Breast cancer risk factors and outcome: A global perspective

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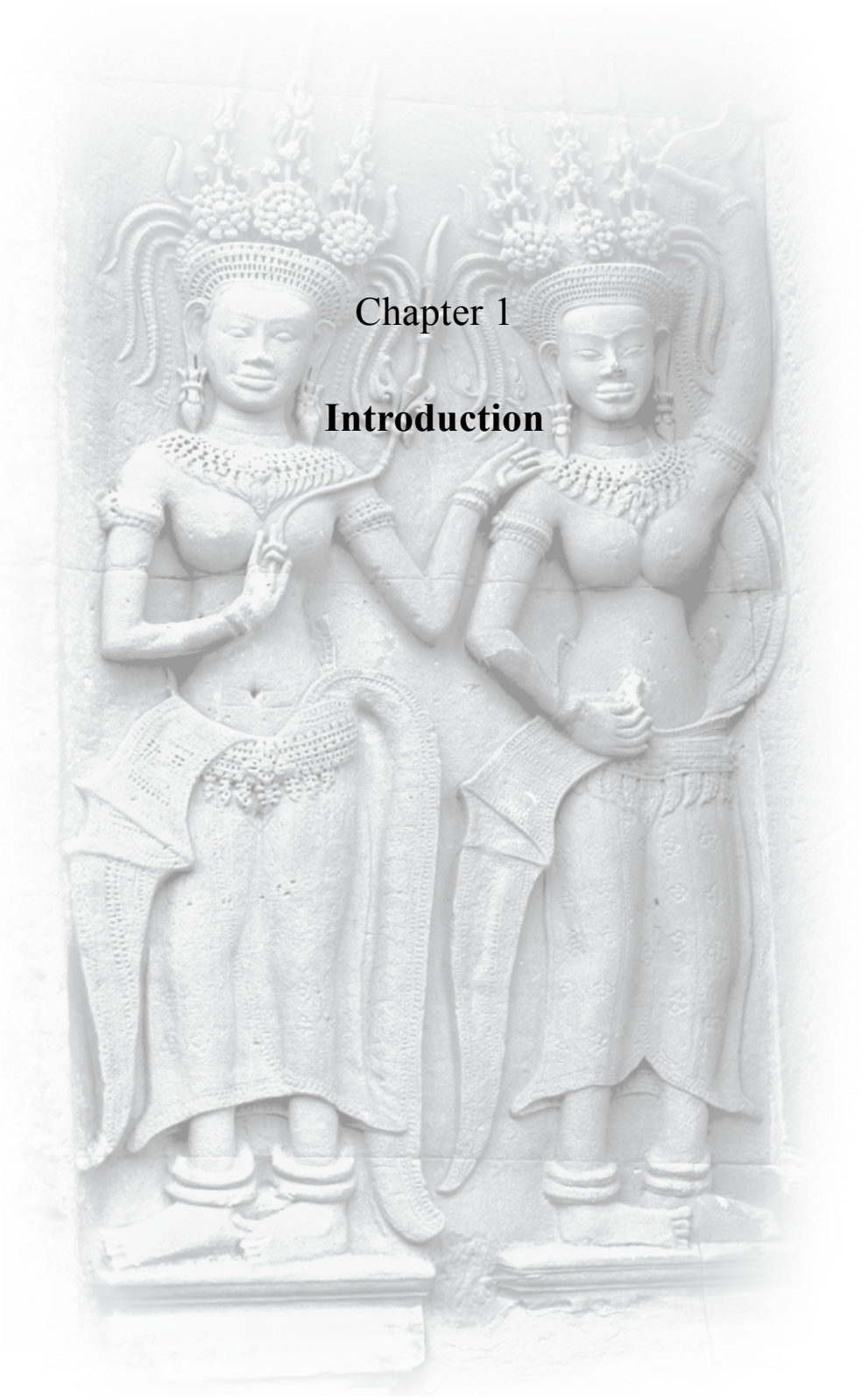

Chapter 1

Introduction

Background

Breast cancer comprises 23% of all female cancers making it by far the most common female malignancy.[1] In contrast to the West, where breast cancer incidence rates have stabilized or even decreased, the incidence of breast cancer has escalated in most Asian countries over the past two decades.[2] As a result, the burden of breast cancer is increasing in Asia.

However, little is known regarding the presentation, management and outcome of breast cancer among multi-ethnic Asian women as there seems to be a paucity of high-quality breast cancer data with sufficiently long follow-up in Asian settings. Moreover, extending breast cancer research onto Asia is very important because there are numerous indications that western based knowledge on breast cancer etiology,[3] diagnosis,[4] prognosis[5] and treatment[6] cannot simply be transferred to Asian populations. Asian ethnicities, genetic backgrounds, lifestyles, diets, cultures, health beliefs, and even life expectancies are substantially different from those of western women, and each of these may play a distinct role in breast cancer incidence, prognosis and treatment. Health care systems are also different in Asia whereby resources are limited, thus requiring adapted approaches towards preventive strategies and treatment of breast cancer.[7] It is such considerations that are currently widely recognized to constitute an important knowledge gap in breast cancer research, and most of the work presented in this thesis is the first result of an initiative to close it.

Outline of the thesis

Asia

The Singapore-Malaysia Breast Cancer Working Group (SMBCWG) was established in November, 2009 as a joined effort between a group of epidemiologists, breast surgeons, and oncologist from two tertiary hospitals in Malaysia and Singapore.[8] The aim of this international, multidisciplinary collaboration is to improve the understanding of breast cancer in Asian women by studying its clinical characteristics, treatment patterns, prognostic factors and outcome. Under this initiative, the breast cancer registries of two academic hospitals (National University Hospital, Singapore and University Malaya Medical Centre, Malaysia) were merged to form an international hospital based breast cancer registry.

The first part of this thesis (**Chapter 2** to **Chapter 6**) focuses on research questions that we have answered pertaining to breast cancer in Asian women, using data from this registry. In **Chapter 2**, we have described the setting-up of the Singapore-Malaysia Hospital-based Breast Cancer Registry and also the clinical characteristics, treatment patterns, and outcome of breast cancer among this cohort of 4058 South-East Asian women.

Observational studies from Caucasian populations have suggested that removal of the primary breast tumor may improve survival in patients with metastatic breast cancer at diagnosis.[9] This finding is of particular importance in Asia, where 10-25% of patients present with stage IV disease.[10-12] However, the profile of metastatic breast cancer in Asian patients is often more advanced than in the West,[13] necessitating us to confirm the potential benefit

of surgery on survival of these women. In **Chapter 3**, we investigated the impact of breast surgery on survival of women presenting with stage IV breast cancer in an Asian setting.

In clinical (breast) cancer research, there is substantial interest in new biomarkers which may serve as prognostic or predictive indicators. Many recently published studies have investigated the prognostic value of such new biomarkers in breast cancer using data from cancer registries which often span long periods whereby the biomarkers may not have been assessed routinely in the initial phase.[14-17] In an attempt to highlight the limitations associated with performing naive complete case analysis on registry based data when studying a newly introduced biomarker (such as HER2 status in early 2000s), we have in **Chapter 4** studied the differences between patients who were tested for HER2 status against those who were not tested. We also determined the association between testing for HER status and prognoses of patients with breast cancer as deemed by physicians at time of diagnosis.

Adjuvant! Online is a free, web-based prognostication tool which was developed based on the Surveillance, Epidemiology and End Results (SEER) database from United States, and treatment efficacy data from meta-analyses.[18] It predicts the benefit of adjuvant therapy for breast cancer by estimating the ten year survival probability of an individual patient given her age, co-morbidity, tumor size, number of involved nodes, tumor grade and estrogen receptor status. As it is used by a substantial proportion of clinicians in Asia for patient counseling and decision making, we undertook a study to validate this program in a cohort of Asian women. This study is described in **Chapter 5** of this thesis.

Studies conducted in multiethnic populations in the Western settings have highlighted that the spectrum of breast cancer may vary across ethnic groups, and further implicated ethnicity as a predictor of survival following breast cancer.[19] As Malaysia and Singapore are multiethnic South-East Asian nations comprising 3 major ethnic groups i.e. Malays, Chinese and Indians,[20,21] we undertook a study to evaluate the impact of ethnicity on survival after breast cancer in multiethnic Asian women. This study is described in **Chapter 6**.

Europe

In the past few decades, lifestyle related behaviors have been investigated extensively both as etiologic[22] as well as prognostic factors[19] in relation to breast cancer. It has been estimated that 30% of all cancer occurrence is related to diet.[23] This may potentially provide an avenue for cancer prevention by adjustments of dietary intake. The fact that currently established risk factors in conjunction only explain some 10-15% of breast cancer incidence further highlights the importance of studying the impact of such modifiable factors in relation to breast cancer.

In the last thirty years, a multitude of epidemiological studies have embarked on investigating the association between coffee and tea consumption and the risk of breast cancer. The sparked interest in studying these associations is largely attributed to the public health implication of the potential findings. The fact that coffee and tea are the most popular and widely consumed beverages worldwide renders them as relevant daily dietary exposures. Furthermore, breast cancer is by far the commonest cancer in women. The second part of this thesis which had been conducted in Europe focuses on the main research question of

whether coffee and tea intake are associated with the risk of breast cancer. In **Chapter 7**, we investigated the association between coffee and tea intake and risk of breast cancer in a large cohort of Dutch women. **Chapter 8** is an extension of this study to include a larger study population spanning from the south to north of Europe. This allows us to study some specific subgroups such as premenopausal breast cancers, as well as studying different types of coffee i.e. caffeinated and decaffeinated coffee. In **Chapter 9**, we have summarized the evidence from previous research on the association between coffee and tea intake and breast cancer, followed by a discussion on the limitations associated with this type of epidemiological studies.

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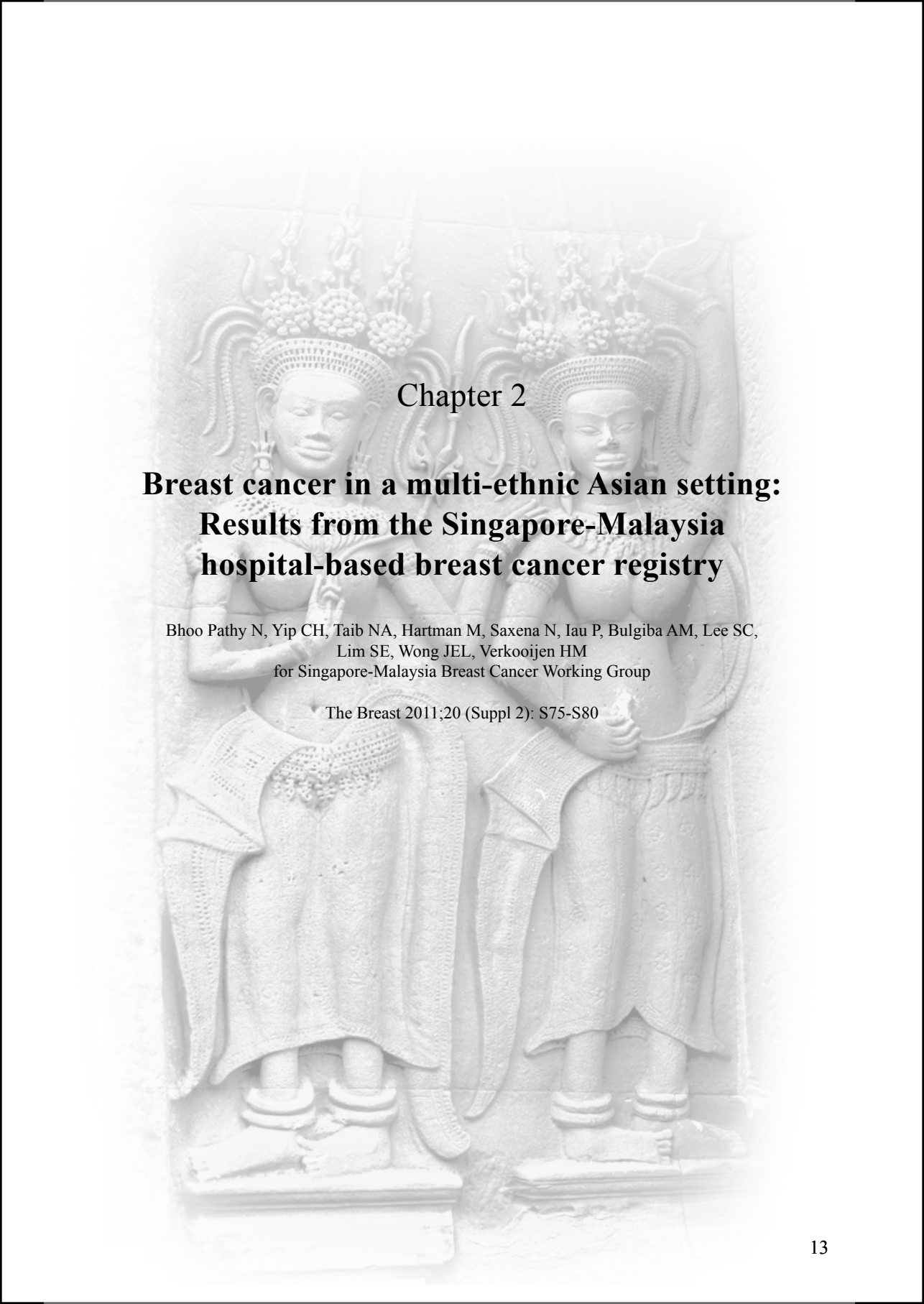

Chapter 2

Breast cancer in a multi-ethnic Asian setting: Results from the Singapore-Malaysia hospital-based breast cancer registry

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for Singapore-Malaysia Breast Cancer Working Group

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Abstract

Two hospital-based breast cancer databases (University Malaya Medical Center, Malaysia [n=1513] and National University Hospital, Singapore [n=2545]) were merged into a regional registry of breast cancer patients diagnosed between 1990 and 2007. A review of the data found that 51% of patients were diagnosed before the age of 50 years. Seventy-two percent of the women were Chinese followed by Malays (16%), Indians (8%), and other races (4%). Median tumor size at presentation was 26 mm and about 25% of patients presented with TNM stage III or IV disease. Most tumors were of ductal histology (87%). Fifty-seven percent of tumors were estrogen receptor positive and 40% were poorly differentiated. Of those patients who had surgery, 70% had mastectomy while 30% had breast conserving surgery. Overall, chemotherapy was administered to 56% of patients and hormonal treatment to 60%. Five-year overall survival was 82.5% in patients with TNM stage 0 to stage II cancer, and 30.2% in those with later stages.

Introduction

In contrast to the West, where breast cancer incidence rates have stabilized or even decreased,[1-3] the incidence of breast cancer has escalated in most Asian countries over the past two decades.[4-7] Changes in reproductive factors, environmental exposures, and lifestyle such as dietary intake and physical activity have all been proposed to explain this trend. With the westernization of Asian countries, one can expect this trend to continue and it is not unthinkable that in the relatively near future, the majority of breast cancer patients will be of Asian ethnicity. Therefore, it is crucial that we improve our understanding of breast cancer among Asian women.

An important step in the above process warrants monitoring of the nature of disease presentation, tumor characteristics, management, and survival of Asian women with breast cancer. Since longitudinal studies of breast cancer are scarce in this part of the world, we have set up the Singapore-Malaysia Breast Cancer Working Group (SMBCWG), which is an international, multidisciplinary collaboration between epidemiologists, breast surgeons and oncologists of the National University Hospital, Singapore (NUH), National University of Singapore (NUS), collectively known as National University Health Systems or NUHS, University Malaya Medical Center (UMMC) and University of Malaya (UM), Kuala Lumpur, Malaysia. Under this initiative, the breast cancer registries of two academic hospitals (NUHS, UMMC) were merged, to allow a multitude of clinical studies on breast cancer and facilitate implementation of research projects, including clinical trials and detailed molecular studies. The mission of the SMBCWG is to optimize the management, survival, functional status, and long-term quality of life of Asian breast cancer patients.

In the current study, we describe the setting-up of the Singapore-Malaysia Breast Cancer Registry (SMBCR) as well as the clinical and pathological tumor characteristics, treatment patterns, and outcomes of breast cancer among our cohort of Southeast Asian women.

Methods

Data for this study were retrieved from the hospital-based breast cancer registries of two teaching hospitals in Singapore and Malaysia; the NUHS Breast Cancer Registry and the UMMC Breast Cancer Registry.

The NUHS Breast Cancer Registry currently consists of 2545 consecutive patients who were newly diagnosed with breast cancer between 1990 and 2007. Details of this registry have been described elsewhere.[8] Data was collected retrospectively for patients diagnosed between 1990 and 1995 and prospectively for patients diagnosed after 1995. The database includes data on patient's basic demography, tumor characteristics and treatment profile, follow-up and vital status. This registry has been approved by the Institutional Ethics Review Board.

The breast cancer registry in UMMC was started in 1993 and currently encompasses 1513 patients, newly diagnosed with breast cancer between 1993 and 2002. Data on basic demography, clinical and pathological tumor profile, as well as treatment details was collected prospectively for each patient, using a written form (proforma) based on the input from patient interview and medical records, as well as radiology and pathology reports. The details from the proforma were

gradually transferred into an electronic database. Ten percent of patients from the database were randomly selected and had their data verified with their proforma for quality audit purposes. Errors were found in 8% of the sub-sample of 148 patients. This registry has received approval from the Ethical Review Committee of UMMC.

In both centers, patients were monitored through follow-up in the specialist outpatient clinics. Data on mortality were obtained from the hospitals' medical records, as well as active follow-up through the patients' next-of-kin. In addition, we regularly updated vital status through direct linkage with the respective National Registration Department in both countries. Follow-up time was calculated for all patients, starting at date of diagnosis with breast cancer until death (all causes) or date of last contact, whichever came earlier.

Variables

In both registries, we had data on basic demography of patients such as age at diagnosis, ethnicity and nationality. Other variables such as occupation, age at menarche, age at first delivery, parity, breastfeeding, use of oral contraceptive, menopausal status, use of hormone replacement therapy (HRT), and family history of breast cancer were largely unavailable. Information on patients' comorbidities was available from the Malaysian registry but not from the Singaporean registry.

