Ethnic disparity in breast cancer survival in southern Thai women

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**ABSTRACT**

**Background:** Breast cancer has the highest incidence in women of all cancers and its burden is expected to continue to increase worldwide, especially in middle-income countries such as Thailand. The southern region of Thailand is unique in that it is comprised of 30% Muslims, whereas the rest of Thailand is 95% Buddhist. Breast cancer incidence and survival differ between these religious groups, but the association between clinical subtype of breast cancer and survival has not yet been assessed.

**Methods:** Here we characterized differences in breast cancer survival with consideration to clinical subtype by religious group (Muslim Thai and Buddhist Thai women). We compared distributions of age, stage and clinical subtype and assessed overall survival by religion.

**Results:** Our findings show that Muslim Thai women with breast cancer are diagnosed at a younger age, at later stages and have shorter overall survival times compared to Buddhist Thai women with breast cancer. We also observe a higher proportion of triple negative tumors characterized in Muslim Thai women.

**Conclusions:** Our findings confirm previous studies that have shown lower survival rates in Muslim Thai women compared to Buddhist women with breast cancer and offer novel information on subtype distribution. To date, this is the first study assessing clinical subtypes in southern Thailand by religious status.

**Impact:** Our findings are critical in providing information on the role of clinical subtype in cancer disparities and provide evidence from the Southeast Asian region for global studies on breast cancer survival.

1. Introduction

Breast cancer contributes approximately a quarter of female cancer incidence in Thailand [1]. Incidence of this cancer is expected to continue to increase in the future as the population in Thailand is aging [2]. Breast cancer is a heterogeneous disease, comprising several different subtypes that correspond to specific risk factors and population characteristics [3]. Despite the existence of a strong network of population-based cancer registries in Thailand, there is limited research on the prevalence of these subtypes in Thailand, particularly in the southern region where risk factor profiles may vary between ethnically and culturally diverse populations. Contrary to the rest of Thailand which is 95% Buddhist, the Thai population in the south is comprised of 30% Muslims, making up the second largest religious denomination in Thailand [4]. Cancer incidence trends are different between these two religious groups, likely due to their ethnic and cultural makeup. It is difficult to trace the ethnicity of these groups due to historical influx and mixing of populations from other countries, but differences have been noted by religious status. Specifically, Muslim Thai women had lower incidence of breast, cervical, colorectal and liver cancers compared to Buddhist Thai women [5]. However, Muslim Thai women in the south generally had worse survival from breast and cervical cancers compared to Buddhist Thai women [6]. Therefore, due to the difficulty in assessing cancer trends by ethnicity, we focus on religious status to understand differing trends of these population subgroups.

While incidence and survival information by religion is available, clinical subtype distributions of breast cancer has not yet been assessed by religion. Invasive breast cancers have been classified into four main

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subtypes based on expression of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) [7–9]. These subtypes are traditionally classified into luminal A, luminal B, triple negative and HER2-overexpressing and are associated with risk factor patterns, response to treatment and overall prognosis [3,10–12]. Clinical subtype information is used to inform treatment and prognosis, and is critical to consider when determining survival rates. Locoregional and adjuvant treatment protocols follow National Comprehensive Cancer Network guidelines [13].

Given that the Muslim and Buddhist women of southern Thailand live in the same environment and have similar access to health care, the characterization of breast cancer subtypes in Thai Muslim and Thai Buddhist women will address the existence of a biological basis of the observed differences between these two population subgroups. Here, we provide breast cancer characterization and estimates of survival by religious group in southern Thailand. We aim to assess differences in age of onset and breast cancer subtype by religion, in an effort to indicate where tailored prevention strategies are needed to address the growing burden of breast cancer in southern Thailand.

