remain to be studied. Genes associated with tumor progression, metastasis and poor prognosis such as CXCR4, ERBB2, TOB1, EZH2, HIF1A, S100A7, are found significantly more expressed in the late-onset breast cancer. The overall expression pattern suggests that the late-onset tumors are more advanced in tumorigenesis than that of the early-onset tumors which constitute mostly benign luminal A subtype in Taiwan.

Cyto Location	**Gene related to breast cancer**	**Early-onset (n=15)**	**Late-onset (n=15)**	***P*- value**
Gains				
16p13.3	MSLN, CACNA1H, PDPK1, SRMM2, TRAP1 *STUB1, TSC2, PKD1, ABCA3, DNAJA3*	6.67%	60.00%	0.0026
8q11	PRKDC, SNAI2 *CEBPD, MCM4, ST18, RB1CC1*	6.67%	46.67%	0.0176
16q23.2	-	53.33%	13.33%	0.0251
20q12-q13.1	PLCG1, ADA, WISP2, CD40, NCOA3, SULF2, PREX1 *PTPRT, MYBL2, SDC4, UBE2C*	53.33%	13.33%	0.0251
17q23	RPS6KB1, USP32, PAT1, PPM1D, BCAS3, TBX2, MRC2	26.67%	0.00%	0.0498
Losses				
1p36.22	-	6.67%	53.33%	0.0071
22qtel	*PARVB, PARVG, PRR5, FNLN1, PPARA, GRAMD4*	6.67%	46.67%	0.0176
1p13.1	VANGL1, VTCN1	0.00%	33.33%	0.0211
11q22.3	PDGFD, ALKBH8, RDX *CASP-12, -4, -5, -1, CUL5, ATM*	0.00%	26.67%	0.0498
Xq25	XIAP, SMARCA1, APLN *AIFMI*	0.00%	26.67%	0.0498

Table 5. Significant difference between early- and late-onset breast cancers by array-CGH (aberrant genes correlated with early- or late-onset breast cancers were evaluated by using the Fisher's exact test).

3. Conclusion

In this report we show that early-onset breast cancer has different genetic alterations as compared with that of late-onset cancer, suggesting that different molecular pathways are involved in the generation of these two types of cancer. The genes strongly associated with early-onset breast cancer such as those in 17q23 amplicon may be useful for deducing the molecular mechanism of breast cancer in young women as well as for serving as candidate biomarkers.

Early-onset breast cancer has been a major health concern and had poor prognosis compared with late-onset in Taiwan. We are interested in comparing the genome aberrations between early- and late-onset breast cancers. Although we study the genome aberrations in Taiwan, we also explore the public data which are associated with early-onset and late-onset breast cancers. The findings can help us to address early-onset breast cancer specific gene aberrations and explore the unique tumor biology in Taiwan through this broad view.

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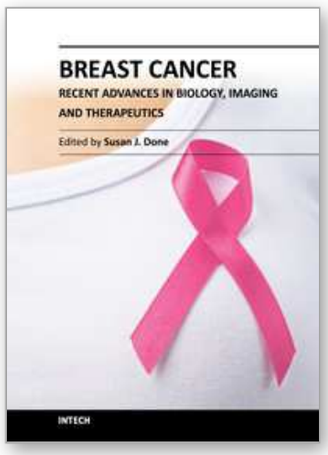
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In recent years it has become clear that breast cancer is not a single disease but rather that the term encompasses a number of molecularly distinct tumors arising from the epithelial cells of the breast. There is an urgent need to better understand these distinct subtypes and develop tailored diagnostic approaches and treatments appropriate to each. This book considers breast cancer from many novel and exciting perspectives. New insights into the basic biology of breast cancer are discussed together with high throughput approaches to molecular profiling. Innovative strategies for diagnosis and imaging are presented as well as emerging perspectives on breast cancer treatment. Each of the topics in this volume is addressed by respected experts in their fields and it is hoped that readers will be stimulated and challenged by the contents.

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