Data on clinical tumor characteristics included tumor size, laterality of tumor (right, left, bilateral), lymph node involvement (clinical staging: N0-N3), presence of distant metastasis (yes/no), and metastatic site. Pathological tumor characteristics included number of lymph nodes resected, number of lymph nodes involved, tumor histology, tumor grade (Scarff-Richardson-Bloom classification; grade 1 (lowest) – well-differentiated cells, grade 2 – moderately-differentiated cells, grade 3 (highest) – poorly-differentiated cells) as well as estrogen receptor (ER) status, and progesterone (PR) receptor status. Hormonal receptor status (ER and PR) was determined via immunohistochemical staining and deemed positive when >10% cells stained positive. In both registries, analysis of ER and PR hormone receptor status was not routinely assessed in the early 1990s. HER2/neu status was only available in patients diagnosed since mid 2000. All breast cancers diagnosed in 2002 and before were staged according to the 5th edition of TNM classification by American Joint Committee on Cancer (AJCC), while cancers diagnosed after 2002 were staged according to the 6th edition of AJCC.

Treatment data consisted of type of initial treatment (surgery, chemotherapy, radiotherapy, hormone therapy), surgery (yes/no), type of surgery (mastectomy, breast conserving surgery [BCS]), chemotherapy (yes/no), chemotherapy regime, radiotherapy (yes/no), hormone therapy (yes/no), and type of hormone therapy. Both the databases were synchronized into a standard template and subsequently merged. Quality checks were carried out where results were cross-checked between the individual registries and the SMBCR to ensure uniformity. In July 2010, the SMBCR consisted of 4058 patients who were newly diagnosed with primary breast cancer between 1990 and 2007. Prospective registration is currently ongoing.

Overall, histological characteristics were missing in 2% (lymph node staging) to 41% (PR status) of the cases, whereas treatment data was missing in 3%–5% of patients. The vital status of 0.1% of patients in Singapore and 8.6% in Malaysia could not be determined. In both registries,

causes of death, as well as data on local or systemic recurrences were not available to a large extent.

Statistical Analysis

All categorical variables were described by proportions and compared using the Chi square test. Continuous variables were expressed in medians and compared using the Kruskal-Wallis test. Kaplan-Meier analyses were conducted to estimate overall survival (OS) and compared by log-rank test. Two-tailed P value < 0.05 was considered as statistically significant. All statistical analyses were performed using SPSS for Windows version 16.0 (SPSS Inc., Chicago, Illinois, USA).

Results

In this cohort of Southeast Asian women with breast cancer, the age at diagnosis ranged between 21 and 94 years. Approximately half of the patients were diagnosed before the age of 50 years (median = 49 years). Fifteen percent of patients were aged younger than 40 years at presentation. The majority of patients were of Chinese ethnicity (72%), followed by Malays (16%), Indians (8%), and other races (4%).

Median tumor size at presentation was 26 mm and there was a decrease with calendar time from 40 mm in patients diagnosed from 1990–1994 to 20 mm in those diagnosed in 2005 onwards (P < 0.001, Figure 1). A quarter of the patients presented with advanced stage disease, including 15% with stage III and 10% with stage IV disease. Only 7% of patients presented with ductal carcinoma in situ (DCIS) and 21% with stage I disease. Forty-three percent of patients presented with stage II. While the proportion of patients presenting with early stage disease (DCIS and

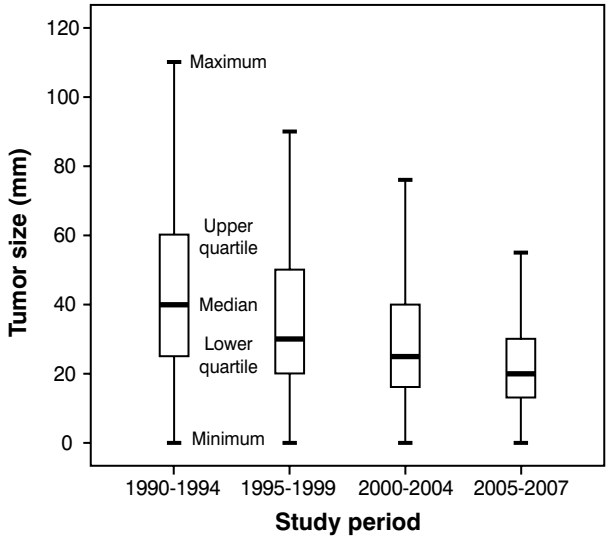

Figure 1. *Breast cancer tumor size at diagnosis for the four study periods*

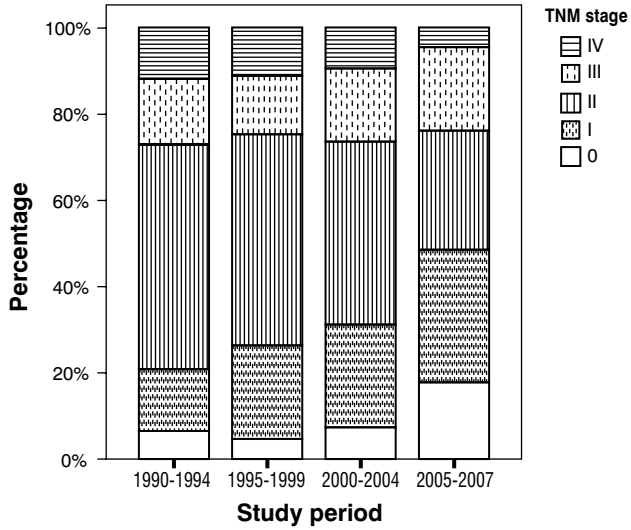

Figure 2. *Percentage of patients with different TNM stage (0-IV) at presentation for the four study periods*

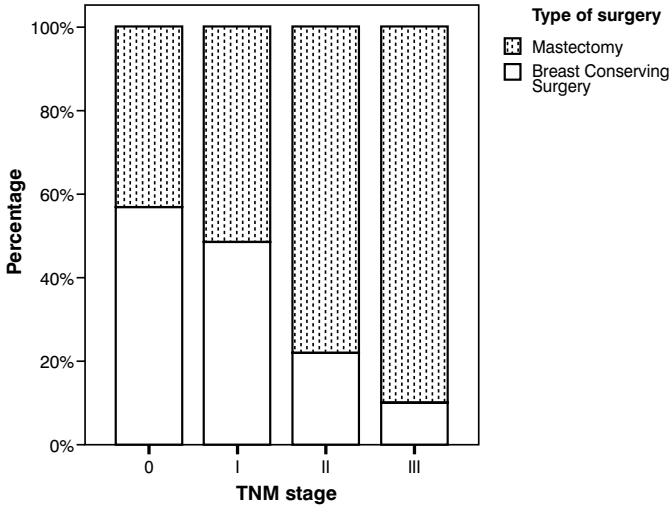

Figure 3. *Type of surgery (mastectomy or breast conserving surgery) by TNM stage (0-III) in women with non-metastatic breast cancer.*

stage I) increased over the years ($P < 0.001$), there was no decrease in the proportion of patients presenting with advanced stages (stage III and IV) over time ($P = 0.56$). Figure 2 shows that even though the proportion of stage IV had decreased with time, the proportion of patients with stage III breast cancer seems to have increased.

Forty-three percent of patients had lymph node positive disease, and 40% of tumors were poorly differentiated (Table 1). A great majority of tumors were of invasive ductal histology

Table 1. *Distribution of Histological Tumor Characteristics in 4058 Patients with Breast Cancer*

Histological Tumor Characteristic	n (%)
Pathological lymph node staging	
N0	2256 (57)
N1	1041 (26)
N2	425 (11)
N3	236 (6)
Unknown	100
ER status	
Positive	1706 (57)
Negative	1301 (43)
Unknown	1051
PR status	
Positive	1315 (54)
Negative	1120 (46)
Unknown	1623
ER/PR combination	
ER+/PR+	1071 (44)
ER+/PR-	292 (12)
ER-/PR+	244 (10)
ER-/PR-	828 (34)
Unknown	1623
Histologic grade	
Grade 1	383 (13)
Grade 2	1345 (47)
Grade 3	1153 (40)
Unknown	1177
Lymphovascular invasion	
Present	2102 (52)
Absent / Unknown	1956 (48)

(87%) while invasive lobular cancers made up 4%, and another 9% of tumors were of other histological types. Overall, 43% of patients had ER negative and 46% had PR negative cancer. Fifty-two percent of patients had tumors exhibiting lympho-vascular invasion.

Overall, 97% of patients were treated either with loco-regional, systemic or both types of treatment while 3% of patients did not receive any therapy. Patients who did not receive any treatment were more likely to be older (median age = 62 years), and have larger tumor size at diagnosis (median = 45 mm). A vast majority of patients (98%) with non-metastatic breast cancer (stage 0 to stage III) received surgical intervention (Table 2). Seventy percent of them received mastectomy while another 30% received breast conserving surgery (BCS) (Figure 3). Eighty-six percent of patients treated with BCS received radiotherapy post surgery.

Table 2. *Treatment Distribution and Patterns in 4058 Southeast Asian Women with Breast Cancer*

Treatment	n (%)
Received surgery[a]	
Yes	3355 (98)
No	67 (2)
Unknown	77
Type of surgery[a,b]	
Mastectomy	2360 (70)
Breast conservation surgery	995 (30)
Received radiotherapy[a]	
Overall	
Yes	1858 (55)
No	1508 (45)
Unknown	133
By surgical status	
Yes, after breast conserving surgery	849 (86)
Yes, after mastectomy	1000 (43)
Yes, with no surgery/ unknown surgical status	9 (1)
Received chemotherapy	
Overall	
Yes	2167 (56)
No	1719 (44)
Unknown	172
ER negative and lymph node positive disease	
Yes	488 (85)
No	87 (15)
Unknown	6
Received hormone therapy	
Overall	
Yes	2319 (60)
No	1573 (40)
Unknown	166 (4)
By ER status	
ER positive	1436 (85)
ER negative	447 (35)
ER status unknown	436 (46)

[a] Excluding patients with stage IV breast cancer (n=387)
[b] Confined to those who were subjected to surgery

Table 3. *Survival Estimates (Median Survival (months), 2-year Survival, 5-year Survival) by Stages of Breast Cancer*

	Stage 0	Stage I	Stage II	Stage III	Stage IV
Median survival, months (95% CI)	*	*	164 (*)	53 (47-59)	17 (15-19)
2-yr survival, % (95% CI)	99.5 (98.5-100.0)	98.9 (98.1-99.7)	94.0 (92.8-95.2)	77.9 (74.4-81.4)	36.3 (33.7-44.7)
5-yr survival, % (95% CI)	95.6 (91.7-99.5)	93.6 (91.4-95.8)	76.0 (73.5-78.5)	44.1 (39.2-49.0)	9.3 (5.8-12.8)

* Data unavailable

Overall, 56% of patients received chemotherapy. Most (85%) patients with ER negative and lymph node positive disease were given chemotherapy. Sixty percent of women were given hormonal therapy, where 85% of those with ER positive tumors received hormone treatment.

Of 745 patients who did not receive any form of systemic therapy (i.e. 20% of the study patients), 56% were either in stage 0 or stage I disease. Twelve percent of patients received neo-adjuvant chemotherapy. Median tumor size at diagnosis in these patients was 80 mm.

A total of 1165 deaths occurred in 16,795 person-years of observation with a 5-year overall survival of 67.6% (65.8%–69.4%). In patients with TNM stage 0 to stage II cancer, 5-year overall survival was 82.5% (95% CI: 80.7%–84.3%), and 30.2% (95% CI: 26.7%–33.7%) in those with later stages. Table 3 shows the 2-year and 5-year survival of patients by stages of breast cancer.

Discussion

The results of this study indicate that the presentation of breast cancer of women in an Asian setting may indeed be different from the Caucasian/Western settings. Approximately 50% of Asian women in our study were diagnosed before the age of 50 years. This is in contrast to the Western settings where breast cancers in women aged younger than 50 years accounts for about 23% of the total breast cancer incidence.[9] Previous studies have suggested that younger age at onset may be attributed to the relatively young population in Asian countries as well as birth cohort effect[8,10] and this may well explain our findings. Breast cancer in young women is exceptionally impactful, since these women may still have young children, a wish to conceive, and may be in the mid-stage of their career life.

Compared to the West, our patients presented with larger tumors, a finding similar to a previous Asian study conducted in Hong Kong, India and Malaysia.[11] We also observed a decreasing trend in tumor size, which may be associated with increasing breast cancer awareness in the population and, to a certain extent, with the introduction of the mammographic breast screening program in Singapore since 2002. This trend was complemented with an increasing proportion of patients presenting with DCIS and stage I disease over time. Even though, in aggregate, the proportion of patients presenting with advanced stages (stage III and IV) did not

decrease, the proportion of those presenting with metastatic breast cancer had declined over time. Overall, 10% of patients had metastatic breast cancer at initial presentation as opposed to 3%–6% in the Western settings.[12]

We observed that the proportion of poorly differentiated tumors (40%) was similar to Caucasian (41%), and lower than African-American populations (57%).[13] As in the Western settings, invasive ductal carcinomas were the main histological type of breast cancer, but lobular cancers were far less common in our Asian setting (i.e. only 4% versus 12%–18% in Western settings).[13] Previous studies have suggested a positive association between postmenopausal hormone replacement therapy (HRT) and the incidence of lobular breast cancers.[14,15] Therefore, the lower use of postmenopausal HRT in Asian versus Western populations (less than 20% use of HRT versus up to 60%, respectively),[16,17] in combination with the higher proportion of premenopausal cases, could explain the lower incidence of lobular-type breast cancers. Compared to women registered in the Surveillance, Epidemiology, and End Results (SEER) database in the USA, the proportion of patients with ER+/PR+ tumors in our study was lower (63% versus 44%) whereas the proportion of those with ER-/PR- tumors was higher (21% versus 34%).[18] This may be related to the younger age of our patients since it has been previously shown that the incidence of ER+/PR+ tumors is positively associated with age.[19] In addition, lower HRT use in our postmenopausal women may also explain the above finding whereby HRT use has been associated with development of ER+/PR+ tumors.[20]

Besides describing the clinical and histological tumor characteristics of the patients, this study was conducted to shed light into the management and overall survival of patients following the diagnosis of breast cancer in an Asian setting. Compared to patients in the West, the overall mastectomy rates in our population were higher (71% versus 31%–45%),[21] whereas BCS rates for stage I patients were lower (48% versus 60%).[22] This may be due to the larger tumor size at presentation,[11] smaller breast volume in Asian patients,[23] patients' decision, and preferences of physicians. Patients eligible for BCS may opt to undergo mastectomy to feel safer and reduce the risk of loco-regional recurrence,[24-26] to avoid radiotherapy,[26] as well as for financial reasons and convenience as BCS followed by radiotherapy requires more intense follow-up and frequent commuting to the hospital.[24]

The overall proportion of patients receiving chemotherapy was 56%, which is higher than in countries like Australia (32%–49%), Canada (40%–42%), Sweden (30%–40%), United Kingdom (29%) and USA (40%).[27] A possible explanation for this is the higher proportion of ER negative tumors and more advanced disease in our patients. A majority of patient with ER positive tumors (85%) were given hormonal treatment. Prior to the era of routine hormonal receptor assessment at UMMC, the treatment policy was routine prescription of tamoxifen to patients deemed clinically eligible by the treating physicians.

The proportion of patients not treated (loco-regional, systemic or both), or receiving incomplete treatment may well be a reflection of patient choice and not a consequence of management policies, as it is not uncommon for Asian breast cancer patients to decline treatment or follow-up in order to seek alternative or traditional treatment.[11,24,28-30] Studies in Malaysia have shown that approximately 5% of patients with breast cancer attending the Kuala Lumpur Hospital

decline further treatment.[31] In an East Malaysian hospital, 55% of patients who did not adhere to treatment refused surgical intervention, followed by non-adherence to chemotherapy (29%), and non-adherence to radiotherapy (13%).[24] The rate of non-adherence in the current study is higher than the reported rate among patients with non-metastatic breast cancer in Geneva, Switzerland where 1.3% of women refused surgery.[32] However, our patients who declined treatment were also older and had bigger tumors similar to the study in Geneva.

After stratifying for stage, our patients with early breast cancer (carcinoma in situ and stage I) had similar 5-year overall survival as patients registered in the National Cancer Database in the United States (accession year 1999); stage 0 (96% versus 97%), stage I (94% versus 90%) [http://www.gundluth.org/?id=885&sis=1]. However, Asian patients with more advanced stages had worse 5-year overall survival rates than their counterparts in the United States: stage II (76% versus 85%), stage III (44% versus 55%), and stage IV (9% versus 13%). This may be due to a combination of disparities in treatment options, more severe metastatic profile at presentation in Asian women,[11] as well as lower treatment uptake or adherence related to the health behavior of patients.

To our knowledge, this is one of the largest multi-ethnic collaborative studies in Asia assessing the presentation, management and survival following breast cancer among Asian women. However, we do acknowledge that this study suffers from limitations. While Malaysia is an upper-middle income nation, Singapore is a high income nation, making populations heterogeneous from socio-economic perspectives. However, the two hospitals in this study are tertiary academic centers with fairly comparable diagnostic and therapeutic facilities. On the other hand, since UMMC is a tertiary center and serves a predominantly middle income urban population, our findings may not necessarily reflect the overall situation of breast cancer in Malaysia. The presentation of breast cancer in the rural Malaysian settings for instance, may be more advanced than in our study. However, our results may be regarded as the best available information to date. Another limitation of our study is that some prognostic factors, such as body mass index (BMI), lifestyle, HER2/neu status, and local/systemic recurrence were largely missing. Missing data on histological characteristics and recurrence were not at random. Histological data was missing largely in patients who refused surgery and to a certain extent due to lack of routine assessment for hormonal receptor status in the early 1990s. Recurrence is difficult to capture in a hospital-based registry as patients may subsequently decide to seek treatment in other hospitals. The authors had limited information on existing comorbidities of the patients and were also unable to estimate breast cancer specific survival as cause of death of a majority of our patients was not available.

