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Original Article

Clinicopathological Finding and Prognosis in Bilateral Breast Cancer: Nakhonphanom Hospital

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ABSTRACT

Background and Objectives: The incidence of bilateral breast cancer is 2-12% of patients with breast cancer. This study aimed to study and compare clinicopathological finding, associated factor, previous treatment and prognosis of patients with bilateral breast cancer, both of synchronous and metachronous bilateral breast cancer (SBBC and MBBC) who visited Nakhonphanom Hospital.

Material and Methods: This study was a single center, retrospective descriptive study. Data was collected from medical records. 32 patients with bilateral breast cancer. (24 MBBC and 8 SBBC) who visited at Nakhonphanom Hospital between 1st October 2014 – 30th September 2024 were selected from the database. A total of 196 patients with unilateral breast cancer were selected as the control group. Data was analyzed by statistical distribution, frequency, mean and standard deviation (SD). The continuous data was tested for normal distribution. Quantitative variables were compared mean among two groups by independent t-test and compared the mean more than two groups using one-way ANOVA test. Nominal categorical data was compared proportion using Fisher's exact test. The statistically significant variance was p-value < 0.05.

Result: The incidence of bilateral breast cancer in Nakhonphanom Hospital is 4.15%. Diagnosis breast cancer at premenopausal period is associated risk of bilateral breast cancer, significantly (p = 0.003), especially SBBC. (p = 0.008) ER negative and PR negative of the first cancer is associated factors of bilateral breast cancer, significantly. (p < 0.001, p = 0.047) The interval between diagnosis the first and the second cancer in MBBC ranged 7-216 months. Patients who were lost to follow up had poor prognosis.

Conclusion: Associated factors of bilateral breast cancer are diagnosis breast cancer in premenopausal period and ER/PR negative. Breast cancer patients should be followed up and surveillance to prevent and aware breast cancer in contra lateral breast.

Keywords: Bilateral breast cancer, synchronous bilateral breast cancer, metachronous bilateral breast cancer, clinicopathological finding, prognosis, associated factor

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Introduction

Bilateral breast cancer is uncommon. The incidence varies between 2-12% of all breast cancer patients.[1,2,4,5] The risk of developing the second contralateral breast cancer is 2-6 times higher than the risk of developing the initial breast cancer in general population.[1,5,6] The prognosis of patients with BBC depends on the stage at the detection of both breast cancer.[6] The risks of BBC include family history of cancer, diagnosed breast cancer at early age less than 40 years old, lobular carcinoma, hormonal receptor status, HER2 expression positive, treatment for the first breast cancer and BRCA mutation.[1,2,4-7]

Bilateral breast cancer is divided to synchronous bilateral breast cancer (SBBC) and metachronous bilateral breast cancer (MBBC), depending on the time interval between the diagnosis of BBC in both breasts. The time interval to determine between SBBC and MBBC is controversial.[1,3] Synchronous bilateral breast cancer defines as the cancers diagnosed at the same time or within 6 months.[1,12,13] Metachronous bilateral breast cancer defines as the second breast cancer occurs after 6 months the first breast cancer was diagnosed.[1,12,13] The literature[3] reported the incidence of SBBC and MBBC was 2% and 3%, respectively. The literature[5] shown 5 years overall survival in SBBC was 60% and 78.7% for MBBC. Chaudary et al. proposed the following criteria to differentiate second primary breast cancer from metastasis to contralateral breast: in the case of a second primary.

1. The tumor in the second breast is histologically different from the primary tumor.

2. Presence of in situ change in the contralateral breast.

3. The degree of histological differentiation in the second breast is distinctly greater than the lesion in the first breast.

4. There is no evidence of local, regional, or distant metastases from cancer of the ipsilateral breast.

5. Presence of DCIS (in situ component) in contralateral breast favors a primary over metastatic lesion.[15]

There were an increasing number of bilateral breast cancer patients visited at Nakhonphanom Hospital last 3 years. (3 in 2022, 9 in 2023 and 7 in 2024) There were an increasing number of unilateral breast cancer at Nakhonphanom Hospital also. There is no previous study about BBC in Nakhonphanom Hospital. The aim of this study is to study clinicopathological report, previous treatment and associated factor of BBC, lead to surveillance and prevention BBC for Nakhonphanom Hospital in the future.