2. Methods

2.1. Hospital registry

Songklanagarind Hospital is the Prince of Songkla University (PSU) hospital located in Hat Yai, Songkhla Province, Thailand. Thai patients are primarily referred from all fourteen provinces in southern Thailand to this hospital (Fig. S1), with a small number of cases from provinces in other regions in Thailand (n = 104). The hospital registry includes cancer cases from 1989 to 2014. Breast cancer cases were extracted from the cancer registry using ICD-10 codes C50.X. Information on age at diagnosis, stage, and religious status was extracted from this hospital registry. Stage at diagnosis characterizes cancers at localized, regional, distant or unknown stage as is common in cancer registries. Localized tumors are limited to where they begin with no signs of spreading; regional tumors have spread to nearby lymph nodes, tissue or organs; distant tumors have metastasized to distant parts of the body and unknown tumors lack enough information to determine stage.

2.2. Patients

Six thousand nine hundred and seventy-two breast cancer cases underwent surgical treatment at Songklanagarind Hospital from 1989 to 2014. After removing male, in situ, and Christian cases (n = 71 cases), our study population consisted of 6901 cases. A subset of these cases (736 patients) had estrogen receptor (ER), progesterone receptor (PR) and/or human epidermal growth factor receptor 2 (HER2) measured in the tumor tissue. We identified cases with complete ER/PR/HER2 clinical subtype and limited the dataset to the years 2010–2012 due to small sample sizes in all other years. A total of 635 (9%) patients were available for subset analyses of clinical subtypes of breast cancer.

Follow-up data was from date of pathological diagnosis to the date the patient was last observed or the date of death by the end of 2014. Patients were passively followed in the hospital registry by recording dates of doctor appointments. Death information was updated once per year through death certificates from the population registry in the Ministry of Interior. Right censoring was used for patients who were alive at end of the study or lost to follow-up. This study was approved by the Faculty of Medicine PSU Ethical Clearance Committee (REC: 57-273-18-1).

2.3. Immunohistochemical staining

Breast tumors were stained for estrogen (ER) and progesterone (PR) receptors in the Pathology Department at Songklanagarind Hospital between 2010 and 2012. Formalin fixed paraffin embedded sections were cut at 3 μm thickness and placed on slides coated with 3-Aminopropyltriethoxysilane (APES). The tissue sections were incubated in a hot air oven at 60 °C for 15 min and then run in an autostainer (Bond Max, Leica). The dilutions of ER (clone SP1, Neomarker, USA), PgT (clone 16, Novocastra, Australia) and HER2 (polyclonal antibody A0485, DAKO, Denmark) were 1:200, 1:300, and 1:1000, respectively. DAB (3,3’-Diaminobenzidine) was used for visualization and hematoxylin was used as counter stain. Samples with no cells with the receptor were classified as receptor negative.

Status for ER and PR were defined as positive in the presence of tumor nuclei staining. Therefore, ER and PR positivity included low positive (1–10% tumor nuclei staining) and positive (> 10%) staining. HER2 positivity was defined as membrane staining in > 10% of invasive tumor cells. Molecular subtypes were determined by presence or absence of staining of ER, PR, and HER2 for each patient. Subtypes were grouped into 4 categories: Luminal A: ER/PR + HER2-; Luminal B: ER/PR + HER2++; triple negative: ER/PR/HER2-; and HER2-overexpressed: ER-PR- HER2+.

2.4. Statistical analysis

The first analysis considered the total population diagnosed from 1989 to 2014 (n = 6901). Univariate analysis, including Kruskal-Wallis, chi-square and Fisher’s exact tests were used to test for differences in age, stage and survival time by religion. Kaplan-Meier curves were used to visualize probability of overall survival after diagnosis by religious status, and by age and stage in the total population and separately by religion. Age at diagnosis was grouped into below 40, 40–50 years and 50 years and above to determine differences in survival in premenopausal, menopausal and postmenopausal stage [14–16]. Log-rank tests were used to test for differences in survival distributions.