Based on this study, we conclude that late stage at presentation remains a problem in Asian women and poses a challenge to the health care fraternity in this region. Our patients are also more often diagnosed at a younger age when family and professional commitments hold major importance in their life. In order to reduce the burden of breast cancer in this part of the world, a multi-sectoral approach is required. Evidence-based cancer control strategies aiming at early detection and effective management may be the best way forward.

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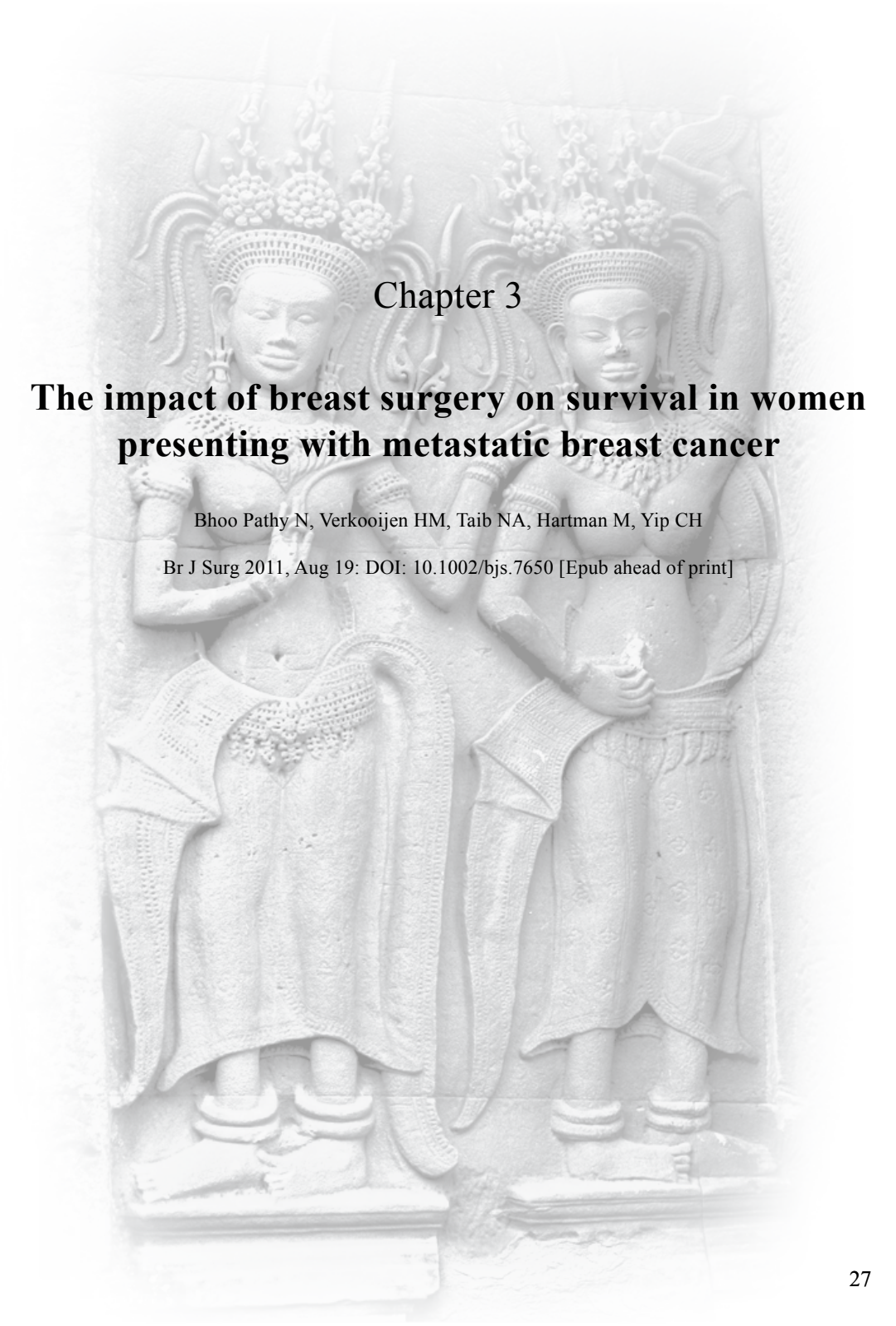

Chapter 3

The impact of breast surgery on survival in women presenting with metastatic breast cancer

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Abstract

Background

Advanced breast cancer is common in less affluent parts of Asia. The impact of breast surgery on survival of women presenting with metastatic breast cancer in this setting was investigated.

Method

Women presenting with metastatic breast cancer at the initial diagnosis at the University Malaya Medical Center (Malaysia) between 1993 and 2008 were included in the study. Mortality of patients subjected to primary breast surgery were compared to those without surgery, and adjusted for possible confounders with propensity score.

Results

Of 3689 patients, 375 (10.2%) presented with metastatic disease. One-hundred thirty-nine patients (37.1%) underwent surgery. During 6814 person-months of follow-up, 330 deaths occurred. The two-year survival was 21.2% (95% confidence interval 15.9 to 26.5%) in women not subjected to surgery, and 46.3% (37.7 to 54.9%) in patients with breast surgery. Breast surgery was associated with 28% lower risk of mortality (hazard ratio 0.72, 95% confidence interval 0.56 to 0.94), after adjustment for patient and tumor characteristics, metastatic profile and treatment.

Conclusion

Surgical resection of the primary breast tumor is independently associated with a survival advantage in patients presenting with metastatic breast cancer.

Introduction

Traditionally, 'no surgery of the primary tumor' had been the standard of care in the management of patients presenting with metastatic breast cancer at the initial diagnosis. Experimental studies have suggested that removal of the primary tumor could induce release of angiogenetic and other growth factors, thereby promoting growth of otherwise dormant distant metastases.[1] There is no clinical evidence supporting this hypothesis. A growing body of evidence from observational studies suggests that surgery of the primary breast tumor may have a positive impact on survival.[2-11] A recent meta-analysis showed that in patients with metastatic breast cancer at diagnosis, surgery of the primary breast tumor is associated with lower mortality compared to no surgery.[3]

Approximately three to eight per cent of women with breast cancer in Europe and the United States have metastatic disease at their initial presentation.[12] In most Asian countries, about ten to twenty-five per cent of patients[13-15] present with distant metastases. The spectrum of disease in Asian patients with metastatic breast cancer is more advanced than that of their Western counterparts.[16] In Europe and the United States, breast cancer patients often receive intensive work-up leading to detection of often small and solitary metastases. In low or middle income countries, higher proportions of locally advanced tumors are seen and systematic work-up for detection of asymptomatic metastatic lesions is rare due to limited resources.[16] Distant metastases are mostly detected due to symptoms and are more likely to involve multiple metastatic sites. An uncertainty therefore prevails on whether resection of the primary breast tumor is associated with any survival advantage in this particular group of women. If such benefit exists in a limited resource setting, the potential impact on the overall burden of breast cancer may be substantial.

The aim of the study was to investigate the association between surgery of the primary breast tumor and overall survival in women presenting with metastatic breast cancer in Malaysia. Propensity score analysis was used to control for confounders.[17]

Materials And Methods

Study population

Patients from the University Malaya Medical Centre (UMMC) Breast Cancer Registry were studied. UMMC is an academic tertiary hospital situated in the city of Kuala Lumpur, Malaysia and manages approximately ten per cent of the registered annual new cases of breast cancer in the country.[18] Since 1993, all patients with newly diagnosed breast cancer are entered into a hospital-based breast cancer registry and data on demography, tumor profile and treatment have been collected prospectively.[19] The registry has been approved by the Ethical Review Committee of UMMC. Women with newly diagnosed metastatic breast cancer (stage IV) at their initial presentation between 1993 and 2008 were included in the study. Patients diagnosed prior to 2002 were staged according to the 5th edition of TNM classification by American Joint Committee on Cancer (AJCC), while patients diagnosed from 2002 onwards were staged

according to the 6th edition of AJCC. Distant metastases were diagnosed either by histology or imaging. For women receiving breast surgery, diagnosis of metastatic breast cancer was made either before or within 31 days of resection of the primary breast tumor.

Study variables

Patients with breast surgery were operated either with mastectomy or breast conserving surgery. Socio-demographic variables included age at diagnosis, and ethnicity (based on the main ethnic groups in Malaysia; Chinese, Malay, Indian).[18] Primary tumor characteristics included tumor size, lymph node involvement (clinical or pathological), estrogen receptor (ER) status (positive if more than ten per cent of tumor cells stained on immunohistochemistry), and tumor margins for operated patients. Data on metastasis included number of metastatic sites involved, and site of metastasis. Patients who had more than one metastatic site could belong to more than one category of site of metastases. Treatment data consisted of radiotherapy to breast or other metastatic sites, hormone treatment and chemotherapy before surgery and after surgery

Follow-up and outcome assessment

Patients were followed-up via scheduled appointments in the outpatient clinics. Data on mortality were obtained from the hospitals' medical records, as well as follow-up through the next-of-kin of patients. In addition, vital status was updated through direct linkage with the Malaysian National Registration Department. The outcome of interest was all-causes of death.

Statistical Analysis

All categorical variables were described by proportions and compared using the Chi square test. Continuous variables were expressed in medians and compared with the Mann-Whitney U test. Univariable logistic regression analyses were performed to assess the association between the demographic and clinical variables with breast surgery as the dependent variable. Overall survival was estimated using Kaplan-Meier analyses and compared by log-rank test. Propensity score was initially used to balance demographics, tumor and treatment characteristics which were unequally distributed between the 'surgery' and 'no surgery' groups.[17,20] Subsequently a Cox regression model stratified by the propensity score of patients was fitted to estimate the effect of surgery on overall survival.

Propensity score was calculated for each patient. The score expresses a patient's probability of being subjected to breast surgery given her demographics, tumor, and treatment characteristics. Since the probability of surgery in clinical practice depends on the surgeon's and patient's decision, predictors that were most likely to influence this decision and associated with overall survival were identified.[21] These variables included age at diagnosis, ethnicity, tumor size, lymph node involvement, estrogen receptor status, number of metastatic sites, site of metastases, and other modalities of treatment except for surgery. The variables were entered into a multivariable logistic regression model as predictors with breast surgery as the outcome. From this model, the expected probability of surgery for each patient given their

clinical variables was estimated. Patients were subsequently grouped into deciles based on their propensity score.

Since patient accrual spanned over a long period, time dependent covariates (age and calendar time) were included in the analysis.[22] Cox regression modeling was used to estimate crude all-causes of mortality risk with hazard ratio (HR) comparing patients presenting with metastatic breast cancer who were subjected to surgery versus patients who did not receive surgery. Time at entry was date of diagnosis with metastatic breast cancer, and exit time was the date of death, date of last known contact or Nov 1, 2010, whichever came first. Subsequently, the model was stratified by propensity score in deciles to ensure that within each stratum, comparisons were made for patients whom had similar expected probability of being operated and to a large extent, similar distribution of confounders.[23] The resulting HR therefore is an adjusted estimate of the effect of breast surgery across these groups of patients presenting with metastatic breast cancer.

Further analyses were performed as previous studies have shown that patients with free surgical margins[4,5] and patients with single site bone metastasis benefited most from surgery.[5] Interactions with age at diagnosis, and number of metastatic sites were tested using likelihood ratio test within nested models to identify patients in whom breast surgery may be associated with higher survival advantages.

A conventional multivariable Cox regression analysis was fitted with breast surgery as the independent variable and all-causes of mortality as the dependent variable. The model was adjusted as previously described.

Two-tailed p-values less than 0.05 and 95% confidence intervals (CI) for HR not including 1 were considered statistically significant. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

Results

Between 1993 and 2008, 3689 women were diagnosed with breast cancer in UMMC. Three-hundred and seventy-five women (10.2%) presented with metastatic disease at diagnosis. The median age was 50 years (Table 1). A majority of patients presented with locally advanced breast cancer (T4). Two-hundred-seven patients (55.2%) presented with single-site metastasis. A total of 139 patients (37.1%) received breast surgery; the majority of patients were subjected to mastectomy while only six patients received breast conserving surgery. Radiotherapy was administered either locally or to other metastatic sites in 131 (34.9%) patients. Three-hundred and ten patients (82.6%) received either chemotherapy or hormone therapy. Forty-three (11.5%) patients did not receive any form of treatment following the diagnosis of metastatic breast cancer. Patients subjected to breast surgery were significantly less likely to be of Malay ethnicity, and more likely to have smaller tumors, and less nodal involvement. There were significant differences in the number of metastatic sites between those subjected to breast surgery and those without surgery; p less than 0.001. Among patients subjected to breast surgery, 103 patients (74.1%) had single site metastases compared to 104 patients (44.1%)

Table 1. *Clinical Characteristics of 375 Women Presenting with Metastatic Breast Cancer*

Variable	No breast surgery (n= 236)	Breast surgery (n= 139)	p -value	Unadjusted odds (ratio (95% CI))
Age, years (median)	50	49	0.645[a]	1.00 (0.98-1.02)
Ethnicity			0.026	
Chinese	116 (49.2%)	86 (61.9%)		1.00
Malay	95 (40.3%)	37 (26.6%)		0.53 (0.33-0.84)
Indian	25 (10.6%)	16 (11.5%)		0.86 (0.43-1.72)
Tumor size, cm (median)	10.0	9.0	0.004[a]	0.96 (0.93-0.98)
Tumor stage			0.517	
T1	2 (0.8%)	2 (1.4%)		1.80 (0.25-12.99)
T2	21 (8.9%)	12 (8.6%)		1.03 (0.49-2.18)
T3	20 (8.5%)	18 (12.9%)		1.62 (0.82-3.20)
T4	193 (81.8%)	107 (77.0%)		1.00
ER status			<0.001	
Positive	64 (27.1%)	57 (41.0%)		1.00
Negative	53 (22.5%)	51 (36.7%)		0.93 (0.55-1.56)
Unknown	119 (50.4%)	31 (22.3%)		0.27 (0.16-0.47)
Site of metastases [c]			0.060[b]	
Bone	37 (36%)	48 (47%)		1.00
Lung	31 (30%)	32 (30%)		0.80 (0.41-1.53)
Liver	16 (15%)	11 (11%)		0.53 (0.22-1.28)
Soft tissue	15 (14%)	10 (10%)		0.51 (0.21-1.27)
Brain	5 (5%)	0 (0%)		-
Other organ	0 (0%)	2 (2%)		-

[a] Mann-Whitney U test; [b] Fishers Exact test; [c] Site of metastases shown only for those with single site involvement.

in the group not subjected to surgery. Seven (5.0%) patients in the group subjected to breast surgery had three or more metastatic sites compared to 37 patients (15.7%) in the no surgery group. Ninety-three (66.9%) of the patients subjected to surgery had received radiotherapy compared to only 34 patients (14.4%) in those not undergoing surgery; *p* less than 0.001. Hormone therapy administration was also more frequent in women who underwent breast surgery compared to women without surgery 92 patients (66.2%) versus 86 patients (36.4%) respectively; *p* less than 0.001). There was no difference in chemotherapy administration between the groups (89 patients (64.0%) in the group undergoing surgery versus 136 patients (57.6%) in those without surgery; p = 0.22). Among patients undergoing surgery, seventy-five patients (54.0%) had received chemotherapy prior to surgery.

The multivariable logistic regression model constructed to estimate the propensity score was able to predict breast surgery correctly in 340 (90.7%) patients.

Between 1993 and 2008, 330 deaths were observed during 6814 person-months of follow-up. Median survival in the overall cohort of patients with metastatic breast cancer was 12.2 months. Patients subjected to breast surgery had a significantly higher overall survival compared to those not receiving surgery (p for log rank test less than 0.001) (Figure 1). Median survival

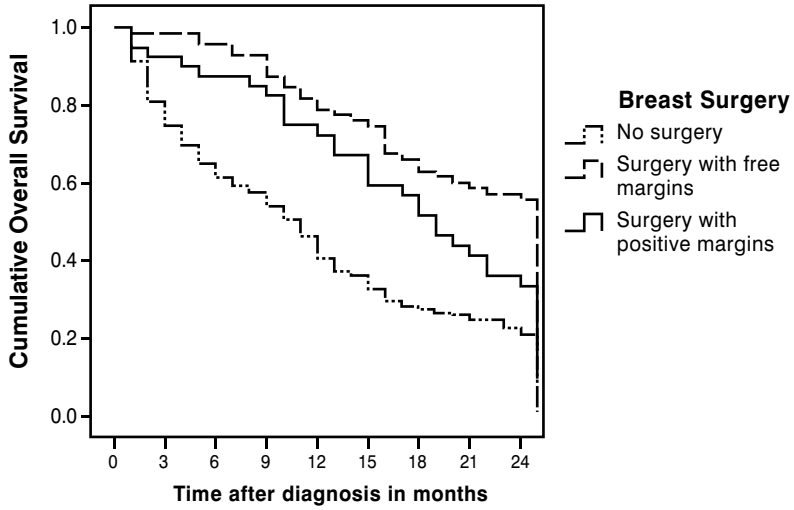

Figure 1. *Overall survival estimates in women presenting with metastatic breast cancer at diagnosis with no breast surgery and breast surgery with free respectively positive resection margins.*

Breast Surgery	Number of patients at risk at begining of each period*				
	0	**6**	**12**	**18**	**24**
No	236	142	93	62	46
Yes with free margins	75	69	55	43	34
Yes with positive margins	41	35	28	20	12

* Excluding 23 patients who underwent surgery whose surgical margin status were unknown

in patients subjected to breast surgery was 21.3 months (95% CI 15.8 to 26.8 months), whereas median survival in those without surgery was 10.1 months (95% CI 8.4 to 11.8 months). Two-year survival was 46.3% (95% CI 37.7 to 54.9%) for patients subjected to surgery, and 21.2% (95% CI 15.9 to 26.5%) in patients with no surgery.

Breast surgery was associated with a lower risk of mortality compared to no surgery in crude Cox regression analysis (Table 2). Following stratification by propensity score in deciles, resection of the primary breast tumor was associated with a 28% lower risk of death compared with no surgery (Table 2).