Methods

This study was a single center, retrospective descriptive study. All patients with bilateral breast cancer who visited at Nakhonphanom Hospital

between 1st October 2014 – 30th September 2024 were selected from the database. Patients who underwent surgery at other hospitals and patients who were referred out or referred from other hospital were included. The exclusion criteria were patients who missing important clinicopathological report or required data. The data were extracted from the hospital database, which included age at diagnosis each tumor of breast cancer, menopausal status, family history of breast cancer, cell type, tumor grade, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2) status and TMN stage, according to National Comprehensive Cancer Network. (NCCN)

Menopause defined according to National Comprehensive Cancer Network (NCCN) 1) age ≥ 60 years old, 2) patients who underwent bilateral oophorectomy. 3) patients who younger than 60 years old with amenorrhea for 12 months or more in the absence of chemotherapy, endocrine therapy or ovarian suppression, FSH and estradiol (E2) level were in postmenopausal range. 4) patients who younger than 60 years old and taking endocrine drugs with FSH and estradiol (E2) level were in postmenopausal range.[3]

Family history of cancer was defined as one or more first-or second-degree relatives of patients had cancer (breast cancer or another cancers).[3]

For bilateral breast cancer, the first tumor was defined as breast cancer which was confirmed by pathological report from biopsy.[3] The second tumor was defined as breast cancer which was confirmed after that.[3] TMN stage was defined according to the staging of National Comprehensive Cancer Network. (NCCN) The cutoff value for Ki 67 was set at 20% due to the patients' probability of receiving more aggressive treatment, according to National cancer institute guideline.

After determining the number of patients with bilateral breast cancer, unilateral breast cancer patients (UBC) who visited at Nakhonphanom Hospital at the same time were selected randomly from the database by simple random with Excel program, as the control group at a ratio 1:6. Assuming that the critical data loss rate is 15%. Patients who underwent surgery at another hospitals and patients who were referred out or referred from another hospital were included. The exclusion criteria were patients who missing important clinicopathological report or required data.

From the hospital database 771 patients with all breast cancer patients who visited Nakhonphanom Hospital between 1st October 2014 – 30th September 2024, we found 739 patients with unilateral breast cancer and 32 patients with bilateral breast cancer. (24 MBBC and 8 SBBC) After excluding 5 patients with unilateral breast cancer who missing required data, a total of 221 patients with unilateral breast cancer were selected as the control group and all patients with

bilateral breast cancer were enrolled. (As Figure 1: flow diagram)

Statistical analysis

This study was performed with Stata version 17.0. Data was collected from medical records. Patients characteristic information, age at diagnosis each side breast cancer, family history of cancer, interval between diagnosis each side breast cancer, follow up as an appointment, previous treatment of first breast cancer, pathological report was collected and analyzed by statistical distribution, frequency, mean and standard deviation (SD). The continuous data was tested for normal distribution. Quantitative variables were compared mean among two groups by independent *t*-test and compared the mean more than two groups using one-way ANOVA test. Nominal categorical data was compared proportion using Fisher's exact test. The statistically significant variance was *p*-value < 0.05. This study was approved by the institutional ethics committee with approval number NP-EC11-No.49/2567