Cox proportional hazards models were used to test the association between religious status and overall survival time in univariate and in multivariable models adjusting for age and stage in a stepwise fashion. Due to violations of the proportional hazards assumption, time-dependen-effects models were used to adjust for different baseline hazards by religion before and after 5 years of overall survival time. Models were recognized for best fit using the Aïkake information criterion (AIC).

The second analysis repeated these methods in the subset of population with clinical subtype information (n = 635) diagnosed from 2010 to 2012 to assess the role of clinical subtype by religion in breast cancer survival. Due to the small sample size of patients with clinical subtype information available, a comparative analysis was done between patients with and without clinical subtype to assess utility of clinical subtype and determine potential biases.

3. Results

3.1. Breast cancer incidence by religion for total population (n = 6901)

Of the 6901 surgically treated female breast cancer cases from 1989 to 2014 at Songklanagarind Hospital, 5919 patients (86%) religiously identified as Buddhist while 982 cases (14%) identified as Muslim (Table 1). The mean age at diagnosis was 50.5 years (standard deviation (SD): 11.5) with patients ranging in age from 18 to 94 years. Age at breast cancer diagnosis was significantly lower in Muslims (mean (SD): 48.3 years (11.0)) than in Buddhists (mean 50.8 years (11.6), p-value < 0.001). The distribution of cancer stage significantly differed by religious group (p-value < 0.001) with a higher proportion of Buddhists diagnosed at earlier stages compared to Muslims.

In the total population, those who lived in Songkhla province, where Songklanagarind Hospital is located, had significantly more tumors at the localized stage compared to those living outside the province (p < 0.001; data not shown), Buddhists who lived in Songkhla province were staged significantly earlier compared to Buddhists from
outside of Songkhla (p = 0.002). However, Muslims who lived in Songkhla had similar stage distributions as Muslims who lived outside of Songkhla (p = 0.24).

Median follow-up time for overall survival (OS) was 2.8 years (Table 1). The 5-year survival rate for the total population was 61.9%. Buddhists had a significantly higher 5-year OS rate (63.6%) compared to Muslims (51.4%, p-value < 0.001). Buddhists had higher probabilities of survival at any time point compared to Muslims (log-rank p-value < 0.0001) (Fig. 1a).

Probability of OS was higher for women between the ages of 40 and 50 years, particularly 5 to 15 years after diagnosis. Women older than 50 years diverged from other age groups to exhibit increasing poorer survival over years after diagnosis (Fig. 1b; p < 0.0001). Probability of survival was significantly different by stage (p-value < 0.0001). Localized tumors had the highest survival probability compared to all other stages while distant tumors had the lowest (Fig. 1c). Regional tumors had a similar trend compared to tumors of unknown stage, but higher probabilities of survival. Survival by age and stage within each religious group exhibited similar trends as described (Fig. S2).

### 3.2. Cox proportional hazards models for total population diagnosed from 1989 to 2014

Model diagnostic plots for women diagnosed between 1989 and 2014 indicated baseline hazards to be different for women who survived up to 5 years and for those surviving longer (data not shown). The proportional hazards model indicated that the hazard ratio for religious group was not constant over time. Applying time-dependent-effects models indicated that during the first 5 years after diagnosis, Muslim