Compared to patients not operated, patients with free surgical margins after breast surgery had a lower risk of death. In patients with positive margins, mortality was not reduced significantly (adjusted HR 0.82, 95% CI 0.62 to 1.09. Breast surgery was not associated with survival in patients with bone metastases only (Table 2)

Patients aged below 65 years benefited most from breast surgery (adjusted HR 0.51, 95% CI 0.37 to 0.69), while surgery was not significantly associated with survival in elderly patients; p for interaction was 0.199. There was effect modification by number of metastatic sites involved (p for interaction less than 0.001). While breast surgery was associated with significantly lower mortality risk in patients presenting with only one or two metastatic sites,

Table 2. *Impact of Breast Surgery on All-Cause Mortality in 375 Women with Metastatic Breast Cancer at Initial Presentation.*

	Number of patients	Crude HR (95%CI)	Adjusted HR (95%CI)
Overall mortality[a]			
No breast surgery	236	1.00	1.00
Breast surgery	139	0.40 (0.36-0.45)	0.72 (0.56-0.94)
Surgical margin status[a b]			
No surgery	236	1.00	1.00
Free margins	75	0.36 (0.31-0.42)	0.63 (0.48-0.84)
Positive margins	41	0.46 (0.39-0.54)	0.82 (0.62-1.09)
Age category[c]			
< 35 years	26	0.54 (0.33-0.90)	-
36-64 years	286	0.39 (0.34-0.44)	0.51 (0.37-0.69)
>= 65 years	63	0.74 (0.52-1.04)	0.74 (0.41-1.35)
Number of metastatic sites [c]			
One	207	0.52 (0.45-0.61)	0.75 (0.56-1.00)
Two	124	0.44 (0.34-0.57)	0.51 (0.26-1.01)
Three or more	44	0.63 (0.29-1.38)	1.76 (0.52-5.96)

HR = hazard ratio

[a] Adjusted HR was derived from Cox regression analysis which was stratified to deciles of propensity score for breast surgery

[b] Excluding 23 patients with unknown surgical margin

[c] HR was estimated comparing breast surgery versus no surgery within each subgroup. Adjusted HR was derived from Cox regression model which was stratified to quintiles of propensity score for breast surgery

it was associated with a non-significantly increased mortality risk among patients with three or more metastatic sites.

Excluding patients who only had supraclavicular lymph-node metastasis (Stage IV according to AJCC 5th edition), and those who died within one month from date of diagnosis, three patients (2.2%) in the surgery group versus 20 patients (8.5%) in the 'no surgery' group, only marginally changed the results (adjusted HR 0.76, 95% CI 0.58 to 0.98, and adjusted HR 0.73, 95% CI 0.56 to 0.96, respectively). The association remained significant when patients who received chemotherapy before surgery were excluded from the analysis (adjusted HR 0.72, 95% CI 0.55 to 0.94).

A second propensity score was estimated without using information on other modalities of treatments. Using this score, patients subjected to surgery were associated with lower risk of mortality compared to those without surgery (adjusted HR of 0.56; 95% CI 0.45 to 0.70).

Conventional multivariable Cox regression analysis showed that breast surgery is associated with lower risk of mortality compared to no breast surgery (HR 0.58, 95% CI

0.48 to 0.69) following adjustment for patient and tumor characteristics, metastatic profile, and treatment.

Discussion

In this study, resection of the primary breast tumor was independently associated with a survival advantage in patients presenting with metastatic breast cancer, especially among younger patients and in patients with only one or two metastatic sites.

These results complement the findings of most previous studies which were conducted in Caucasian populations.[3-11] However, the effect size associated with breast surgery in the current study seems smaller than most previous studies.[3-10] A potential explanation for this difference is that the study population is substantially different from the Western populations in terms of disease profile. Routine mammography screening is not practiced in Malaysia, and the tumor diameter at diagnosis is larger than in countries with population based mammographic screening programs.[16] It is likely that the potential benefit from surgical removal of the primary tumor is lower in this group of patients since they have a high proportion of locally advanced tumors and multiple metastases.

As in previous observational studies, the surgeon's decision 'to operate or not to operate' was influenced by the underlying prognosis of the patient whereby those who are deemed fit or those with limited metastatic involvement are more likely to receive breast surgery. These decisions are inherently difficult to capture and can potentially over-estimate the 'surgery effect'. The propensity score method was used to minimize the effect of confounding arising from imbalances in known prognostic variables between the 'surgery' and 'no surgery' group, and thereby reduce over-estimation of the 'surgery effect'.[17,20,23] The magnitude of difference between the hazard ratio estimated by the traditional Cox model and the propensity score model of approximately 15%, may represent such over-estimation. A previous study from SEER registry also used propensity score adjustment, but the investigators were not able to adjust for systemic treatment which is a strong predictor of survival in patients with metastatic breast cancer.[8]

The finding that free surgical margin is associated with a higher survival benefit compared to no surgery corresponds with previous studies.[4,5] However, there was no added benefit of surgery in patients with bone metastasis only. This needs to be interpreted with caution as there is a possibility that some patients in this category may have had asymptomatic metastases at other sites which had been missed due to limited metastatic work-up.

While similar studies have already been conducted among women from more affluent settings,[4,11] it remained unclear whether those findings could be inferred to patients whom present with a relatively more severe metastatic profile. However, it is acknowledged that this study suffers from limitations. While the propensity score method is able to balance the known confounders which have been measured in the study, unknown confounders may still be a problem. Information on socio-economic status, co-morbidity and detailed

treatment, for instance response to chemotherapy, were not available, and there was minimal information on the tumor grade and HER2 receptor status which are potential confounders.[3]

Some plausible explanations for the survival benefit associated with breast surgery include that resection of the primary breast tumor eliminates the source of on-going tumor seeding, and reduces the total body tumor burden.[4] Primary tumor removal may allow recovery of the immune response even in the presence of extensive metastatic mammary carcinoma.[24] Currently, randomized controlled trials to investigate the effectiveness of breast surgery in patients presenting with metastatic breast cancer are underway in India[25] and Turkey.[26]

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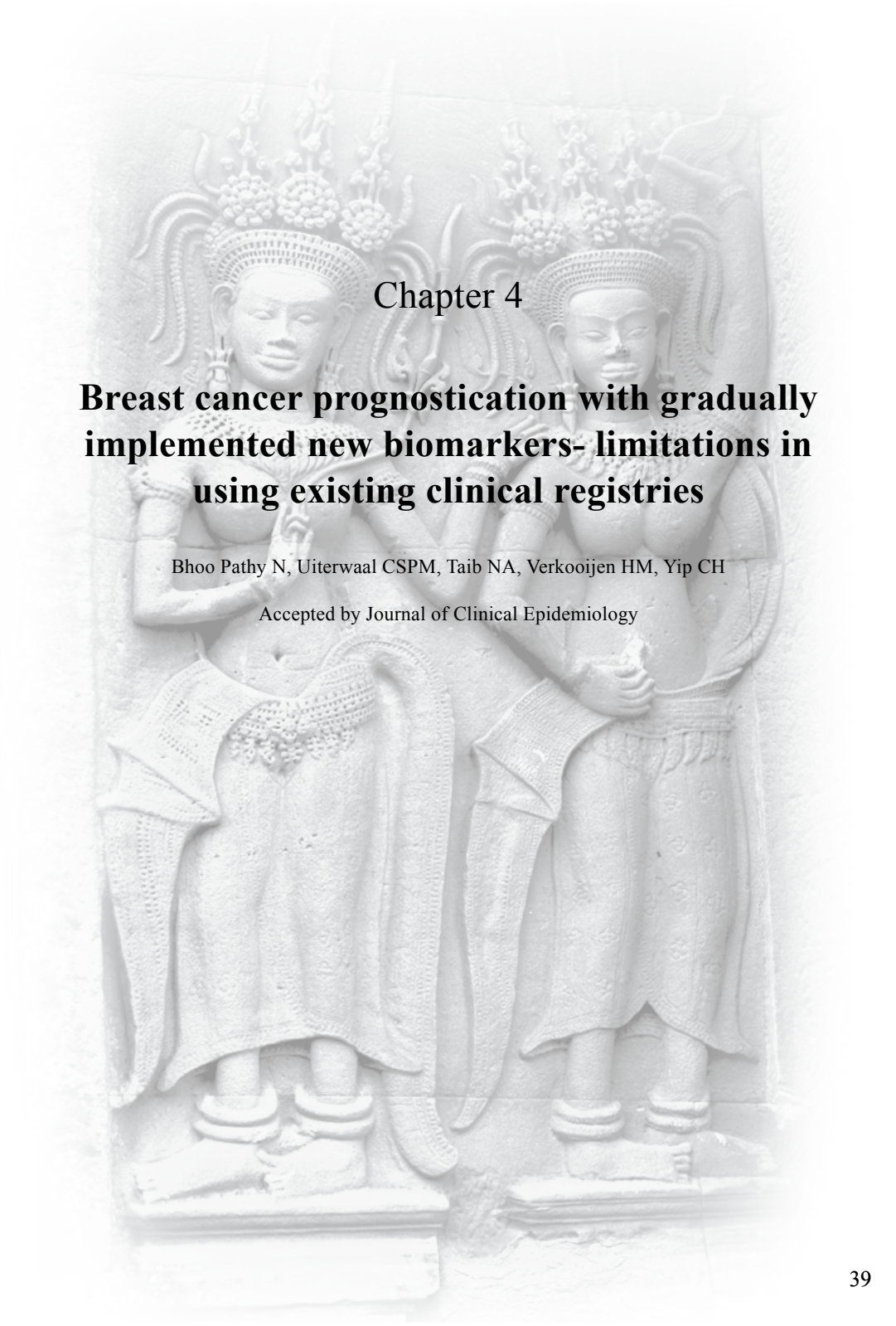

Chapter 4

Breast cancer prognostication with gradually implemented new biomarkers- limitations in using existing clinical registries

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Abstract

Background

Many recent studies investigated the prognostic value of new biomarkers in breast cancer using data from cancer registries which often span long periods whereby the biomarkers may not have been assessed routinely in the initial phase. Some of these studies have been conducted using only patients for whom biomarker status was available. Using Human epidermal growth factor receptor 2 (HER2) as an example, we determined whether testing for a recently implemented biomarker was associated with the prognoses of women with breast cancer.

Methods

Nine-hundred ten women with newly diagnosed breast cancer in a tertiary academic hospital in Kuala Lumpur, Malaysia during the early years following implementation of HER2 testing were followed-up. Individual predicted 2-year mortality risk was estimated using Cox regression analysis. Logistic regression was used to determine the association between predicted mortality risk and assessment of HER2 status.

Results

In this study, testing for HER2 status was significantly associated with the patient's age, tumor size and stage at diagnosis. There was a significant inverted u-shape association between predicted mortality risk and HER2 status determination.

Conclusion

Our finding underlines the limitations associated with naïve prognostic research where only patients with available biomarker status are studied. Therefore, making inferences from such studies should be practiced with caution.

Introduction

Accurate prediction of survival in patients with breast cancer is important because it drives treatment and monitoring decisions. In clinical (breast) cancer research, there is substantial interest in new biomarkers which may serve as prognostic or predictive indicators.[1]

A number of recent prognostic studies investigating these biomarkers have been performed in existing registries of breast cancer patients.[2-6] These registries usually span over periods during which implementation of the biomarker under study is a gradual process. In the earlier years of the registry, such biomarkers may have been sporadically tested for, whereas in the later years, as the role of the biomarker becomes clearer, the test became routine. Therefore, using such registry data for prognostic studies focusing on newly implemented biomarkers may pose a problem. There are studies that provide data on biomarkers as prognostic factors using complete case analysis; based on patient groups whom have available information on biomarker status. This may yield valid estimates if the selection process for biomarker determination at diagnosis is a random process. It will however yield biased prognostic estimates if such selection is non-random.

Since the implementation of a new biomarker measurement in clinical practice is a gradual process, we speculated that a clinician's decision to determine new biomarkers depends on the patient's prognosis, around time of diagnosis. Our research question was whether in clinical settings, testing for a recently implemented biomarker in newly diagnosed breast cancer patients was associated with their prognosis. We have used HER2 assessment in an existing breast cancer registry as an example.

Methods

Data from the University Malaya Medical Centre (UMMC) Breast Cancer Registry was used in this study. UMMC is a tertiary academic hospital in Kuala Lumpur, Malaysia which caters to a predominantly middle class urban population. Since testing for HER2 status in UMMC started in mid 2000s, 910 consecutive patients who were newly diagnosed with invasive breast cancer between 2005 and 2007 were included in this analysis.

In this registry, the following characteristics were available to clinicians at the time of breast cancer diagnosis; age, TNM stage, tumor size. Since histopathologic characteristics such as tumor grade, and estrogen / progesterone receptor status were mostly determined following surgery and concurrently with HER2 status, they were not included in the current analysis. The assumption in this study was that clinicians prognosticate outcome for women with breast cancer around the time of diagnosis using the above mentioned patient characteristics. The registry data were used to mimic that process by estimating 2-year absolute predicted mortality based on these characteristics for all women.

Data analysis

We attempted to assess whether clinicians in their daily practice between 2005 and 2007, had based their decision to determine HER2 status on specific patient characteristics. Therefore,

characteristics of patients which were available at time of diagnosis were compared between those who were tested and untested for HER status using logistic regression.

Subsequently, individual absolute risk for 2-year mortality for all women who were newly diagnosed with breast cancer between 2005 and 2007 were calculated, based on their classical prognostic indicators. Survival analysis was performed using Cox regression with time to death as dependent variable, and age, tumor size and TNM stage as independent variables. Observation times of women were calculated as time between diagnosis and death (all-causes), last contact or Nov, 2010. Clinical indicators of prognosis used were age (years), tumor size (cm) and TNM stage (Stage I-IV). From patient specific survival, absolute individual 2-year mortality risks were estimated for all women, using methodology as described previously.[7,8]

We then used univariable logistic regression to estimate the association between the individual 2-year mortality risk (quintile) as independent variable and assessment of biomarker status (yes/no) as the dependent variable. To test for trends, we entered the quintiles as a continuous variable (assess linear trend) and squared term (assess quadratic trend) into the logistic regression model. All analyses were performed using SPSS version 17.0 for Windows.

***Table 1**. Differences in Patient Characteristics between Women Diagnosed with Breast Cancer Who Were Tested for HER2 status and Those Who Were Not Tested*

	HER2 status determined		**Odds Ratio[a]**
	Yes *N*=855	No N=55	
Age (mean)	53	56	0.98 (0.96-1.00)[b]
Age category			
< 35 years	42 (5%)	3 (5%)	0.73 (0.22-2.46)
35-64 years	674 (79%)	35 (64%)	1.00
>=65 years	139 (16%)	17 (31%)	0.43 (0.23-0.78)[b]
Tumor size (mean)	3.80	6.20	0.89 (0.84-0.93)[b]
TNM Stage			
Stage I	231 (27%)	13 (24%)	0.75 (0.34-1.46)
Stage II	454 (53%)	18 (33%)	1.00
Stage III	123 (14%)	6 (11%)	0.81 (0.32-2.09)
Stage IV	47 (5%)	18 (33%)	0.10 (0.05-0.21)[b]

[a] Derived using logistic regression model with determination of HER2 status (yes/no) as the dependent variable and patient characteristic as independent variable

[b] Statistically significant

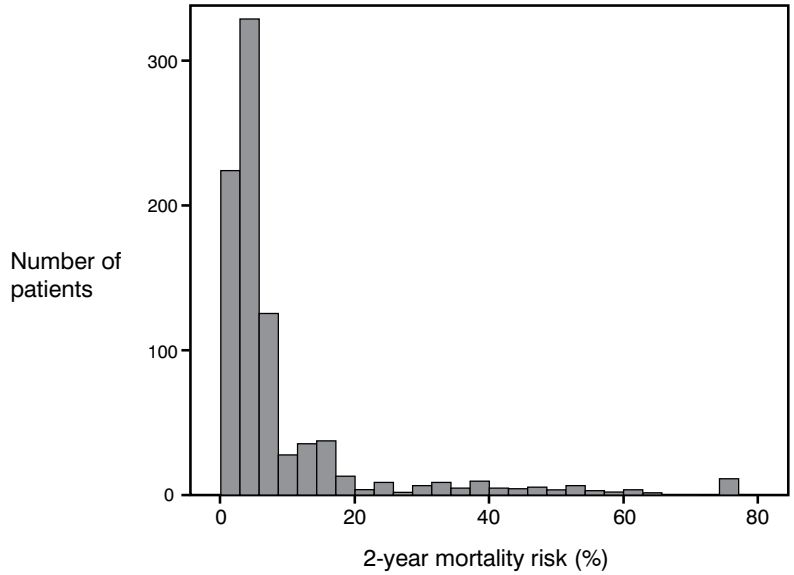


Figure 1. *Distribution of absolute 2-year mortality risk as predicted from age, tumor size and TNM stage in 910 women with breast cancer*

Results

Of 910 women in this study, 855 (94%) were tested for HER2 status whereas 55 were not. Patients who were tested were significantly more likely to be younger, have smaller tumors, and less likely to have metastatic breast cancer (Table 1).

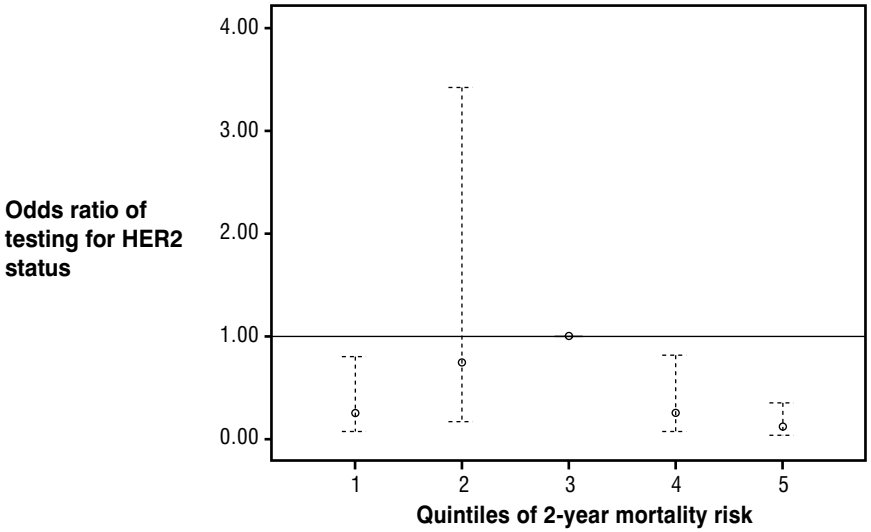
Figure 1 shows the distribution of predicted absolute 2-year mortality risks at diagnosis for 910 women with breast cancer between 2005 and 2007. Most women had low predicted mortality risks, but the range of predicted risks spanned from 0 to almost 100%.