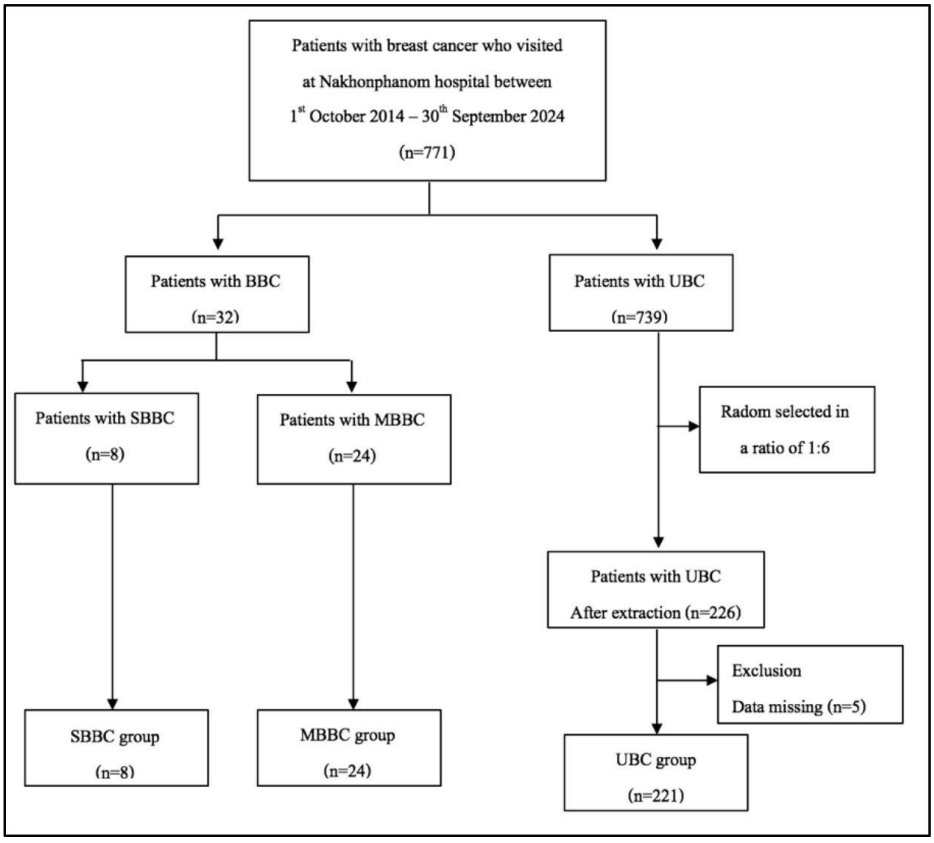

Figure 1 Flow diagram of this study. BBC = bilateral breast cancer, SBBC= synchronous bilateral breast cancer, MBBC = metachronous bilateral breast cancer, UBC = unilateral breast cancer.

Results

771 patients with breast cancer were screened, all 32 bilateral breast cancer patients were selected. (8 were synchronous and 32 were metachronous) 739 were patients with unilateral breast cancer and 226 patients were selected by Excel program computer randomly as a ratio of 1:6. After 5 patients with unilateral breast cancer were excluded due to missing required data, 221 patients with unilateral breast cancer were enrolled as a control group. (Figure 1)

The overall incidence of bilateral breast cancer is 4.15%. The incidence of SBBC and MBBC in this study were 25% and 75% from all BBC, respectively. All patients in this study were female. The average age at the first diagnosis of cancer in SBBC, MBBC and UBC were 61.13 ± 5.11, 47.83 ± 8.50 and 54.64 ± 10.25 years, respectively. The average age at the second diagnosis of cancer in MBBC was 57.63 ± 6.51 years. There was no significant difference in the average age at the first and the second diagnosis of cancer in all group. (Table 1) All patients with SBBC developed cancer at the same time. For MBBC, the interval between diagnosis two cancer ranged since 7 to 216 months, mean 113 ± 59.63 months. Most patients developed MBBC between more than 10 to 15 years after the date of first diagnosis cancer (9 patients). The risk persisted after that until nearly 20 years. (As table 1 and figure 2) About the menopausal status, all patients with SBBC were in postmenopausal period. (n = 8,100%) Mostly patients with MBBC were in premenopausal period. (n = 16, 66.67%) The number of postmenopausal periods in patients with UBC were higher than patients in premenopausal period. (n = 114, 51.58%) Summary, patients with BBC were in premenopausal period, higher than UBC, significantly (p = 0.003), especially in SBBC. (p = 0.008) But there was no significant difference between UBC and MBBC. (Table 1) In BBC groups, there were only 10 (31.25%) had a family history of cancer, 4 (40%) for history of breast cancer and 6 (60%) for others cancer. In the UBC groups, only 44 (19.91%) had family history of cancer which 17 (38.64%) for history of breast cancer and 27 (61.36%) for others cancer. from this study, we found that there was no significant difference in family history of cancer in all group. (p = 0.272, p = 0.663, p = 0.185 respectively.) (Table 1) About surgical methods, all patients with BBC underwent MRM (n = 32, 100%) Most of patients with UBC underwent MRM (n = 218, 98.64%), only 2 (0.90%) underwent BCS and 1 (0.45%) underwent mastectomy with SLNB. However, there was no significant difference in surgical methods in three groups. (Table 1)

Pathological features in the first cancer, the most patients in all groups were invasive ductal carcinoma. (7 in SBBC, 22 in MBBC and 208 in UBC) Patients with tumor grade 2 were found the most in BBC and UBC groups, n = 19 (59.38%) and n =

Table 1 Baseline characteristic of bilateral breast cancer and unilateral breast cancer patients.