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**Table 1**

Patient characteristics for total population diagnosed from 1989 to 2014.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 6901)</th>
<th>Buddhist (n = 5919)</th>
<th>Muslim (n = 982)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (sd), range</td>
<td>N (%) among Buddha</td>
<td>Mean (sd), range</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40 years</td>
<td>1343</td>
<td>50.5 (11.6) 18–94</td>
<td>1112 (18.8%)</td>
<td>231 (23.5%)</td>
</tr>
<tr>
<td>40–50 years</td>
<td>2420</td>
<td>50.8 (11.6) 22–94</td>
<td>2037 (34.4%)</td>
<td>383 (39.0%)</td>
</tr>
<tr>
<td>&gt; 50 years</td>
<td>3138</td>
<td>48.3 (11.0) 18–91</td>
<td>2770 (46.8%)</td>
<td>468 (37.5%)</td>
</tr>
<tr>
<td>Cancer Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>937</td>
<td>13.6%</td>
<td>852 (14.4%)</td>
<td>85 (8.7%)</td>
</tr>
<tr>
<td>Regional</td>
<td>4090</td>
<td>93.9%</td>
<td>3513 (59.4%)</td>
<td>577 (58.8%)</td>
</tr>
<tr>
<td>Distant</td>
<td>1011</td>
<td>14.7%</td>
<td>831 (14.0%)</td>
<td>180 (18.3%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>863</td>
<td>12.5%</td>
<td>723 (12.2%)</td>
<td>140 (14.3%)</td>
</tr>
<tr>
<td>Median Follow-up for Survival</td>
<td></td>
<td></td>
<td>3.0 years</td>
<td>1.8 years</td>
</tr>
<tr>
<td>KM Estimated 5 year survival time*</td>
<td></td>
<td></td>
<td>61.9%</td>
<td>51.4%</td>
</tr>
</tbody>
</table>

std = standard deviation; p-values from Fisher’s exact test and Wilcoxon test, *proportion of survival at 5 years post diagnosis.

---

**Table 2**


<table>
<thead>
<tr>
<th></th>
<th>Model 1 (n = 6864)</th>
<th>Model 2 (n = 6864)</th>
<th>Model 3 (n = 6864)</th>
</tr>
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<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Religion at or below 5 years*</td>
<td>1.5 (1.4, 1.7)**</td>
<td>1.6 (1.4, 1.8)**</td>
<td>1.4 (1.2, 1.6)**</td>
</tr>
<tr>
<td>Religion greater than 5 years*</td>
<td>1.0 (0.7, 1.4)</td>
<td>1.0 (0.7, 1.4)</td>
<td>0.8 (0.5, 1.1)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-40 years</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>40-50 years</td>
<td>0.9 (0.8, 0.96)**</td>
<td>0.9 (0.8, 0.99)</td>
<td>1.1 (1.0, 1.2)</td>
</tr>
<tr>
<td>&gt; 50 years</td>
<td>1.1 (1.0, 1.2)</td>
<td>1.1 (1.0, 1.2)</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>1</td>
<td>1</td>
<td>3.1 (2.6, 3.8)**</td>
</tr>
<tr>
<td>Regional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIC</td>
<td>41571.1</td>
<td>41552.2</td>
<td>40354.9</td>
</tr>
</tbody>
</table>

**Fig. 1.** Survival distributions stratified by a) religious status; b) age group; and c) stage at diagnosis for total population diagnosed from 1989 to 2014.

Sample sizes of 6864 because 37 patients are missing death status.

* significant at α < 0.05.
** significant at α < 0.01.
*** significant at α < 0.001 in comparison with the reference.
$^*$ Reference Religion: Buddhist.
* = 2 log(likelihood) + 2 number of estimated parameters. The lower the AIC, the better the model fit.
women had an overall 1.5 times hazard of a death event compared to Buddhists (95% CI: 1.4, 1.7; Table 2); however, this difference between Buddhists and Muslims disappeared during subsequent follow-up. Adjustments for age increased the hazard of death to 1.6 times higher for Muslim Thai women compared to Buddhist Thai women (95% CI: 1.4, 1.8). The hazard of death in women older than 50 years was similar to that in women below age 40; however, women between the ages of 40-50 years had a lower hazard of death compared to younger women (HR: 0.88, 95% CI: 0.8, 0.99). Adjustment for both age and stage reduced the hazard of death for Muslim women compared to Buddhist women to 1.4 (95% CI: 1.2, 1.6). Regional, distant and unknown stage tumors had higher hazards of death compared to localized tumors, particularly distant tumors (Table 2). From AIC values, model 3 adjusting for age and stage provides the best fit for the data.