Following logistic regression analysis, we found that compared to women with intermediate risk of mortality (quintile 3- reference), those with low mortality risk (quintile 1) and high mortality risk (quintile 5) were significantly less likely to have their HER2 status tested; OR: 0.25 (95%CI: 0.08-0.80) and OR:0.12 (95%CI: 0.04-0.35) respectively (Figure 1). This association seems to assume a statistically significant inverted U-shape (*P* for quadratic trend <0.001).

Discussion

Using HER2 testing as an example, we have demonstrated a significant association between prognoses of patients as deemed by clinicians at the time of breast cancer diagnosis and the choice to determine a new biomarkers status. There was a significant inverted u-shape association between predicted mortality risk and testing for HER2 status.

Many prognostic studies investigating biomarkers have been conducted using cancer registry data. Even though the testing techniques for the biomarkers are rightly emphasized,



2-year mortality risk (%)	Odds Ratio	95% Confidence Interval
Quintile 1	0.25 [a]	0.08-0.80
Quintile 2	0.75	0.17-3.42
Quintile 3	1.00	-
Quintile 4	0.25 [a]	0.08-0.82
Quintile 5	0.12 [a]	0.04-0.35

[a] Statistically significant

Figure 2. *Association between 2-year predicted mortality risk (quintiles) and odds ratio of being tested for HER2 status in 910 women newly diagnosed with breast cancer*

some of these studies had performed complete case analysis with minimal attention paid to identify or address possible selection bias.[3,4]

It is important to realize that new biomarkers are not tested randomly among patient populations in clinical settings, as our study shows. Clinicians apparently base their choices on indications, whereby they intrinsically estimate their patients' prognoses around diagnosis. These estimated prognoses play a role in their decision to test for a new biomarker status. In the current study, a possible reason for not determining biomarker status in women with poor prognosis i.e. metastatic breast cancer in mid 2000s, could have been that the information would not change the management of these patients in our limited resource setting, as testing for HER2 status was costly and a majority of our patients were unable to afford treatment with trastuzumab or lapatinib.

Our finding clearly poses limits to naïve prognostic research in registries based on complete case analysis. The prognostic value of a new biomarker initially tested only in women with clinically perceived outcome risks may deviate in any direction from its true value.Possible solutions to address this would be to assess whether missing information on

biomarkers of interest is random or non random by comparing characteristics or survival of patients who had information against those with missing information,[2] or restricting study to the part of the cohort where biomarkers were routinely determined.[5] Investigators may also employ statistical methods such as imputation which have been found to yield more precise[9] and valid[10,11] results compared to complete case analysis.

In conclusion, selection of women for determination of new biomarkers in regular clinical care for breast cancer is not a random process, but rather based on patients' prognoses. Therefore, studies on the prognosis of (breast) cancer focusing on gradually implemented new biomarkers using complete case analysis from existing cancer registries are to be interpreted with caution.

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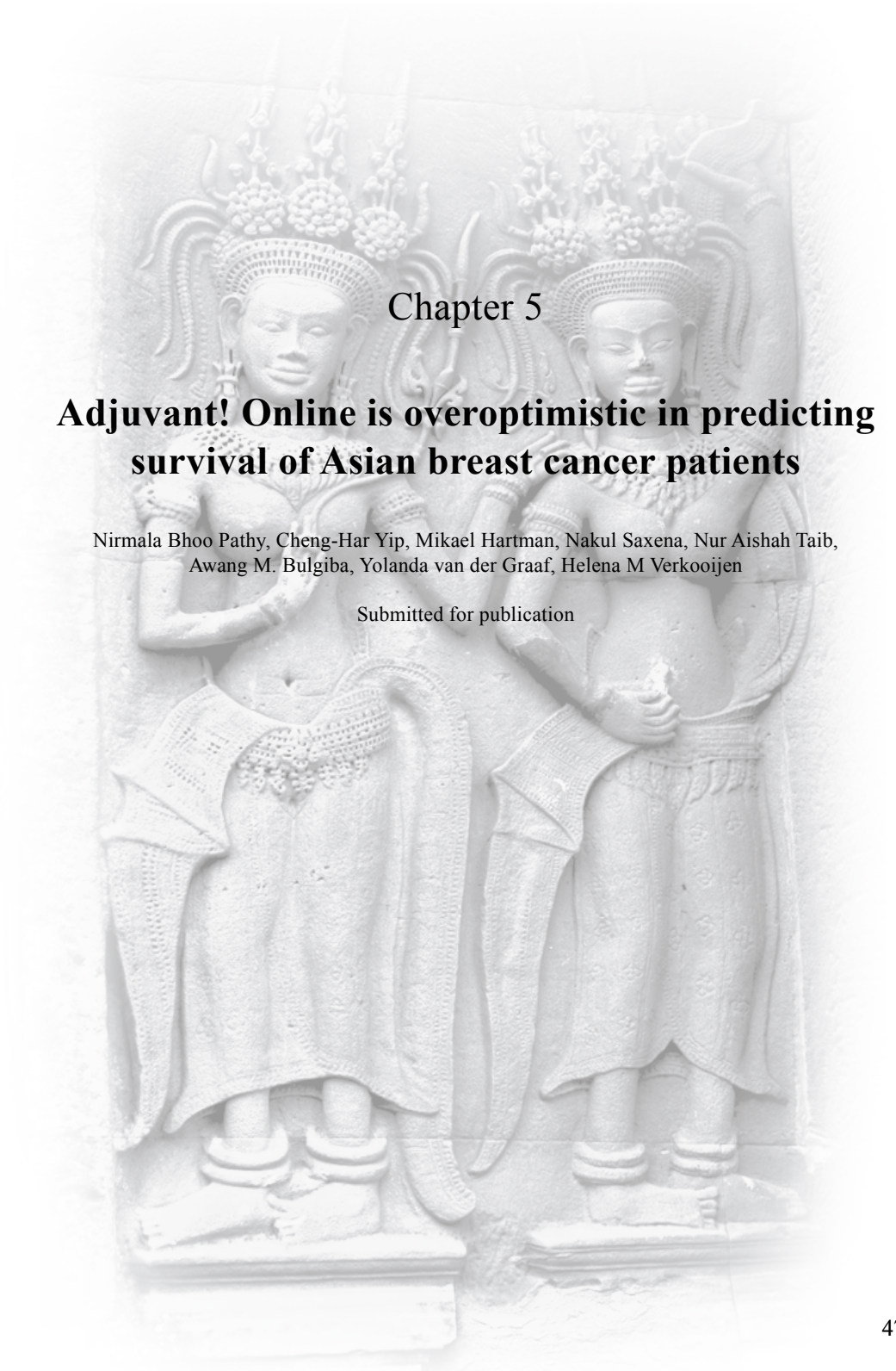

Chapter 5

Adjuvant! Online is overoptimistic in predicting survival of Asian breast cancer patients

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Submitted for publication

Abstract

Background

Adjuvant! Online is a free web-based tool which predicts 10-year breast cancer outcomes and efficacy of adjuvant therapy in patients with breast cancer. As its prognostic performance has only been validated in high income Caucasian populations, the model was validated in a middle income Asian setting.

Methods

Within the University Malaya Hospital-Based Breast Cancer Registry, all 631 women who were surgically treated for invasive non-metastatic breast cancer between 1993 and 2000 were identified. Calibration of Adjuvant! Online was evaluated by comparing predicted 10-year overall survival with observed 10-years survival. Discrimination of the model was tested by receiver operating characteristic (ROC) analysis.

Results

For the entire cohort, Adjuvant! Online predicted 10 year survival (70.3%) was significantly higher than the observed 10 years survival (63.6 %, difference of 6.7%; 95%CI: 3.0- 10.4%). The model was especially overoptimistic in women under 40 years and in women of Malay ethnicity, where survival was overestimated by approximately 20% (95%CI: 9.8- 29.8%) and 15% (95%CI: 5.3- 24.5%) respectively. Adjuvant! Online performed fairly in terms of discrimination, with an area under ROC curve of 0.73 (95%CI: 0.69-0.77).

Conclusion

Even though Adjuvant! Online is capable of discriminating between good and poor survivors, it systematically overestimates survival. These findings suggest that the model requires adaptation prior to use in Asian settings.

Introduction

In contrast to the West, where breast cancer incidence rates have stabilised or even decreased,[1-3] breast cancer incidence[4] and mortality[5] have increased dramatically in Asian countries. Despite this alarming trend, surprisingly little research has addressed determinants of survival following breast cancer in Asia. Most prognostic factors for breast cancer have been established in Caucasian populations. The validity of these prognostic factors, however, has only been marginally, if at all, investigated in other parts of the world.

Adjuvant! Online for Breast Cancer is a free web-based prognostication tool which was developed based on the Surveillance, Epidemiology and End Results (SEER) database and treatment efficacy data from meta-analyses.[6] It estimates individual ten year survival probabilities, and risks of relapse in patients with breast cancer, based on clinical characteristics and systemic treatment. In addition, Adjuvant! Online helps to predict the absolute benefit of adjuvant therapy in individual patients.

Since its introduction in early 2000s, Adjuvant! Online has gained worldwide recognition among clinicians as a tool to aid patient counselling and clinical decision making in the management of women with early breast cancer.[7] The program has been validated by several groups in Canada and Europe.[7-9] Two studies have shown that the model accurately predicts survival probabilities across most patient groups,[7,8] whereas the study conducted in United Kingdom found that Adjuvant! Online systematically overestimated survival by about 5.5 percent.[9]

Little is known on the prognostic performance of Adjuvant! Online in non-Western, low or middle income settings. In multi-ethnic Asia, genetic backgrounds, socio-economic profiles, lifestyles, diets, cultures, health beliefs, and life expectancies are substantially different from those in the US and Europe, and each of these factors may play a distinct role in breast cancer prognosis and treatment. Furthermore, it has been highlighted that there is an urgent need to validate Adjuvant! Online in different regions since geographical locations may play an important role in influencing adjuvant treatment decisions.[10]

Malaysia is a high-middle income country in South East Asian comprising 3 major ethnic groups i.e. Malays, Chinese and Indians.[11] We undertook a study to evaluate whether Adjuvant! Online is a reliable prognostic tool in a cohort of Malaysian women with early breast cancer.

Methods

Data from the University Malaya Medical Center (UMMC) Breast Cancer Registry was used.[12] UMMC is an academic tertiary hospital situated in the relatively affluent part of Kuala Lumpur, Malaysia and caters to a predominantly middle class urban population. The UMMC Breast Cancer Registry is a prospective hospital-based database of 2449 consecutive women who were newly diagnosed with breast cancer between 1993 and 2008. This registry has been approved by the institution's ethical review committee and encompasses data on patient's demography (including age and ethnicity), tumor characteristics (including pathological data on tumor size, number of involved lymph nodes, tumor grade based on Bloom-Scarff-Richardson classification,

estrogen receptor status [determined via immunohistochemical staining and positive when >10% cells stained positive]) and treatment. Treatment data include type of treatment (surgery, chemotherapy, radiotherapy, hormone therapy), type of surgery (mastectomy, breast conserving surgery), chemotherapy regimen, and type of hormone therapy.

Between 1993 and 2000, the treatment protocol in UMMC for invasive non-metastatic breast cancer was mastectomy and axillary clearance for larger tumors, and breast conservation surgery followed by radiotherapy for localized small tumors. Between 1993 and 1996, intravenous cyclophosphamide, methotrexate, and fluorouracil (CMF) was the routine chemotherapy regimen, and from 1997 onwards, fluorouracil: 500 mg/ m^2, epirubicin: 75 mg/m^2, and cyclophosphamide: 500 mg/m^2 (FEC75) was used. Tamoxifen was prescribed routinely for women with hormone-receptor positive breast cancer and postmenopausal women with unknown hormone receptor status.

For the present study, 824 consecutive women who were newly diagnosed with invasive non-metastatic breast cancer between 1993 and 2000 (allowing at least 10 years of follow-up) were identified. Patients were included if they had undergone standard surgical treatment (i.e. mastectomy or breast conserving surgery followed by radiotherapy, n= 725).Women treated with neoadjuvant chemotherapy were excluded (n= 56), as were patients with missing information on tumor size and axillary lymph node involvement (n= 38). The final study population consisted of 631 women.

Data on mortality were obtained from the hospitals' medical records, and by means of active follow-up through the patients' next-of-kin. In addition, patients' vital statuses were verified through direct linkage with the National Registration Department in Malaysia which has the mortality records of all Malaysians. In the current study, follow-up time was calculated for all patients, starting at date of diagnosis with breast cancer until death (all causes), or censored at date of last contact, or Dec, 2010 (linkage with national mortality registry). In this hospital based cancer registry, causes of death, as well as data on local or systemic recurrences were not routinely available. Information on co-morbidity was also not available for a majority of patients.

For each patient, data on age (continuous), tumor size (0.1-1.0 cm, 1.1-2.0 cm, 2.1-3.0 cm, 3.1-5.0 cm, > 5.0 cm), number of involved lymph-nodes (0, 1-3, 4-9, >9 nodes), estrogen-receptor status (positive, negative, undefined), tumor grade (grade 1, grade 2, grade 3, undefined) were manually entered into the Adjuvant! Online (Version 8.0) program. Type of adjuvant chemotherapy was categorised as first generation, or second generation. Third generation regimen was not administered in our setting during the study period. Hormone treatment was categorised as tamoxifen, aromatase inhibitors, tamoxifen for 2-3 years followed by aromatase inhibitor for 2-3 years, ovarian ablation, or ovarian ablation plus tamoxifen (or other hormones). Comorbidity was set at 'average for age' for all patients. For every entry, Adjuvant! Online predicted the ten-year overall survival for four different scenarios i.e. survival without any adjuvant treatment, survival with adjuvant chemotherapy only, survival with adjuvant hormone therapy only, and survival with both chemotherapy and hormone therapy. The survival probability corresponding to the actual treatment received by the patient was recorded. Accuracy of the data was verified

by recalculating Adjuvant! Online predicted survival probabilities in a random sample of 10% of the patients.

Statistical Analysis

Kaplan-Meier analysis was used to estimate the observed ten year overall survival in the entire study population and within subgroups. The mean predicted ten year overall survival was calculated by averaging the individual predicted survival probabilities derived from Adjuvant! Online. To assess the calibration of the Adjuvant! Online model, the observed and predicted ten year overall survivals were compared using a one-sample t- test for proportions (as in previous validation studies).[7,8] This test was based on the assumption that the Adjuvant! Online predicted survival was the true population value and thus fixed.[7] Observed 10 year survival probabilities were subsequently plotted against deciles of Aduvant! Online predicted survival.

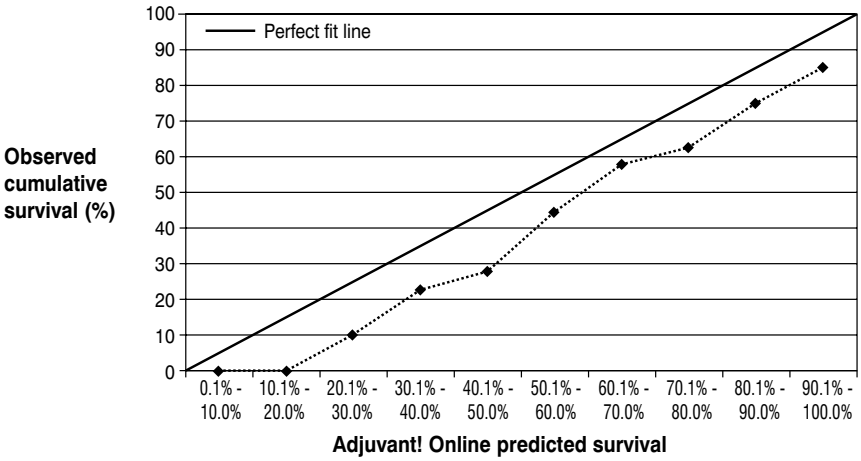
The receiver operating characteristic (ROC) analysis was performed to assess the discriminatory performance of Adjuvant! Online (i.e. its ability to discern patients having good prognosis – alive after 10 years- from those having poor prognosis – death within 10 years). The Area Under the ROC Curve (AUC) gives an indication of the discriminatory performance of the model, whereby it can be interpreted as the proportion of patients who are correctly predicted to be alive or dead at 10 years. An AUC of 0.5 indicates no discriminative performance while an AUC of 1.0 indicates perfect discrimination. This test was repeated in the subgroups.

All statistical analyses were performed using SPSS for Windows version 16.0 (SPSS Inc., Chicago, Illinois, USA).

Results

In this cohort of 631 Asian women with early breast cancer, the median age at diagnosis was 49 years. The majority of patients were Chinese (66.9%), followed by Malays (16.8%), Indians (15.2%), and other races (1.1%). The median tumor size at presentation was 3.0 cm and approximately half of the patients had lymph node involvement. Estrogen receptor status and tumor grade were unknown in approximately 25% of the patients. Four-hundred-fifty-eight (72.6%) patients were given hormonal treatment, two of which received aromatase inhibitors, the rest received tamoxifen. Among 396 (62.8%) patients who were given chemotherapy, 146 (36.9%) had received CMF (first generation regimen), 218 (55.1%) received FEC (75) (second generation regimen), 24 (6.0%) received adriamycin, cyclophosphamide and paclitaxel (second generation), and 4 (1.0%) received mitomycin, methotrexate and mitozantrone (second generation). Chemotherapy was unspecified in four (1.0%) patients.