Characteristics	BBC			UBC	*P* value		
	Overall (n=32)	SBBC (n=8)	MBBC (n=24)	(n=221)	UBC vs. SBBC vs. MBBC	UBC vs. SBBC	UBC vs. MBBC
Age (years) Mean (SD)							
1st cancer	51.16 (9.68)	61.13 (5.11)	47.83 (8.50)	54.64 (10.25)	0.067*	0.077†	0.256†
2nd cancer	58.50 (6.30)	61.13 (5.11)	57.63 (6.51)	-	0.178†	-	-
Interval between two cancers diagnosis (months) Mean ± SD (range)	85.38 ± 71.49 (7-216)	0 (0)	113.83 ± 59.23 (7-216)	-	< 0.001†	-	-
Menopause status (%)							
Pre menopause	16 (50)	0 (0)	16 (66.67)	107 (48.42)	0.003‡	0.008‡	0.131‡
Post menopause	16 (50)	8 (100)	8 (33.33)	114 (51.58)	-	-	-
Family history of cancer (%)							
No	22 (68.75)	6 (75)	16 (66.67)	177 (80.09)	0.272‡	0.663‡	0.185‡
Yes	10 (31.25)	2 (25)	8 (33.33)	44 (19.91)	-	-	-
Breast cancer	4 (40)	1 (50)	3 (37.50)	17 (38.64)	1.000‡	1.000‡	1.000‡
Others	6 (60)	1 (50)	5 (62.50)	27 (61.36)	-	-	-
Surgical methods (%)							
MRM	32 (100)	8 (100)	24 (100)	218 (98.64)	1.000‡	1.000‡	1.000‡
BCS	0 (0)	0 (0)	0 (0)	2 (0.90)	-	-	-
Mastectomy and SLNB	0 (0)	0 (0)	0 (0)	1 (0.45)	-	-	-

SBBC = synchronous bilateral breast cancer, MBBC = metachronous bilateral breast cancer, UBC = unilateral breast cancer, MRM = modified radical mastectomy, BCS = breast conservative surgery, SLNB = sentinel lymph node biopsy

* *P*-value from ANOVA Analysis of variance, †*P*-value from independent *t*-test, ‡*P*-value from Fisher's exact probability test

141 (63.80%) respectively. There was no significant difference in cell type and tumor grade between all group. (Table 2) Considering about hormonal status in the first cancer, both groups of BBC were in ER negative group and positive group equally. (n = 16, 50% in each group) In specific details in each group, the study found that all SBBC had ER positive (n = 8, 100%) but in MBBC, the proportion between ER negative was higher than ER positive. (n = 16, 66.67% and n = 8, 33.33% respectively) In UBC, the number of patients in ER positive were higher than ER negative. (n = 148, 66.97% and n

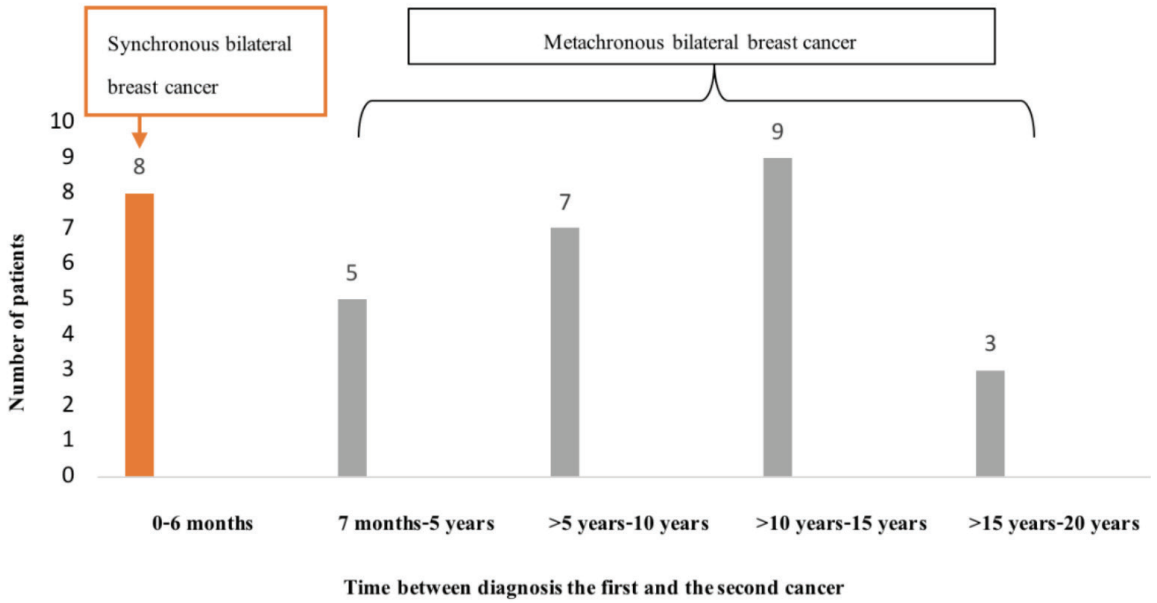

Figure 2 The frequency of bilateral breast cancer depending on the time between diagnosis the first and the second cancer.