3.3. Survival by clinical subtype and religious group for subset with clinical subtype information (n = 635)

Approximately 23% of patients were diagnosed from 2010 to 2012 (n = 1586). Clinical subtype data were available for 635 (40%) of these patients (Table 2). The majority of patients with and without clinical subtype were Buddhist. Patients with clinical subtype characterization were more likely to be in the oldest age group (55.3% vs. 47.1%) in the whole population, as well as for each religious group individually (57.5% vs. 49.5% and 41.8% vs. 38.1% for Buddhists and Muslims, respectively). Greater than 80% of tumors with clinical subtype were localized or regional compared to approximately 70% for those without clinical subtype. Probability of 2-year OS was significantly higher for the total population (p < 0.001), Buddhists only (p < 0.001) and Muslims only (p < 0.001) with clinical subtype compared to those without clinical subtype. Nevertheless, the 2-year OS rate was lower for Muslims compared to Buddhists regardless of availability of clinical subtype information.

Out of the 635 patients with clinical subtype, 291 (45.8%) had tumors characterized as luminal A (45.8%), 179 (28.2%) as luminal B, 80 (12.9%) as triple negative and 85 (13.4%) as HER2-overexpressing tumors. There was no difference in distribution of clinical subtype by religion (p-value = 0.1) (Table 3). Buddhist women with tumors characterized as luminal A were significantly older at diagnosis (p = 0.003) and had a higher 2-year survival rate (92.8%) compared to Muslim women with luminal A tumors (77.2%, p-value = 0.01). Muslim women had a higher proportion of tumors characterized as triple negative (18.7%), but this was not significantly different from the proportion of triple-negative tumors characterized in Buddhist women (11.6%, p-value = 0.09). Buddhist women with tumors characterized as triple negative had a significantly higher 2-year survival rate compared to their Buddhist counterparts (Buddhist: 83.5%; Muslim: 63.7%; p-value = 0.03) (Table 4).

When considering the population with clinical subtype data, the survival rate was highest for women who had tumors characterized as luminal A and lowest for women with tumors characterized as triple negative, with luminal B and HER2-overexpressing tumors at intermediate survival probabilities (Fig. 2a). At three years, women with tumors characterized as luminal A had the highest OS rate of 91%. Women with tumors characterized as triple negative tumors had the lowest OS rate at three years (72%), while women with tumors characterized as luminal B and HER2-overexpressed had OS probabilities of 86% and 76%, respectively (Fig. 2a).

Buddhist women with tumors characterized as luminal A had the highest probabilities of OS at three years followed by women with tumors characterized as luminal B. Women with tumors characterized as triple negative and HER2-overexpressing experienced the lowest OS probabilities. At three years, the rate of OS for women with tumors characterized as luminal A, luminal B, triple negative and HER2-overexpressing were 92%, 88%, 76% and 76%, respectively (Fig. 2b). Muslim women with tumors characterized as HER2-overexpressing and luminal A had the highest rate of survival at 3 years, followed by Muslim women with tumors characterized as luminal B and triple negative (79%, 79%, 77%, and 55%, respectively; Fig. 2c).

3.4. Cox proportional hazards models for subset with clinical subtype information (n = 635)

Due to the fact that patients with clinical subtypes survived a maximum of 4.2 years, models assessing clinical subtype only include the first time varying coefficient for religion. In this patient subset, the hazard of death was 2.6 times higher in Muslim Thai women compared to Buddhist Thai women when adjusting for age and stage (95% CI: 1.6, 4.4) (Table 5). This ratio decreased to 2.4 (95% CI: 1.4, 4.0) when including triple negative status. Patients with triple negative tumors had a 3.2 times higher hazard of death compared to patients without triple negative tumors (95% CI: 1.9, 5.7) (Model 4, Table 5). Model 5 adjusted for age, stage and clinical subtype and the lower AIC value of 91.8 and provided a hazard of death 2.3 times higher in Muslim Thai women compared to their Buddhist counterparts. Patients with triple negative tumors had a hazard of death four times higher than those with luminal