Of the 631 patients, 258 (40.9%) women died during a median follow-up of 10.8 years. Overall, Adjuvant! Online predicted 10-year overall survival was 70.3%, whereas the actual observed 10-year overall survival was 63.6%, indicating an overestimation of survival of 6.7% (95%CI: 3.0% to 10.4%). The model was especially overoptimistic in patients aged less than 40 years at diagnosis (n=96), and in women of Malay ethnicity (n=106), where survival was over-estimated by approximately 20% (95%CI: 9.8- 29.8%) and 15% (95%CI: 5.3- 24.5%)



respectively. In patients with tumors smaller than 2cm, lymph node negative disease, estrogen receptor positive tumors, and low grade tumors, observed and predicted survival probabilities were not significantly different. Figure 1 shows the proportion of observed 10-year survival versus deciles of predicted 10-year survival from Adjuvant! Online, and shows that the model systematically overestimated survival by approximately 7% for the entire range of predicted probabilities.

ROC analysis of the whole cohort showed that the model discriminated fairly between good and poor survivors with an AUC of 0.73 (95%CI: 0.69-0.77). The discriminatory accuracy of Adjuvant! Online was found to be somewhat lower in Indians, as well as in patients with lymph node negative disease, with small and high grade tumors, The discriminatory accuracy was good in patients aged 65 and above.

In this study, 23 patients did not complete chemotherapy (received less than 4 cycles of CMF/FEC). When these patients were excluded, Adjuvant! Online still overestimated survival, both in the overall cohort (by 5.8%; 95%CI: 2.1%-9.5%) and in the subgroup of patients subjected to chemotherapy (by 9.5%; 95%CI: 4.6%-14.5%).

Since previous studies have excluded patients with tumor size of more than 5 cm,[6-8] we repeated the analysis excluding 123 patients with tumors larger than 5 cm. The over-optimism of Adjuvant! Online still persisted with a difference between the predicted and observed 10-year overall survival of 5.9% (95%CI: 1.7%-10.0%).

Discussion

In this cohort of Asian patients, Adjuvant! Online is capable of discriminating between good and poor survivors, but it systematically overestimates survival. This overestimation was present in most subgroups and especially obvious in the very young (aged less than 40 years), as well as in patients of Malay ethnicity.

Table 1. *Calibration of Adjuvant! Online in 631 South East Asian Women with Breast Cancer*

	Number (%)	Overall Survival (%)			
		Adjuvant! Predicted	Observed (SE)	Predicted - Observed (95% CI)	*P* value
All patients	631 (100)	70.3	63.6 (1.9)	6.7 (3.0 to 10.4)	<0.001
Year of diagnosis					
1990-1995	225 (35.6)	67.9	59.1 (3.3)	8.8 (2.3 to 15.3)	0.008
1996-2000	406 (64.3)	71.7	66.2 (2.4)	5.5 (0.8 to 10.2)	0.022
Age (years)					
< 40	96 (15.1)	75.6	55.8 (5.1)	19.8 (9.8 to 29.8)	<0.001
40-64.9	469 (74.3)	71.9	67.3 (2.2)	4.6 (3.7 to 8.9)	0.037
>=65	67 (10.6)	51.8	49.0 (6.2)	2.8 (-9.4 to 15.0)	0.653
Ethnicity [a]					
Chinese	422 (67.6)	71.6	67.7 (2.3)	3.9 (-0.6 to 8.4)	0.091
Malay	106 (17.0)	71.2	56.3 (4.9)	14.9 (5.3 to 24.5)	0.003
Indians	96 (15.4)	64.9	55.5 (5.1)	9.4 (-0.6 to 19.4)	0.068
Tumor size					
< 2	123 (19.5)	81.5	80.0 (3.7)	1.5 (-5.8 to 8.8)	0.686
2-5	385 (61.0)	71.4	64.2 (2.5)	7.2 (2.3 to 12.1)	0.004
>5	123 (19.5)	55.8	45.9 (4.5)	9.9 (1.1 to 18.7)	0.030
Lymph node involvement					
No	329 (52.1)	79.8	77.8 (2.3)	2.0 (-2.5 to 6.5)	0.385
Yes	302 (47.9)	60.0	48.5 (2.9)	11.5 (5.8 to 17.2)	<0.001
Estrogen receptor status					
Negative	212 (33.6)	61.0	51.2 (3.5)	9.8 (2.9 to 16.7)	0.006
Positive	262 (41.5)	78.0	72.6 (2.8)	5.4 (-0.1 to 10.9)	0.055
Unknown	157 (24.9)	70.2	65.3 (3.8)	4.9 (-2.5 to 12.3)	0.199
Grade					
Low	73 (11.6)	82.6	85.9 (4.1)	-3.3 (-11.3 to 4.7)	0.424
Moderate	243 (38.5)	72.5	63.3 (3.1)	9.2 (3.1 to 15.3)	0.003
High	158 (25.0)	64.2	53.8 (4.0)	10.4 (2.6 to 18.2)	0.010
Unknown	157 (24.9)	67.5	63.7 (3.9)	3.8 (-3.8 to 11.4)	0.331
Chemotherapy					
Yes	396 (62.8)	69.7	59.6 (2.5)	10.1 (5.2 to 15.0)	<0.001
No	235 (37.2)	71.4	70.6 (3.0)	0.8 (-5.1 to 6.7)	0.790
Hormone therapy					
Yes	458 (72.6)	72.1	66.3 (2.2)	5.8 (1.5 to 10.1)	0.009
No	173 (27.4)	65.7	56.5 (3.8)	9.2 (1.8 to 16.6)	0.017

[a] Excluding patients from other races (n=7)

Discrepancies in the observed and Adjuvant! Online predicted survival in the Asian setting may be partly explained by differences in life expectancy between our study population (life expectancy at 50 years; 81.2 years) and population in the United States (life expectancy at 50 years; 87.3 years) from which the model was developed.[13] However, other possible explanations

Table 2. *Discriminatory Performance of Adjuvant! Online in 631 South East Asian Women*

	Number	Area Under Curve	95%CI for Area Under Curve [a]	
			Lower limit	Upper limit
All patients	631	0.73	0.69	0.77
Age				
< 40 years	96	0.78	0.69	0.88
40-64 years	469	0.70	0.66	0.75
>= 65 years	67	0.82	0.72	0.92
Ethnicity				
Chinese	422	0.74	0.69	0.79
Malay	106	0.73	0.63	0.82
Indians	96	0.65	0.54	0.76
Tumor size				
< 2 cm	123	0.65	0.54	0.76
2-5 cm	385	0.71	0.65	0.76
>= 5 cm	123	0.75	0.66	0.83
Lymph node involvement				
Negative	329	0.65	0.59	0.72
Positive	302	0.71	0.65	0.76
Estrogen receptor status				
Negative	212	0.67	0.60	0.74
Positive	262	0.72	0.65	0.79
Unknown	157	0.77	0.69	0.84
Grade				
Low	73	0.74	0.60	0.89
Moderate	243	0.74	0.68	0.81
High	158	0.63	0.54	0.71
Unknown	157	0.76	0.68	0.84
Chemotherapy				
Yes	396	0.69	0.64	0.74
No	235	0.79	0.72	0.85
Hormone therapy				
Yes	458	0.75	0.70	0.79
No	173	0.66	0.58	0.74

[a] 95% CI for area under curve that does not include 0.5 is considered as statistically significant

include differences in tumor biology, response to anti-cancer therapy, treatment compliance and differences in lifestyle after cancer between the two populations. Below, we will discuss each of these factors in the context of our study.

There is increasing evidence that tumor biology of Asian patients is different from that of Caucasian women, as certain prognostic factors, such as HER2 expression, are more prevalent in Asian populations.[14] In addition, the case-mix of the Asian population is different, with higher proportions of younger women, and women with unfavorable tumor characteristics such as lymph node involvement, large tumor size, and ER negative disease. In the current study, Adjuvant! Online performed well in women with favorable tumor characteristics (small size, lymph node

negative, estrogen receptor positive and low grade) and elderly patients. These profiles represent the majority of breast cancer patients in Caucasian settings therefore suggesting that Adjuvant! Online may be over fitted to Western populations.

Differences in response to anticancer therapy may partially explain the mechanism behind the lower observed survival. In our cohort of Asian patients, Adjuvant! Online was able to predict survival accurately in the group not receiving chemotherapy, whereas it overestimated survival in patients subjected to chemotherapy by approximately ten percent. A recent review looking at differences in toxicity and clinical outcome following treatment with anticancer drugs highlighted that there may be ethnic differences in tolerability and response to cytotoxic chemotherapy in breast cancer suggesting that anti-cancer drugs may be more effective in certain ethnic groups.[15] Besides this, non-compliance with adjuvant therapy may be responsible for some of the difference in predicted and observed survival. Non-compliance in Asian breast cancer patients can be attributed to financial barriers (in the absence of a health insurance schemes), and socio-cultural factors such as lack of decision making power, belief in alternative therapy, and fatalistic views.[16,17] Cancer fatalism, i.e. the belief that death is inevitable when one has cancer, has been hypothesized to affect cancer prevention behaviour and treatment adherence.[18] Exclusion of patients who did not complete their chemotherapy treatment did not attenuate our findings. However, data on non-compliance with hormone therapy were unavailable.

Lifestyle factors, such as diet and body weight, are increasingly being recognized as important prognostic factors of breast cancer.[19] Owing to cultural and religious differences, lifestyle profiles of Asian women differ substantially from those of Caucasian women and also within South East Asia, we see striking differences. For instance, obesity which is an unfavorable prognostic factor in breast cancer,[20] is more common in Malay and Indian women, where as the Chinese have the lowest body mass index.[21] This difference could explain some of the overestimation in Adjuvant! predicted outcome in Malay women, in whom survival was overestimated by almost 15%.

With this study, which is the first to be done in a middle income, non-Caucasian setting, it is confirmed that Adjuvant! Online in its current form may not be a suitable clinical decision making tool in the management of early breast cancer in Asia. Adaptation of the Adjuvant! Online model may improve its utility in Asian settings.

It is however acknowledged that this study suffers from several limitations. Firstly, the study sample is rather small, making estimates in some subgroups rather unstable. In addition, information on causes of death and breast cancer recurrences was incomplete, making it impossible to study breast cancer specific survival and event free survival. Finally, there were substantial proportions of missing values for some prognostic factors, in particular for grade and ER status, which were not routinely measured in the early years of our study period. Fortunately, the model accommodates patients with missing information on grade and ER status

In conclusion, even though Adjuvant! Online is fairly capable of discriminating between good and poor survivors after breast cancer in Asian women, it substantially overestimates absolute overall survival probabilities.

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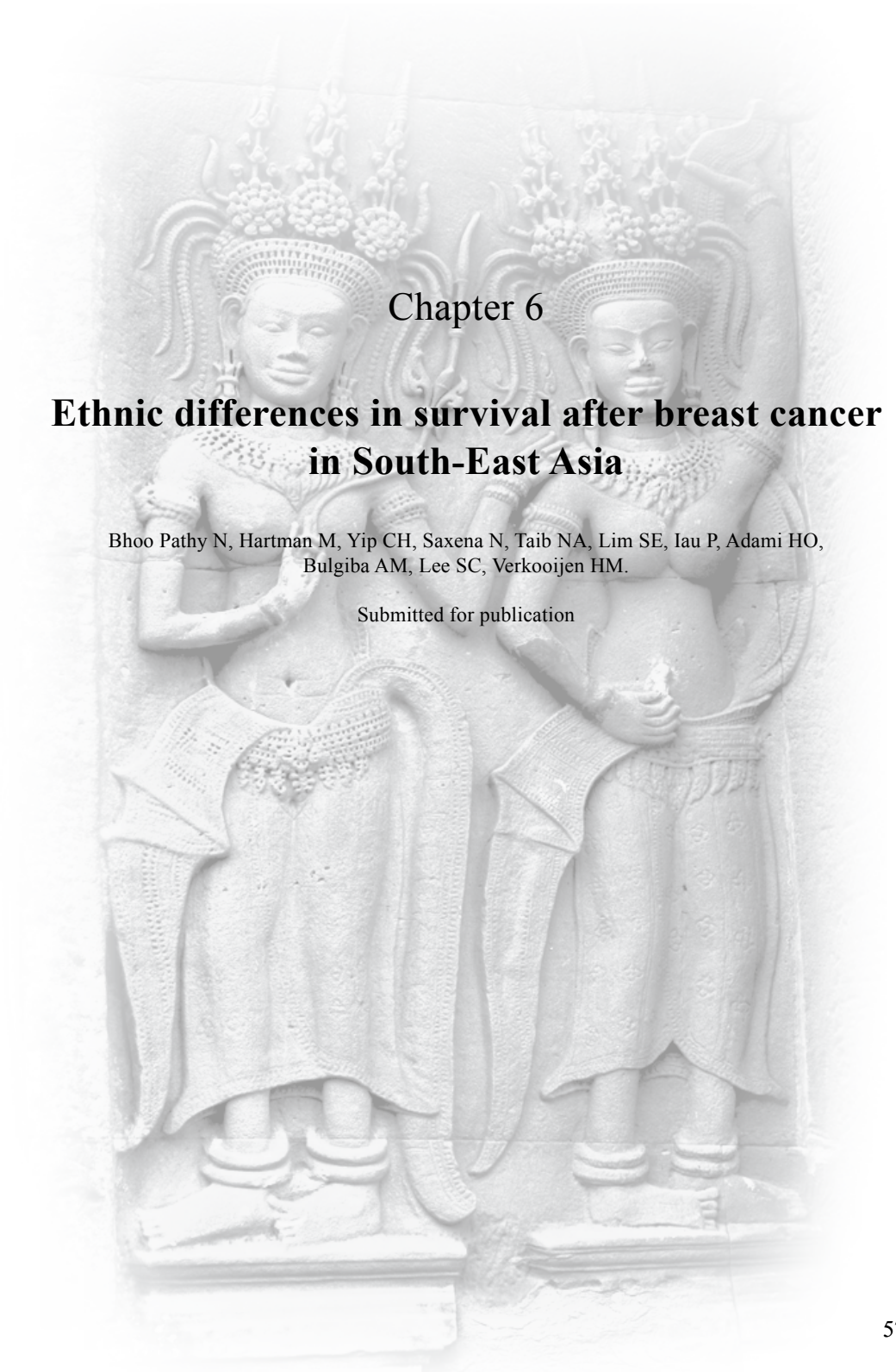

Chapter 6

Ethnic differences in survival after breast cancer in South-East Asia

Bhoo Pathy N, Hartman M, Yip CH, Saxena N, Taib NA, Lim SE, Iau P, Adami HO, Bulgiba AM, Lee SC, Verkooijen HM.

Submitted for publication

Abstract

Background

The burden of breast cancer in Asia is escalating. We undertook a study to evaluate the impact of ethnicity on survival after breast cancer in the multi-ethnic region of South East Asia.

Methods

Using the Singapore-Malaysia hospital-based breast cancer registry, we investigated the association between ethnicity and risk of death following breast cancer in 3,883 patients diagnosed between 1990 and 2007 (Chinese: 75%, Malay: 16%, Indian: 9%). We compared survival rates between ethnic groups and calculated adjusted hazard ratios (HR) to estimate the independent effect of ethnicity on survival.

Results

Malay patients (n=624) presented at a significantly younger age, with larger tumors, and at later stages than Chinese and Indian women. They more often presented with unfavorable characteristics i.e. lymph node involvement, hormone receptor negative and poorly differentiated tumors, and were less likely to receive complete loco-regional treatment. Five year overall survival was not significantly different between the Chinese (72.4%; 95%CI: 70.4%-74.4%) and Indian (65.3%; 95%CI: 59.4%-71.1%) patients, but was substantially lower in Malay patients (47.4%; 95%CI: 42.7%-52.1%). Compared to the Chinese, Malay ethnicity was associated with 60% higher risk of all cause mortality (HR: 1.60; 95%CI: 1.44-1.77), independent of patient profile, TNM stage, tumor characteristics and treatment. Indian ethnicity was also associated with a modest increase in mortality risk (HR: 1.16; 95%CI: 1.03 -1.32).

Conclusion

In South East Asia, Malay and to a lesser extent Indian ethnicity is independently associated with poorer survival after breast cancer. The underlying reasons may include variations in tumor biology, psychosocial and cultural factors, treatment responsiveness and lifestyle after diagnosis of breast cancer.

Background

In contrast to the West where breast cancer incidence rates have plateaued or even decreased,[1,2] the incidence of breast cancer is rapidly escalating in Asia. In China and India, breast cancer rates have increased by up to 30% over the last 10 years, whereas in Japan, Korea and Singapore, incidence rates have doubled or even tripled in the past few decades.[3] A myriad of studies conducted in Western settings have implicated ethnicity as a predictor of survival following breast cancer.[4] However, the impact of ethnicity on survival after breast cancer in Asian settings has hardly been studied.

The region of South East Asia embraces diverse ethnic subgroups with distinct genetic, cultural and lifestyle profiles and was recently highlighted as an emerging focus for global health.[5] Malaysia and Singapore are multiethnic South East Asian nations comprising 3 major ethnic groups i.e. Malays, Chinese and Indians.[6,7] In these populations, age-standardized incidence rates (ASRs - world standardized) of breast cancer differ substantially, whereby the rate is highest among the Chinese (Malaysia: 59.7 per 10^5, Singapore: 57.0 per 10^5 person-years), followed by the Indians (Malaysia: 55.8 per 10^5, Singapore: 45.8 per 10^5 person-years) and the Malays (Malaysia: 33.9 per 10^5, Singapore: 44.8 per 10^5 person-years).[6,7] Despite having the lowest incidence of breast cancer, Malay women have inferior 5-year overall survival probabilities following the diagnosis of breast cancer when compared to their Chinese and Indian counterparts.[8] However, it remains unclear whether ethnicity is independently associated with survival following breast cancer, or whether ethnic differences in prognostic determinants such as early detection and standard treatment explain the survival disparities.

Therefore, we investigated the impact of ethnicity on survival after breast cancer, and possible mechanisms for survival disparites, in a multicenter hospital-based cohort of breast cancer patients from Malaysia and Singapore.