= 73, 33.33% respectively) There was significant difference in ER status between UBC and the first cancer of BBC group ($p < 0.001$), especially between UBC and the first cancer of MBBC. ($p = 0.002$) About PR status in the first cancer, this study found that mostly patients with SBBC had PR positive (n = 6, 75%), but mostly patients with MBBC had PR negative. (n = 16, 66.67%) The proportion between PR negative group in UBC was higher than positive group. (n = 94, 42.53% and n = 127, 57.47% respectively) There were significant difference PR status between three groups, $p = 0.047$, 0.047, $p = 0.030$ respectively. (Table 2)

Most patients in all three groups had HER-2 negative, 6 (75%) in SBBC, 13 (54.17%) in MBBC and 131 (59.28%) in UBC. However, HER2 expression 2+ was not further evaluated on fluorescence in situ hybridization (FISH) due to this test was not available in Nakhonphanom Hospital. Therefore, all patients who had HER2 equivocal could not be determined in positive or negative group. Most patients in MBBC and UBC groups had Ki 67 ± 20%. (n = 18, 75% and n = 147, 66.52% respectively) All patients with SBBC had Ki 67 ± 20%. There was no significant difference between each group whether HER2 expression and Ki 67. (Table 2)

According to this study, most of patients with SBBC were diagnosed in stage 2A (n = 4, 50%)

Table 2 Comparison of pathological features between unilateral breast cancer and bilateral breast cancer patients (1st cancer).

Characteristics	1st BBC			UBC	*P* value		
	Overall (n = 32)	1st SBBC (n = 8)	1st MBBC (n = 24)		UBC vs. 1st SBBC vs 1st MBBC	UBC vs. 1st SBBC	UBC vs. 1st MBBC
Cell type (%)					0.188*	0.217*	0.226*
Invasive ductal	29 (90.63)	7 (87.50)	22 (91.67)	208 (94.12)	-	-	-
Invasive Lobular	3 (9.38)	1 (12.50)	2 (8.33)	5 (2.26)	-	-	-
Others	0 (0)	0 (0)	0 (0)	8 (3.62)	-	-	-
Tumor grade (%)					0.182*	0.569*	0.095*
Grade 1	1 (3.13)	1 (12.50)	0 (0)	27 (12.22)	-	-	-
Grade 2	19 (59.38)	4 (50.00)	15 (62.50)	141 (63.80)	-	-	-
Grade 3	12 (37.50)	3 (37.50)	9 (37.50)	53 (23.98)	-	-	-
ER status (%)					< 0.001*	0.058*	0.002*
Negative	16 (50)	0 (0)	16 (66.67)	73 (33.33)	-	-	-
Positive	16 (50)	8 (100)	8 (33.33)	148 (66.97)	-	-	-
PR status (%)					0.047*	0.047*	0.030*
Negative	18 (56.25)	2 (25)	16 (66.67)	94 (42.53)	-	-	-
Positive	14 (43.75)	6 (75)	8 (33.33)	127 (57.47)	-	-	-
HER2 expression (%)					0.299*	0.157*	0.425*
Negative	19 (59.38)	6 (75.00)	13 (54.17)	131 (59.28)	-	-	-
Positive	5 (15.63)	0 (0)	5 (20.83)	57 (25.79)	-	-	-
Equivocal	8 (25.00)	2 (25.00)	6 (25.00)	33 (14.93)	-	-	-
Ki 67 status (%)					0.097*	0.057*	0.496*
< 20%	6 (18.75)	0 (0)	6 (25.00)	74 (33.48)	-	-	-
≥ 20%	26 (81.25)	8 (100.00)	18 (75.00)	147 (66.52)	-	-	-
Tumor stage (%)					0.198*	0.170*	0.267*
T1	0 (0)	0 (0)	0(0)	19 (8.60)	-	-	-
T2	25 (78.13)	5 (62.50)	20 (83.33)	154 (69.68)	-	-	-
T3	3 (9.38)	1 (12.50)	2 (8.33)	36 (16.39)	-	-	-
T4	4 (12.50)	2 (25)	2 (8.33)	12 (5.43)	-	-	-
Axillary lymph node stage (%)					0.991*	0.899*	0.961*
N0	15 (46.88)	4 (50)	11 (45.83)	109 (49.32)	-	-	-
N1	11 (34.38)	3 (37.50)	8 (33.33)	62 (28.05)	-	-	-
N2	4 (12.50)	1 (12.50)	3 (12.50)	27 (12.22)	-	-	-
N3	2 (6.25)	0 (0)	2 (8.33)	23 (10.41)	-	-	-

Table 2 **(cont.)** Comparison of pathological features between unilateral breast cancer and bilateral breast cancer patients (1st cancer).