Table 3

<table>
<thead>
<tr>
<th></th>
<th>With Clinical Subtype</th>
<th>No Clinical Subtype</th>
<th>Compare by Subtype Status (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients (%)</td>
<td>No. of Patients (%)</td>
<td>p^All</td>
</tr>
<tr>
<td></td>
<td>All (n = 635)</td>
<td>Buddhist (n = 544)</td>
<td>Buddhist (n = 91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p^Religion</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40 years</td>
<td>79 (12.4)</td>
<td>62 (11.4)</td>
<td>17 (18.7)</td>
</tr>
<tr>
<td>40-50 years</td>
<td>205 (32.3)</td>
<td>169 (31.3)</td>
<td>36 (39.6)</td>
</tr>
<tr>
<td>&gt; 50 years</td>
<td>351 (55.3)</td>
<td>313 (57.5)</td>
<td>38 (41.8)</td>
</tr>
<tr>
<td>Cancer Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>135 (21.3)</td>
<td>123 (22.6)</td>
<td>12 (13.2)</td>
</tr>
<tr>
<td>Regional</td>
<td>399 (62.8)</td>
<td>339 (62.3)</td>
<td>60 (65.9)</td>
</tr>
<tr>
<td>Distant</td>
<td>46 (7.2)</td>
<td>38 (7.0)</td>
<td>8 (8.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>55 (8.7)</td>
<td>44 (8.1)</td>
<td>11 (12.1)</td>
</tr>
<tr>
<td>Median Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>for Survival</td>
<td>2.3 years</td>
<td>2.4 years</td>
<td>2.0 years</td>
</tr>
<tr>
<td>KM Estimated 2 year survival time*</td>
<td>87.5%</td>
<td>89.1%</td>
<td>77.3%</td>
</tr>
</tbody>
</table>

p-values from Fisher’s exact test and Wilcoxon test.
* Proportion of survival at 2 years post diagnosis.
A tumors (95% CI: 2.4, 6.9), whereas patients with HER2-overexpressing tumors had twice the hazard of death as those with luminal A tumors (95% CI: 1.2, 3.9). Patients with luminal B tumors had similar hazards to those with luminal A tumors.

4. Discussion

These analyses highlight key differences in breast cancer epidemiology between religious groups in southern Thailand. Muslim Thai women with breast cancer are diagnosed at a younger age, later stages and have shorter overall survival times compared to Buddhist Thai women with breast cancer. Our results are similar to findings in the recent literature of women in Southeast Asia. For example, a study that characterized ethnic differences in Singaporean and Malaysian women with breast cancer found that Malays, consisting mostly of Muslim women, had the youngest age at diagnosis, largest tumor size at presentation, and were most likely to have tumors characterized as aggressive with lymph node involvement, and poorer survival when compared to Chinese and Indian women with breast cancer who were mostly Buddhist and Hindu, respectively [17]. A population-based study in southern Thailand found that Muslim women diagnosed with breast cancer experienced a poorer prognosis compared to Buddhist women [6]. The observation that a higher proportion of Muslim Thai women were diagnosed at later stages has important implications for the utilization of healthcare and early detection practices in southern Thailand. Currently, the Thai Ministry of Public Health promotes breast self-examinations (BSE) with clinical breast examinations (CBE) for follow-up as necessary [18]. However, in 2007 only 30% of Muslim women reported utilizing BSE in the prior year, compared to 41% of Buddhist women [19]. Some factors, such as low awareness of screening methods, fatalistic beliefs, low perceived need, and poor knowledge of breast cancer have been documented in the southern Muslim population as potential barriers to prevention/early detection strategies and should be further explored as factors that might influence poor survival [20,21].