Methods

Study population

Data from the Singapore-Malaysia Breast Cancer Registry which currently encompasses 4,058 women was used. This multi-institutional breast cancer registry is a merger between the National University Hospital (NUH) Breast Cancer Registry, and the University Malaya Medical Center (UMMC) Breast Cancer Registry.[9] The NUH is a tertiary university hospital in the city state of Singapore. Its breast cancer registry includes all consecutive 2,545 women diagnosed with breast cancer between 1990 and 2007. Information has been collected retrospectively between 1990 and 1995 and prospectively from 1995 to 2007. UMMC is an academic tertiary hospital situated in the relatively affluent part of Kuala Lumpur, Malaysia and caters to a predominantly middle class urban population. The UMMC Breast Cancer Registry is a prospective database of 1,513 consecutive women who were newly diagnosed with breast cancer between 1993 and 2002. Both registries have received approval from the respective institutional review boards.

In the current study, we included all 3,883 women from the three major ethnic groups in Malaysia and Singapore i.e. Chinese, Malays and Indians. Women of other ethnic groups (n=175) were excluded as they comprised highly heterogeneous groups.

Study variables

The determinant of interest was ethnicity (Chinese, Malay, Indian), and the outcome was death from all causes. Data on patient characteristics included age at diagnosis, and centre of treatment (NUH, UMMC). Variables on disease characteristics included stage (categorized as stage 0, stage I, stage II, stage III, stage IV and unknown, according to the 5th edition of TNM American Joint Committee on Cancer [AJCC] system if diagnosed before January 1st 2003, and according to the 6th edition of AJCC if diagnosed after this date), tumor size (0.1-2.0 cm, 2.1-5.0 cm, >5.0 cm, unknown), lymph node (LN) involvement (no nodes, 1-3 nodes, 4-9 nodes, >=10 nodes, unknown), estrogen receptor (ER) status / progesterone receptor (PR) status (positive [when > 10% of tumor cells stained positive during immunohistochemical testing], negative, unknown), and tumor grade (Scarff-Bloom-Richardson classification; grade 1, grade 2, grade 3, unknown). Loco-regional treatment was classified as no loco-regional treatment, complete loco-regional treatment (i.e. mastectomy, or breast conserving surgery [BCS] followed by radiotherapy), incomplete treatment (i.e. BCS only, or radiotherapy only), or unknown treatment. Administration of chemotherapy, and hormone therapy were categorized as yes, no, or unknown.

Follow-up and outcome assessment

In both centers, patients were monitored via scheduled appointments in the specialist breast clinics. Data on mortality were obtained from the hospitals' medical records, as well as active follow-up through the next-of-kin of patients. In addition, vital status was verified through direct linkage with the National Registration Department in Malaysia. Patients were followed from date of diagnosis until death or date of last contact whichever came first. In this hospital based cancer registry, causes of death, as well as data on local or systemic recurrences were not available to a large extent.

Statistical analysis

All categorical variables were described by proportions and compared using the Chi square test. Continuous variables were expressed in medians and compared using the Kruskal Wallis test. Overall survival was estimated using Kaplan-Meier analyses and compared by log-rank test.

To understand the association between tumor biology and ethnicity, we analyzed patients with invasive breast cancer and surgically confirmed tumor size and lymph node status (N= 2,382). Patients were grouped according to tumor size (i.e. < 2cm, 2 to 5cm, and > 5cm), and within each category, logistic regression analysis was used to determine the association between lymph node involvement (outcome) and ethnicity (predictor). This model was then adjusted for tumor size (continuous), tumor grade, ER status and PR status.

Since patient accrual spanned over a long period of time (1990-2007), time dependent covariates (age, calendar time) were introduced in the analysis.[10] Cox regression analysis was

performed to estimate the relative risk for all-cause mortality expressed as hazard ratio [HR] between women of different ethnicities. Time at entry was age at diagnosis of breast cancer, and exit time was age at death (from all causes), or age at last contact. All analyses were stratified by center to control for center-related differences, and also by TNM stage. This model was further adjusted with tumor size, lymph node involvement, estrogen and progesterone receptor status, tumor grade, loco-regional therapy, chemotherapy, hormone therapy, and year of diagnosis.

Two-tailed *p*-values below 0.05 and HRs with 95%CI which did not include 1.00 were considered as statistically significant. All analyses were performed using SAS version 9·1 (SAS Institute Inc, Cary, NC).

Results

Demographics

In this hospital based cohort of 3,883 multi-ethnic Asian women with breast cancer, there were 2,930 Chinese (75%), 624 Malays (16%) and 329 Indians (9%). Median age at diagnosis was 49 years (Table 1). Malay patients were significantly younger at diagnosis (median=46 years) than Chinese (50 years) and Indian (52 years) women; $p<0{\cdot}001$.

Stage and tumor characteristics

Malay women were more likely to present with advanced stages (stage III or IV), and with larger tumors than the Chinese and Indians (35mm vs 25mm vs 30mm, respectively; $p<0{\cdot}001$). Seventeen percent of Malay women were diagnosed with distant metastases (TNM stage IV) at presentation compared to 9% among Chinese and Indian women (Table 1). Chinese women were more likely than women of other ethnicities to present with early stage disease (*in situ* or stage I) and were more likely to exhibit favorable tumor characteristics such as ER positivity (p=0·01), PR positivity (p<0·001) or low grade tumors (p<0·001).

Within the subgroup of tumors < 2cm, Malay patients were significantly more likely to have lymph node involvement compared to the Chinese and Indian women with breast cancer (45% versus 25.2% versus 19.0%, respectively; p=0.005) (Table 2). Following adjustment, Malay ethnicity was significantly associated with an increased risk (adjusted OR 1.78, 95% CI: 1.09-2.91) of axillary lymph node metastasis. In tumours measuring 2-5 cm, Malay patients were also more likely to have lymph node involvement compared to the Chinese, though the association was attenuated (adjusted OR: 1.37; 95%CI: 1.01-1.85). In both of the above categories, Indian ethnicity was not associated with lymph node involvement compared to the Chinese women. In tumors > 5 cm, there was no significant association between lymph node status and ethnicity.

Treatment

Malay women were least likely to receive complete loco-regional treatment (Table 1). Within the subgroup of women who underwent breast surgery, a higher proportion of Malay women underwent breast conserving surgery compared to Chinese or Indian women (37% vs 28% vs

Table 1. *Distribution of Patient Profile, Tumor Characteristics and Treatment According to Ethnicity in 3,883 Southeast Asian Women with Breast Cancer*

	Total *N*=3 883 N (%) [a]	Chinese *N*= 2 930 n (%) [a]	Malay *N*=624 n (%) [a]	Indian *N*=329 n (%) [a]	*P* value [b]
Median age at diagnosis, years	49	50	46	52	<0.001
Center					<0.001
NUH, Singapore	2 335 (100)	1 947 (83)	262 (11)	126 (5)	
UMMC, Malaysia	1 455 (100)	910 (63)	344 (24)	201 (14)	
TNM Stage					<0.001
Stage 0	274 (7)	248 (9)	12 (2)	14 (4)	
Stage I	835 (22)	685 (24)	84 (14)	66 (21)	
Stage II	1 663 (45)	1 237 (44)	269 (44)	157 (49)	
Stage III	586 (16)	390 (14)	140 (23)	56 (17)	
Stage IV	377 (10)	247 (9)	102 (17)	28 (9)	
Unknown	148	123	17	8	
Median tumor size, mm [c]	26	25	35	30	<0.001
Lymph node involvement					<0.001
No nodes	2 162 (57)	1 694 (59)	295 (49)	173 (53)	
1-3 nodes	994 (26)	731 (26)	169 (28)	94 (29)	
4-9 nodes	409 (11)	280 (10)	90 (15)	39 (12)	
>=10 nodes	225 (6)	152 (5)	52 (8)	21 (6)	
Unknown	93	73	18	2	
Estrogen receptor status					0·01
Positive	1 638 (57)	1 275 (59)	247 (53)	116 (48)	
Negative	1 236 (43)	895 (41)	216 (47)	125 (52)	
Unknown	1 009	760	161	88	
Progesterone receptor status					<0.001
Positive	1 239 (54)	983 (55)	180 (53)	76 (49)	
Negative	1 049 (46)	814 (45)	157 (47)	78 (51)	
Unknown	1 595	1 133	287	175	
Tumor grade					<0.001
Good differentiation	368 (13)	315 (15)	35 (8)	18 (8)	
Moderate differentiation	1 294 (47)	988 (47)	201 (47)	105 (47)	
Poor differentiation	1 093 (40)	802 (38)	189 (45)	102 (45)	
Unknown	1 128	825	199	104	
Loco-regional therapy [d]					<0.001
Complete treatment	3 079 (92)	2 393 (94)	419 (83)	267 (91)	
Incomplete treatment	146 (4)	116 (5)	20 (4)	10 (3)	
None	30 (4)	8 (1)	20 (13)	2 (6)	
Unknown	103	43	46	14	
Chemotherapy					<0.001
Yes	2 064 (53)	1 481 (51)	397 (64)	186 (57)	
No	1 648 (47)	1 356 (49)	168 (36)	124 (43)	
Unknown	171	93	59	19	
Hormone therapy					<0.001
Yes	2 224 (57)	1 711 (58)	319 (51)	194 (59)	
No	1 496 (43)	1 137 (42)	239 (49)	120 (41)	
Unknown	163	82	66	15	

[a] Column percentage is presented except for center where row percentage is presented
[b] Compared using χ^2 test for categorical variable and Kruskal Wallis test for continuous variable
[c] Only available in 2852 patients
[d] Only includes patients with TNM stage 0 to stage III breast cancer. Complete treatment consists of mastectomy or breast conserving surgery followed by radiotherapy. Incomplete treatment includes breast conserving surgery only or radiotherapy only.

Table 2. *Association between Ethnic Groups and Lymph Node Involvement by Tumor Size in 2,382 Asian Women with Breast Cancer* [a]

	Ethnicity			P value [b]
	Chinese	Malay	Indian	
Tumor size less than 2 cm (N = 672)				0.005
No nodal involvement, N (%)	409 (74.8)	49 (59.0)	34 (81.0)	
Lymph node involvement, N (%)	138 (25.2)	34 (41.0)	8 (19.0)	
Crude OR for lymph node involvement	1.00	2.06	0.70	
95% confidence interval for crude OR		(1.28-3.32)	(0.32-1.54)	
Adjusted OR for lymph node involvement [c]	1.00	1.78	0.65	
95% confidence interval for adjusted OR		(1.09-2.91)	(0.29-1.47)	
Tumor size 2 to 5 cm (N = 1359)				0.028
No nodal involvement, N (%)	520 (52.2)	95 (42.8)	66 (46.8)	
Lymph node involvement, N (%)	476 (47.8)	127 (57.2)	75 (53.2)	
Crude OR for lymph node involvement	1.00	1.46	1.28	
95% confidence interval for crude OR		(1.09-1.96)	(0.89-1.85)	
Adjusted OR for lymph node involvement [c]	1.00	1.37	1.31	
95% confidence interval for adjusted OR		(1.01-1.85)	(0.91-1.89)	
Tumor size more than 5 cm (N = 351)				0.217
No nodal involvement, N (%)	69 (30.7)	26 (31.7)	8 (18.2)	
Lymph node involvement, N (%)	156 (69.3)	56 (68.3)	36 (81.8)	
Crude OR for lymph node involvement	1.00	0.95	1.99	
95% confidence interval for crude OR		(0.55-1.64)	(0.88-4.51)	
Adjusted OR for lymph node involvement [c]	1.00	1.03	2.15	
95% confidence interval for adjusted OR		(0.58-1.81)	(0.93-4.96)	

OR = Odds ratio

[a] Only including patients with invasive breast cancer and surgically confirmed tumor size and lymph node status (N= 2382).

[b] Using Chi Square test

[c] Logistic regression model adjusted for tumor size (continuous), tumor grade, estrogen receptor status, and progesterone receptor status

31%, respectively; p<0.001). Malay women were also more likely to receive chemotherapy across all stages, compared to women from other ethnic groups (Table 1).

Survival

After 16,415 person-years of follow-up, a total of 1140 deaths from all causes had occurred. While the overall survival of the Chinese (5-year OS: 72.4%; 95%CI: 70.4%-74.4%) and Indian patients (5-year OS: 65.3%; 95%CI: 59.4%-71.1%) did not differ significantly, Malay women experienced a significantly lower survival (5-year OS: 47.4%; 95%CI: 42.7%-52.1%). Among patients with early breast cancer (stage 0-stage II), 5-year overall survival was highest among the Chinese (86.3%; 95%CI: 84.3%-88.3%), followed by the Indians (74.9%; 95%CI: 68.6%-

81.2%) and the Malays (68.0%; 95%CI: 62.1%-73.9%) (Figure 1 panel A). In the more advanced stages (stage III & IV), the survival of the Chinese and Indian patients did not differ significantly (32.7%; 95%CI: 28.2%-37.2% and 41.7%; 95%CI: 30.1%-53.3%, respectively), whereas the Malays had significantly lower survival (20.8%; 95%CI: 14.7%-26.9%) (Figure 1 panel B).

Breast cancer patients of Malay ethnicity had a more than two fold increase in risk of death from all causes as compared to Chinese women (crude HR: 2.26; 95%CI: 2.06-2.48). Indian ethnicity was associated with 23% increased risk of death (crude HR: 1.23; 95%CI: 1.10-1.39) (Table 3). When the model was stratified to center, there was only a marginal change in this association. Risks of mortality associated with Malay and Indian ethnicity, compared to the Chinese were slightly attenuated when we further adjusted for stage at presentation and tumor profile (multivariable HR: 1.84; 95%CI: 1.67-2.04, and HR: 1.16; 95%CI: 1.02-1.32, respectively). Following subsequent adjustment for treatment, Malay ethnicity continued to be an independent predictor of overall survival with a 60% increased risk of all-cause mortality (multivariable HR: 1.60; 95%CI: 1.44-1.77), compared to Chinese ethnicity. Indian ethnicity was also independently associated with a modest increase in mortality risk compared to Chinese women; multivariable HR: 1.16; 95%CI: 1.03-1.32 (Table 3).

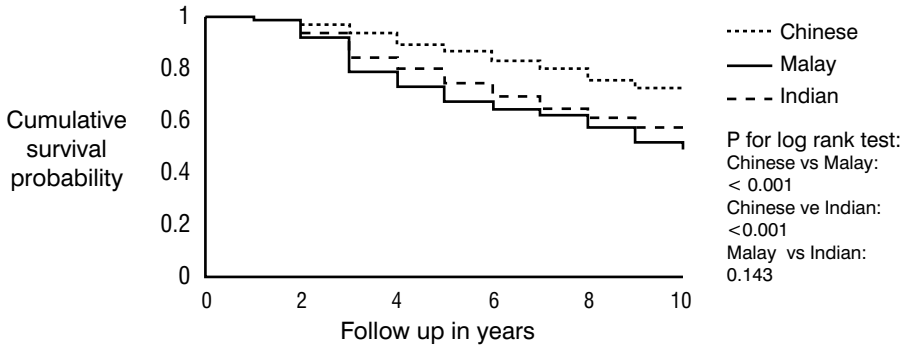

Figure 1A. *Cumulative overall survival by ethnicity in South East Asian women with early breast cancer (TNM stage 0 to II).*

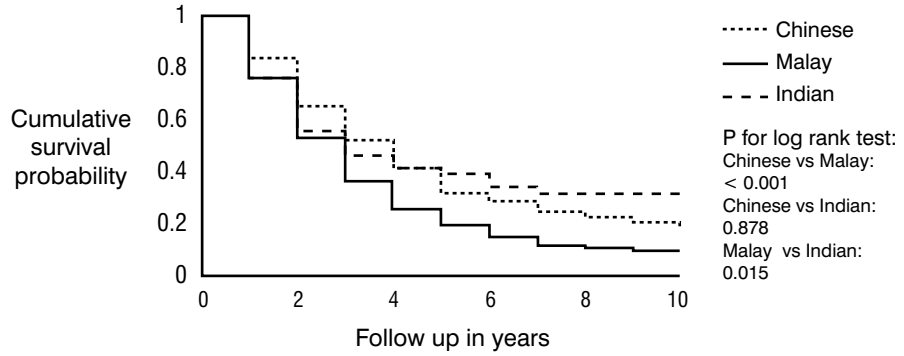

Figure 1B. *Cumulative overall survival in South East Asian women with advanced breast cancer (TNM stage III to IV).*

As age at onset of breast cancer was substantially lower in Malay women, we performed a subgroup analysis within very young patients with breast cancer (<35 years at diagnosis, n= 228) (Table 4). Here, Malay and Indian ethnicities were also found to be significant independent predictors of survival compared to Chinese ethnicity (HR: 3.50; 95%CI: 2.06-5.95, and HR: 3.26; 95%CI: 1.55-6.88, respectively, adjusted for patient / tumor profile and treatment). Possible effect modification by age was further assessed by including the interaction terms 'ethnic groups multiplied by age at diagnosis in 3 categories (<35 years, 35-64.9 years, 65 and above)' into the model; *p* for likelihood ratio test was 0.12 (not significant).

Discussion

With this study we have shown marked ethnic differences in disease presentation, treatment patterns, and survival of breast cancer patients in South East Asia. Women of Malay ethnicity presented at more advanced stages of breast cancer than other races. They also seem to have a more aggressive tumor biology compared to the Chinese. Furthermore, Malay and to a lesser extent Indian ethnicity is associated with higher risk of death following breast cancer, even after accounting for patient profile, cancer stage, tumor characteristics and treatment.

The relationship between ethnicity and breast cancer survival seems complex and a variety of factors have been proposed to explain the ethnic disparities in breast cancer survival.[4] These factors, which include ethnic differences in socio-economic status and cultural values, tumor biology, response to treatment, and lifestyle, are discussed below.