Characteristics	1st BBC			UBC	*P* value		
	Overall (n = 32)	1st SBBC (n = 8)	1st MBBC (n = 24)		UBC vs. 1st SBBC vs 1st MBBC	UBC vs. 1st SBBC	UBC vs. 1st MBBC
Distant metastasis (%)**					0.706*	1.000*	0.606*
No	32 (100)	8 (100)	24 (100)	211 (95.48)			
Yes	0 (0)	0 (0)	0 (0)	10 (4.52)	-	-	-
Lung	0 (0)	0 (0)	0 (0)	8 (80)	-	-	-
Liver	0 (0)	0 (0)	0 (0)	5 (50)	-	-	-
Stage (%)					0.547*	0.291*	0.789*
1A	0 (0)	0 (0)	0 (0)	14 (6.33)	-	-	-
1B	0 (0)	0 (0)	0 (0)	1 (0.45)	-	-	-
2A	13 (40.63)	4 (50)	9 (37.50)	86 (38.91)	-	-	-
2B	11 (34.38)	1 (12.50)	10 (41.67)	59 (26.70)	-	-	-
3A	4 (12.50)	1 (12.50)	3 (12.50)	30 (13.57)	-	-	-
3B	2 (6.25)	2 (25.00)	0 (0)	8 (3.62)	-	-	-
3C	2 (6.25)	0 (0)	2 (8.33)	16 (7.24)	-	-	-
4	0 (0)	0 (0)	0 (0)	7 (3.17)	-	-	-

ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor 2
* *P*-value from Fisher's exact probability test
** Some patients had more than one distance metastasis
* *P*-value from ANOVA Analysis of variance, †*P*-value from independent *t*-test, ‡*P*-value from Fisher's exact probability test

and most of patients with MBBC were in stage 2B at the first diagnosis of cancer. (n = 10, 41.67%) There was no distant metastasis in SBBC and at the first diagnosis of MBBC but distant metastasis was found in UBC (n = 10, 4.52%) which were lung and liver metastasis. (n = 8, 80% and n = 5, 50% respectively) However, TMN stage was not significant difference between three groups. (Table 2)

There was no significant difference between the first and second cancer of bilateral breast cancer in specific details in pathological report whether cell type, tumor grade, ER/PR status HER2 and Ki 67. However, HER2 expression 2+ was not further evaluated on fluorescence in situ hybridization (FISH) due to this test was not available in Nakhonphanom hospital. Therefore, patients who were in HER2 equivocal group could

Table 3 Comparison of pathological features between synchronous and metachronous bilateral breast cancer (1st and 2nd cancer)

Characteristics	SBBC (n = 8)			MBBC (n = 24)		
	1st cancer	2nd cancer	*P* value	1st caner	2nd cancer	*P* value
Cell type (%)			1.000*			0.489*
Invasive ductal	7 (87.50)	7 (87.50)	-	22 (91.67)	24 (100)	-
Invasive lobular	1 (12.50)	1 (12.50)	-	2 (8.33)	0 (0)	-
Others	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Tumor grade (%)			1.000*			0.760*
Grade 1	1 (12.50)	1 (12.50)	-	0 (0)	1 (4.17)	-
Grade 2	4 (50)	5 (62.50)	-	15 (62.50)	16 (66.67)	-
Grade 3	3 (37.50)	2 (25.00)	-	9 (37.50)	7 (29.17)	-
ER status (%)			-			0.380*
Negative	0 (0)	0 (0)	-	16 (66.67)	12 (50)	-
Positive	8 (100)	8 (100)	-	8 (33.33)	12 (50)	-
PR status (%)			1.000*			0.380*
Negative	2 (25)	2 (25)	-	16 (66.67)	12 (50)	-
Positive	6 (75.00)	6 (75)	-	8 (33.33)	12 (50)	-
HER2 expression (%)			0.467*			0.606*
Negative	6 (75)	8 (100)	-	13 (54.17)	14 (58.33)	-
Positive	0 (0)	0 (0)	-	5 (20.83)	2 (8.33)	-
Equivocal	2 (25)	0 (0)	-	6 (25)	8 (33.33)	-
Ki 67 status (%)						0.245*
< 20%	0 (0)	0 (0)	-	6 (25)	2 (8.33)	-
≥ 20%	8 (100)	8 (100)	-	18 (75)	22 (91.67)	-
Tumor stage (%)			1.000*			0.001*
T1	0 (0)	0 (0)	-	0 (0)	5 (20.83)	-
T2	5 (62.50)	5 (62.50)	-	20 (83.33)	7 (29.17)	-
T3	1 (12.50)	2 (25.00)	-	2 (8.33)	4 (16.67)	-
T4	2 (25)	1 (12.50)	-	2 (8.33)	8 (33.33)	-
Axillary lymph node stage (%)			0.765*			0.814*
N0	4 (50)	6 (75)	-	11 (45.83)	10 (41.67)	-
N1	3 (37.50)	1 (12.50)	-	8 (33.33)	6 (25.00)	-
N2	1 (12.50)	1 (12.50)	-	3 (12.50)	6 (25.00)	-
N3	0 (0)	0(0)	-	2 (8.33)	2 (8.33)	-