To date, this is the first study assessing clinical subtypes in southern Thailand by religious status. Almost half of all patients with clinical subtypes had tumors characterized as luminal A subtype. Patients with luminal A tumors have a low risk of local and regional recurrences or distant metastasis, and tend to have the best prognosis and high overall survival [22,23]. The observation that Muslim women have tumors less likely to be characterized as luminal A may explain their less favorable prognosis compared to Buddhist women with breast cancer although the effect of religion persists even with adjustment for clinical type, so

Table 4
Patient Characteristics for Those with Clinical Subtype Information available from 2010 to 2012 (n = 635).

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Luminal A (n = 291)</th>
<th>Luminal B (n = 179)</th>
<th>Triple Negative (n = 80)</th>
<th>HER2-overexpressing (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients (%)</td>
<td>No. of Patients (%)</td>
<td>No. of Patients (%)</td>
<td>No. of Patients (%)</td>
<td>No. of Patients (%)</td>
</tr>
<tr>
<td></td>
<td>Buddhist</td>
<td>Muslim</td>
<td>p</td>
<td>Buddhist</td>
</tr>
<tr>
<td>No. (%)</td>
<td>257 (47.2)</td>
<td>34 (37.4)</td>
<td>154 (28.3)</td>
<td>25 (27.5)</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>&lt; 40 years</td>
<td>25 (9.7)</td>
<td>7 (20.6)</td>
<td>0.03</td>
<td>16 (10.4)</td>
</tr>
<tr>
<td>40-50 years</td>
<td>82 (31.9)</td>
<td>17 (50.0)</td>
<td>0.003</td>
<td>56 (36.4)</td>
</tr>
<tr>
<td>&gt; 50 years</td>
<td>150 (58.4)</td>
<td>10 (29.4)</td>
<td>0.05</td>
<td>82 (53.2)</td>
</tr>
<tr>
<td>Cancer Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>62 (24.1)</td>
<td>4 (11.8)</td>
<td>0.06</td>
<td>39 (25.3)</td>
</tr>
<tr>
<td>Regional</td>
<td>164 (63.8)</td>
<td>21 (61.8)</td>
<td>0.01</td>
<td>87 (56.5)</td>
</tr>
<tr>
<td>Distant</td>
<td>15 (5.8)</td>
<td>5 (14.7)</td>
<td>0.01</td>
<td>15 (9.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>16 (6.2)</td>
<td>4 (11.8)</td>
<td>0.01</td>
<td>13 (8.4)</td>
</tr>
<tr>
<td>KM Estimated 2 year survival time</td>
<td>2.4 years</td>
<td>1.8 years</td>
<td>0.03</td>
<td>2.3 years</td>
</tr>
</tbody>
</table>

p-values from Fisher’s exact test and Wilcoxon test.

Proportions add up to 100% by row for totals given religion to provide distribution and by column for all other variables.

* Proportion of survival at 2 years post diagnosis.

# p-value for comparison of survival by religion.

Fig. 2. Survival by subtype for a) all patients with clinical subtype information from 2010 to 2012 (n = 635); b) Buddhist women (n = 544); c) Muslim women (n = 91).
this is unlikely. We also observe a higher proportion of triple negative tumors characterized in Muslim Thai women. Although this difference was not statistically significant, this finding suggests an explanation for shorter survival times in Muslim Thais with breast cancer. This finding is consistent with a study that found that Malay women with breast cancer, who were mostly Muslim, had double the risk of being diagnosed with a tumor characterized as triple negative compared to tumors diagnosed in other races [24]. However, another study in Singapore found that ethnic or religious background is not associated with a diagnosis of a tumor characterized as triple negative tumors although Malays, who tend to be Muslim, generally had worse prognosis compared to other ethnic groups [25]. These findings suggest that tumor biology likely plays a role in the observed differences in survival, although the exact contribution will require more extensive studies that include epidemiologic characterization of women with breast cancer in southern Thailand.

