



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 $^{\circ}\text{C}$ for 15 min and then run in an autostainer (Bond Max, Leica). The dilutions of ER (clone SP1, Neomarker, USA), PgR (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 multivariate models adjusting for age and stage in a stepwise fashion. Due to violations of the proportional hazards assumption, time-dependent-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 Akaike 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

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