Table 3 (cont.) Comparison of pathological features between synchronous and metachronous bilateral breast cancer (1st and 2nd cancer)

Characteristics	SBBC (n = 8)			MBBC (n = 24)		
	1st cancer	2nd cancer	*P* value	1st caner	2nd cancer	*P* value
Distant metastasis (%) **			-			0.109*
No	8 (100)	0 (0)	-	24 (100)	20 (83.33)	-
Yes	0 (0)	8 100)	-	0 (0)	4 (16.67)	-
Lung	0 (0)	0 (0)	-	0 (0)	3 (75)	-
Liver	0 (0)	0 (0)	-	0 (0)	2 (50)	-
Bone	0 (0)	0 (0)	-	0 (0)	3 (75)	-
Stage (%)			1.000*			< 0.001*
1A	0 (0)	0 (0)	-	0 (0)	3 (12.50)	-
1B	0 (0)	0 (0)	-	0 (0)	1 (4.17)	-
2A	4 (50)	5 (62.50)	-	9 (37.50)	5 (20.83)	-
2B	1 (12.50)	1 (12.50)	-	10 (41.67)	0 (0)	-
3A	1 (12.50)	1 (12.50)	-	3 (12.50)	4 (16.67)	-
3B	2 (25.00)	1 (12.50)	-	0 (0)	5 (20.83)	-
3C	0	0	-	2 (8.23)	2 (8.33)	-
4	0	0	-	0 (0)	4 (16.67)	-

* *P*-value from Fisher's exact probability test
** Some patients had more than one distance metastasis

not be determined into positive or negative group. (Table 3) According to TMN stage, this study found there was significant difference in tumor grade between the first and second cancer of MBBC. (p = 0.001) Distant metastasis was found in patients with MBBC when the second cancer was diagnosed (n = 4, 16.67%), including lung (n = 3, 75%), liver (n = 2, 50%) and bone (n = 3, 75%) but there was no significantly. However, there was significant different in stage between the first and second cancer of MBBC. (p < 0.001) This study found patients with MBBC were diagnosed as locally advanced breast cancer (stage 3A, 3B, 3C) and metastatic breast cancer (stage 4) more than early breast cancer (stage 1A, 1B, 2A, 2B) when the second cancer was diagnosed. (Table 3)

According to this study, the number of the patients with MBBC who visited a doctor as an appointment and were lost to follow up were equal. (n = 50 in each group) In specific details

about distant metastasis finding when the second cancer was diagnosed in MBBC, patients who follow up as an appointment had no distant metastasis more than patients who were lost to follow up (n = 11, 55% and n = 9, 45% respectively) but there was no significant difference. (Table 4). The reasons patients lost to follow up were financial problem, there was no any caregiver and COVID 19 outbreak. Mostly patients had appointments at the cancer center hospital where are distant from Nakhonphanom province.

Table 4 Comparison of distant metastasis between patients who follow up as an appointment in the second cancer of metachronous bilateral breast cancer.

	Follow up (n=12)	Loss follow up (n=12)	*P*-value
Distant metastasis (%)			0.590*
No	11 (55)	9 (45)	-
Yes	1 (25)	3 (75)	-

* *P*-value from Fisher's exact probability test

Discussion

According to this study, the overall incidence of bilateral breast cancer was 4.15% which makes it comparable to other literatures that reported the incidence of bilateral breast cancer varies between 2-12%.[1,2,4,5] The incidence of SBBC and MBBC in this study were 25% and 75% of the BBC population, similar to the previous literatures.[1,5,6] Most of patients who developed bilateral breast cancer were in premenopausal period. Associated factors of bilateral breast cancer were ER negative, especially metachronous bilateral breast cancer, and PR negative. The interval between diagnosis two cancer ranged for 7 months to 216 months. (nearly 20 years) Metachronous bilateral breast cancer had poor prognosis due to most of patients were in higher stage when the second cancer was diagnosed.

Modified radical mastectomy (MRM) is the most performed surgery for breast cancer in Nakhonphanom Hospital in this study due to sentinel lymph node biopsy and frozen section are not available in Nakhonphanom Hospital. Only 2 patients with UBC had undergone breast conservative surgery. 1 patient with UBC had undergone mastectomy with sentinel lymph node biopsy from other hospital then return to continue surveillance at hometown. All patients with SBBC

decided to undergo MRM the same as patients with MBBC due to conserving contra lateral breast is not necessary if the patients decided to remove entire of breast when the first cancer was diagnosed.