There were significant differences in the distribution of demographic characteristics of breast cancer patients with and without clinical subtype information available in our study population. Patients without clinical subtype information available were more likely to be Muslim, younger, diagnosed at later stages, and have shorter follow-up times and lower OS rates. There are several possible reasons for this. First, there was a higher proportion of Muslim women without clinical subtype. From 2010–2012, 71% of cases were in women from outside of Songkhla province. Of these, 17% were Muslim, compared with only 7.5% of Muslims from inside Songkhla province. A majority (67%) of the Muslim patients who came from outside Songkhla resided in provinces in the south that are predominantly Muslim. We have shown here that the Muslim Thai breast cancer patients with clinical sub-type data tended to be younger, were diagnosed at later stages and had poorer prognosis, which corresponds to characteristics of patients without clinical subtype information. Second, Songklanagarind Hospital is a referral hospital and received cases from provinces throughout the southern and central regions. When women with breast cancer are referred for treatment in Songkhla province, tissue must be obtained from the original hospital where the cancer was diagnosed for pathologic characterization. If tissue and stage information is not available or delayed, treatment is delayed. With longer delays, tumors are re-biopsied and re-staged to update treatment and are, therefore, more likely to be diagnosed at more advanced stages. This can be seen from the distribution of stage by presence or absence of clinical subtype. Patients without clinical subtype had higher proportions of tumors at later stages compared to those with clinical subtype. Without information on clinical subtype, clinicians are less informed on treatment and may pursue suboptimal options. In addition, lost to follow-up can limit treatment adherence. All of these factors can lead to poorer survival. This is seen in patients with no clinical subtype information who had worse survival compared to those with subtype information.

Because the data in this study are from a hospital registry, location is an important consideration when assessing stage distribution. Overall, women living in the same province as the hospital were diagnosed at earlier stages than women living outside the province. However, this did not persist by religion. While Buddhist women living in Songkhla were diagnosed earlier compared to Buddhist women living outside Songkhla, Muslim women both in and outside of Songkhla had similar stage distributions. The reasons for this are unclear, however, 85% of the Muslims in this study resided outside of Songkhla, raising the possibility that there was an insufficient number of Muslim women residing in Songkhla to detect a difference in stage distribution.

There are several limitations in this study. Data on differences in classic risk factors for breast cancer, such as body mass index and breastfeeding, were not available by religion. These factors likely play a role in subtype of tumor and should be considered in future studies [24,25]. Information on treatment regimen, recurrence and disease-specific survival was not available for analysis. Treatment choices can have significant impacts on overall survival, particularly with consideration to patient age, as the presence of comorbidities is associated both with increase in age and response to treatment [26,27]. It is also possible that treatment choices and compliance differ by religion. Muslims present with higher proportions of late-stage tumors, which may be due to poorer compliance arising from cultural factors [28–31]. Future studies should investigate the role of treatment choices and compliance on differences in survival rate between Buddhist and Muslim Thai women. Survival times assessed here were overall survival
times. As patients age, they are at higher risk for comorbidities associated with aging. To isolate the effects of age on survival in breast cancer patients, further studies should utilize disease-specific survival information. There are also several strengths to this study. These include data collected as a part of a long-standing hospital-based cancer registry, with characterization of overall survival information for the women in this study. Additionally, the existence of universal health care in Thailand (established in 2002) with village-level community health volunteers that facilitate health care provides access that allows for high capture of breast cancer cases.

Our analyses indicate that Muslim Thai women are diagnosed with breast cancer at earlier ages compared to Buddhist women diagnosed with breast cancer; there are significant differences in survival based on religion of women diagnosed with breast cancer in southern Thailand; and there is evidence that differences in the distribution of breast cancer subtypes may partially explain these differences between breast cancers diagnosed in Muslim and Buddhist Thai women.

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Final approval of the version to be submitted
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Conflict of interest statement
None declared.

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Appendix A. Supplementary data
Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.canep.2018.02.007.

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