From the data in this study, it shown a family history of cancer does not likely relate to unilateral or bilateral breast cancer. Most of patients had no family history of cancer. In contrast, we found that most of breast cancer patients who had family history of cancer, other cancer was reported more often which was cholangiocarcinoma. This information was supported by National cancer institute which reported cholangiocarcinoma was found the highest rate in northeastern Thai population caused of the consumption of uncooked fish. However, the population in this study was low which may affect the result and can not conclude the result.

All SBBC was found at the same time. The shortest interval between two cancers diagnosis in MBBC was 7 months which not long after the first cancer was diagnosed and treated. According to individual data analysis, mammogram did not be performed to evaluate contra lateral breast before biopsy in this patient. We found that some patients did not be examined by mammogram or ultrasound both breasts before biopsy because a doctor did not request. Furthermore, mammogram was available in Nakhonphanom Hospital after September 2017, for this reason the patients who visited Nakhonphanom Hospital before that period might not be examined by mammogram. However, mammogram and ultrasound breasts are useful for evaluation abnormal lesion in breast, especially non-palpable lesion.[5,6,9]

Consequently, mammogram and ultrasound breasts should be performed in patients who have indication for breast cancer screening and breast cancer patients who need follow up surveillance in order to detecting early-stage breast cancer.[5,6,9,14] The most patients with MBBC were diagnosed the second cancer at the period of more than 5–10 years and more than 10–15 years. From this study, the data shown the period when the disease could be occurred the most in this study. However, the breast cancer patients should be followed up for every 3 to 6 months for the first 2 to 3 years, then every six months until the 5th year and annually thereafter.[14]

In assessing the pathological features, the associated factors increased risk of bilateral breast cancer was hormonal status. ER and PR negative were the factors affecting develop bilateral breast cancer, as the literatures supported.[3,5] In this study, cell type and HER2 expression did not affect increasing incidence of bilateral breast cancer. However, FISH test is not available in Nakhonphanom Hospital so that patients with HER2 expression 2+ (equivocal) could not be determined in positive or negative group. We cannot divide molecular subtypes of breast cancer

in this study.

Patients with MBBC were diagnosed as locally advanced breast cancer and metastatic breast cancer more than early-stage breast cancer when the second cancer was diagnosed. Patients who were lost to follow up had distant metastasis more than the patients who follow up as an appointment. According to the individual data analysis, the reasons for loss follow up were some patients had financial problem, there was no any caregiver and COVID 19 outbreak. Mostly patients had appointments at the cancer center hospital where are distant from Nakhonphanom province. The breast clinic just has been actively established at Nakhonphanom Hospital since 2019 until the present which clearly is the responsibility of surgeons. For this reason, some patients who were sent for treatment at the other hospital were lost to follow up. According to the database from Nakhonphanom Hospital, 2 patients with MBBC (stage 4) from this study died at about 1 year after diagnosis the second cancer.

Many literatures[2,4,6,7] mentioned that BRCA mutation is the risk factor of bilateral breast cancer. No patients in this study were tested for genetic testing. Therefore, genetic testing for BRCA mutation should be considered in patients with bilateral breast cancer to prevent and others related cancer awareness.[8,14] This study was limited by the small number of patients and the absence of FISH test BRCA test. The study about bilateral breast cancer should be observed continuously to verify the risk factors, prognosis and survival rate of bilateral breast cancer when the number of patients is increased in the future.

Conclusion

Breast cancer patients should be continuously followed up and surveillance to prevent and aware breast cancer in contra lateral breast, especially patients who were diagnosed breast cancer at premenopausal period and hormonal receptor negative. BRCA gene mutation is one of the factors increased incidence of bilateral breast cancer (BRCA testing was not available in Nakhonphanom Hospital for this reason, patients in this study were not examined.) Mammogram or ultrasound breasts should be performed at the first visit and at follow up period in order early detection of contra lateral breast cancer.

The provincial hospital should be the important role in follow up and surveillance due to some patients have no ability to go to the distant hospital.

According to the database from Nakhonphanom Hospital, the number of patients with breast cancer, both of unilateral and bilateral keep increasing. In the past, we found that some patients with breast cancer were lost to follow up due to many reasons, for example, financial problem, no care giver or not available to go to the cancer center hospital. So, we expect this study

is useful in the development of Breast cancer of Nakhonphanom Hospital in the future. Moreover, we aim to study about BRCA mutation and study molecular subtype in patients with bilateral breast cancer in the future by improvement the laboratory potentiality of Nakhonphanom Hospital.

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