Table 3. *Association between Ethnicity and All Cause Mortality after Diagnosis with Breast Cancer in 3,883 Southeast Asian Women*

	Total	Chinese	Malays	Indians
No of patients	3 883	2 930	624	329
No of deaths	1 440	716	297	127
Hazard Ratio (95%CI)		1.00	2.26 (2.06-2.48)*	1.23 (1.10-1.39)*
Hazard Ratio (95%CI) [a]		1.00	2.31 (2.11-2.53)*	1.32 (1.17-1.49)*
Hazard Ratio (95%CI) [b]		1.00	1·84 (1.67-2.04)*	1.16 (1.02-1.32)*
Hazard Ratio (95%CI) [c]		1.00	1·60 (1.44-1.77)*	1.16 (1.03-1.32)*

* Statistically significant

[a] Cox regression model using attained age as time variable, stratified to center

[b] Cox regression model using attained age as time variable, stratified to center and TNM stage, and adjusted for tumor size, lymph node involvement, estrogen receptor status, progesterone receptor status, tumor grade

[c] Cox regression model using attained age as time variable, stratified to center and TNM stage, and adjusted for tumor size, lymph node involvement, estrogen receptor status, progesterone receptor status, tumor grade, loco-regional therapy, chemotherapy, hormone therapy, and year of diagnosis

Table 4. *Association between Ethnicity and All Cause Mortality after Diagnosis with Breast Cancer in 3883 South East Asian Women by Age Categories*

Age groups	Total	Chinese	Malays	Indians
≤35 years				
No. of patients	228	155	60	13
Hazard ratio		1.00	3·50	3·26
(95% CI)[a]			(2·06-5·95)*	(1·55-6·88)*
35-64.9 years				
No. of patients	3162	2382	514	266
Hazard ratio		1.00	1·54	1·20
(95% CI)[a]			(1·37-1·74)*	(1·04-1·40)*
>=65 years				
No. of patients	493	393	50	50
Hazard ratio		1.00	2·83	1·25
(95% CI)[a]			(2·04-3·92)*	(0·90-1·73)

* Statistically significant

[a] Cox regression model using attained age as time variable, adjusted for tumor size, lymph node involvement, estrogen receptor status, progesterone receptor status, tumor grade, loco-regional therapy, chemotherapy, hormone therapy, center and year of diagnosis.

Ethnic differences in socio-economic status and cultural values

Ethnicity has been traditionally argued as a proxy factor of socio-economic status,[11] whereby a low socio-economic status has been linked to late stage at diagnosis with cancer,[12] unequal access to optimal treatment,[12] and poorer treatment adherence.[13] African American women, who form the majority of those living below the poverty line in United States,[12] were indeed found to present with more advanced breast cancer,[12] receive less aggressive adjuvant therapy,[13] and were more likely to prematurely terminate chemotherapy.[14] Furthermore, misclassification of stage at diagnosis i.e. under staging may be more pronounced in women from lower socio-economic group as they are less likely to undergo extensive diagnostic work-up. In our population, the Chinese have the highest household income and are most likely to receive tertiary education, the Malays have lowest income and education status, whereas the Indians fall in between.[15,16] In the current study, Malay women presented at later stages of cancer, were more likely to undergo breast conserving surgery, and less likely to receive adequate loco-regional or hormonal therapy. Although socioeconomic status is a strong determinant of outcome in many chronic diseases, it is nevertheless unable to fully explain ethnic disparities in survival.[17,18]

In addition to socio-economic differences, we also see religious differences in our three ethnic groups, whereby the Malays are mostly Muslims, the Chinese are either Buddhists or Christians, and the Indians are mainly Hindus.[15] As religion and culture is intertwined, it is likely that psychosocial and cultural factors such as folk beliefs, fundamentalist religious beliefs, relationship with men, perceived risk, and beliefs in various treatments for breast cancer, may have an impact on stage at presentation of breast cancer.[18] Corroborating these, the emerging themes from a study in Malaysian women who presented at late stage breast cancer were cancer

fatalism (i.e. the belief that death is inevitable when cancer is present), and use of alternative therapy.[19] Besides influencing stage at diagnosis, the above factors may also influence treatment acceptance and adherence.[20]

Ethnic differences in tumor biology

Ethnic variations in tumor biology have been reported, whereby certain ethnic groups are more likely to have hormone receptor negative tumors, HER2 over-expression, basal-like breast tumor types, HER2 positive breast cancer, or high grade tumors.[21] A recent study in California had found that women of Asian ethnicities were independently associated with higher risk of triple negative breast cancers compared to non Hispanic whites.[22] Our results suggest that Malay patients may have a more aggressive tumor biology compared to other races, as evidenced by their higher risk of axillary lymph node involvement with similar tumor size. Moreover, Malay and Indian women were more likely to have unfavorable tumor characteristics such as ER/PR negative and high grade tumors. Adjustment for these factors reduced the excess mortality risk of Malay and Indian women, but did not eliminate it completely.

Ethnic differences in response to treatment

A recent review looking at differences in toxicity and clinical outcome following treatment with anticancer drugs had highlighted that there may be ethnic differences in tolerability and response to hormonal treatment and cytotoxic chemotherapy in breast cancer.[23] The activities of the CYP P450 group of enzymes which are responsible in metabolizing anti-hormonal drugs seem to vary between ethnic groups, due to underlying differences in functional polymorphisms of these patients.[23] This suggests that anti-hormonal drugs such as tamoxifen may be more effective in certain ethnic groups. Furthermore, genotype-phenotype associations have been suggested based on studies among Chinese, Malay and Indian patients receiving doxorubicin,[24,25] whereby the Chinese may be predisposed to higher concentrations of doxorubicin associated with higher frequencies of polymorphism within the SLC22A16 gene,[24] or CBR3 gene[25] compared to other races. Based on the above findings, it is conceivable that certain anticancer therapies are more effective in the Chinese compared to other races.

Ethnic differences in lifestyle

Lifestyle factors, such as diet and body weight, are increasingly being recognized as important prognostic factors of breast cancer.[4] Owing to differences in religious and cultural practices, lifestyle profiles do differ substantially between the ethnic groups in South East Asia. In terms of diet, Malay women, for instance, are less likely to consume alcohol, where as the Chinese women have a high intake of soy and consume the lowest amount of dietary fat.[26] A study conducted in China have suggested that dietary practices such as increased soy intake are associated with decreased risk of death and recurrence among breast cancer survivors.[27]

We also see important differences in prevalence of overweight and obesity in our three ethnic groups. Obesity is more common in Malay and Indian women, where as the Chinese have the lowest body mass index.[28] Obesity has been linked to late stage at presentation of breast cancer

as well as substandard diagnostic work-up.[29] In addition, body weight and weight gain after the diagnosis of breast cancer have also been implicated in prognosis of breast cancer,[30] which might explain some of the excess mortality we see among Malay and Indian women.

To our knowledge, this is the first large study to shed light on the impact of ethnicity on the survival of women following breast cancer in the Asian context. Strengths of our study include detailed information on tumor characteristics and treatment profile which are important prognostic determinants of survival related to breast cancer. Nevertheless, information on HER2 status was lacking, and we are unsure of its influence on the study findings. We also did not have adequate information on the causes of death of patients making it impossible to study breast cancer specific survival.

Our study consists of a hospital-based cohort of breast cancer patients, who are not completely representative of the general Malaysian and Singaporean population. This is largely attributed to the catchment area that the hospitals are serving. Although information on socioeconomic status was not available in this study, it should be noted that UMMC in Malaysia caters to a predominantly middle class urban population owing to its location, making patients relatively homogenous from a socioeconomic perspective. To account for disparity in socioeconomic status between Singapore (high income nation) and Malaysia (upper middle-income nation), we had stratified our analysis by center, which only marginally changed our estimates.

We acknowledge that ethnic differences in co-morbidity and life expectancy may partly explain the observed ethnic disparities in survival. Chinese women in South East Asia have the highest life expectancy at birth (e.g. 77.1 years [Singapore, 1990]) whereas the Malay (73.6 years) and Indian (72.1 years) women have a slightly lower life expectancy.[31,32] Nevertheless, these differences in life expectancy are unlikely to completely explain our results.

Our findings highlight the problem of late presentation among the Malays. As psychosocial and cultural factors as well as socioeconomic status may contribute to delayed presentation,[18,19] culturally-sensitive programs and oncology practices are needed to improve breast health literacy in our region. These programs should aim to encourage early detection of breast cancer especially among the Malay and Indian women via participation in cancer screening activities such as self breast examination, clinical breast examination, mammographic screening etc.

Our results further underline the need for registration of ethnic background in the hospital records and cancer registries of multi-ethnic populations, as this factor should be taken into account as an independent prognostic factor in planning individual patient management, and in clinical studies. More research is needed to investigate the tumor biology in Asian women, to identify genetic variants associated with response to anticancer therapy and to investigate the impact of various cultural and lifestyle determinants on breast cancer survival in the Asian setting.

In conclusion, Malay ethnicity, and to a lesser extent Indian ethnicities are significantly and independently associated with poorer survival following the diagnosis of breast cancer. The underlying reasons for this association are unclear but maybe explained by variations in tumor biology, psychosocial and cultural beliefs, susceptibility to anticancer treatment and lifestyle after diagnosis of breast cancer.

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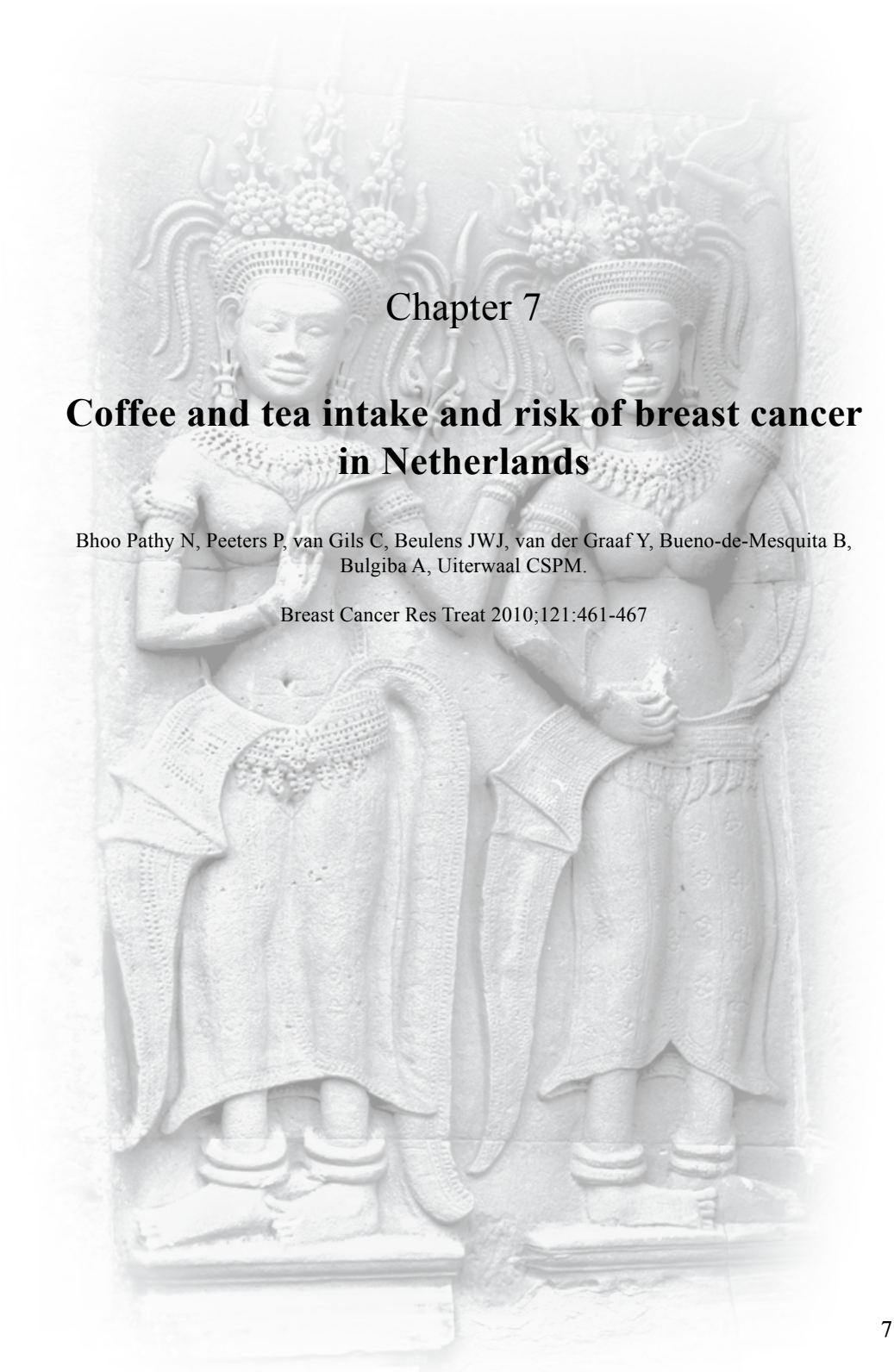

Chapter 7

Coffee and tea intake and risk of breast cancer in Netherlands

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Abstract

Background

Known risk factors account for about 10-15% of breast cancer incidence suggesting that lifestyle exposures are crucial in its etiology. Previous epidemiological studies on the association between coffee and tea consumption and breast cancer risk have been inconsistent.

Methods

We investigated the association of coffee and tea consumption with the risk of breast cancer among women in EPIC-NL cohort, a population-based prospective cohort in Netherlands with 27 323 participants. Exposure was measured by a validated food frequency questionnaire and outcome verified by direct linkage with the Netherlands Cancer Registry.

Results

A total of 681 invasive primary breast cancers were diagnosed in 9.6 years of follow-up. Coffee intake increased the risk of breast cancer by more than twofold as compared to non consumers (HR; 2.25, 95% CI; 1.30-3.90). This association did not hold after multivariate adjustment which resulted in a HR of 1.17, 95% CI; 0.65-2.12. After adjustment to breast cancer risk factors and lifestyle, no association was observed between intake of coffee or tea and risk of breast cancer across all categories of intake. These results were also not altered by body mass index.

Conclusion

Coffee and tea consumption does not seem to be related to the risk of breast cancer in women.

Introduction

Breast cancer is the most common type of female malignancy which results in significant morbidity and mortality across the globe. Currently known risk factors in conjunction only explain some 10-15% of breast cancer incidence. Therefore, lifestyle and environmental exposures may be crucial in the etiology of breast cancer as suggested by international variation in breast cancer incidences and evidence from studies of migrants.[1]

Coffee and tea are the world's most popular beverages, with The Netherlands being one of the top ten countries in the world for coffee consumption per capita. In 2007, the World Cancer Research Fund (WCRF) concluded in its report that for the association between premenopausal and postmenopausal breast cancer with dietary exposures like coffee and tea intake, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached.[2] While some case-control studies showed no association between coffee and tea intake and the risk of breast cancer,[3-7] other studies have shown a protective effect[8-10] or a harmful effect.[11] Meanwhile, data from large prospective studies are limited with most reporting no association between coffee and/or tea and risk of breast cancer[12-18] except for a Norwegian study which showed a significant inverse association among lean women and a non significant positive effect among the obese.[19]

Association between coffee or tea consumption and the risk of breast cancer is biologically plausible since these beverages are a complex mixture of chemicals e.g. caffeine and polyphenolic compounds such as flavonoids and lignans.[20] The hypothesis that caffeine may increase the risk of breast cancer was coined in 1970s and 1980s. Caffeine was found to be carcinogenic in animal models[21] possibly caused by an inhibitory effect of caffeine on the repair of UV damaged DNA, and an enhancing effect on cytotoxic and mutagenic activities of alkylating agents.[22] On the other hand, flavonoids and lignans are members of a diverse group called phytoestrogens which have similar structural properties with estradiol and may likewise act as estrogen antagonists.[23] Phytoestrogens have also been shown in vitro to exhibit a plethora of different anti-cancer effects, including inhibiting proliferation of malignant cells.[24] Lignans may also protect against breast cancer by modulation of local estradiol synthesis by inhibiting 17beta-HSD type 1 enzyme which is necessary for estrogen synthesis.[25]

Therefore, we investigated the association of coffee and tea consumption with the risk of breast cancer within the EPIC-NL cohort which is a large population-based prospective cohort in Netherlands, while enabling solid confounder adjustment.

Methods

Study population and assessment

The EPIC-NL study consists of the Prospect and MORGEN cohorts that cover the Dutch contribution to the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort.[26] In brief, Prospect is a prospective cohort study of women aged 49-70 who participated in the breast cancer screening between 1993 and 1997.[27] The MORGEN-cohort consists of men

and women aged 20-59 years recruited from three Dutch cities (Amsterdam, Doetinchem and Maastricht)[28] between 1993 and 1997. There are 40 011 participants in the EPIC NL cohort.

At baseline, a general questionnaire containing questions on demographic characteristics and the risk factors and presence of chronic diseases were completed, together with a food frequency questionnaire. Although the general questionnaires from both cohorts were not identical, very similar information was reported. Coding of this information was standardized and merged into one uniform database.

The present analysis was restricted to only women, those with no prior history of cancer as well as those with complete information on coffee and tea intake. Initially, 29 751 women were available out of which 27 439 did not have a prior history of cancer but 116 of them had to be excluded due to incomplete coffee or tea data leaving 27 323 women for analysis. Those with prior history of cancer were excluded since they were likely to have changed their lifestyle habits, while the previous lifestyle habits may still have a large impact on subsequent second cancer risk.

Exposure assessment

Daily food intake was assessed using a validated food frequency questionnaire (FFQ) including questions on the usual frequency consumption of 77 main food items during the year preceding enrolment. Overall the questionnaire allows the estimation of the average daily consumption of 178 food types. It was validated against 12 24-hour recalls before the start of the study among 121 men and women.[29,30] This FFQ was used to assess the daily amount of coffee and tea consumption during the preceding year to enrolment of the study. Participants were asked how many cups (250 mls) of coffee and glasses of tea on average they consumed on average per day/ per week/ per month/ per year. Data of the validation study by Ocke et al[29] were used to estimate reliability of the coffee and tea consumption assessment. A Spearman correlation coefficient of 0.74 for coffee consumption and 0.87 for tea consumption was observed between the FFQ and 12 24-hour dietary recalls. For the present analysis, the amount of coffee as well as tea consumption was divided into six categories, 0 cup, 0.1-1.0 cups (reference group), 1.1-2.0 cups, 2.1-3.0 cups, 3.1-5.0 cups and >5.0 cups per day. Since individuals who consumed coffee often also consumed tea and vice versa, we decided to combine coffee and tea intake for further analysis. The number of cups of coffee and tea reported by an individual was combined into 7 categories i.e. group-0 (no tea and coffee), 1 (tea only), 2 (coffee only), 3 (moderate tea and moderate coffee intake), 4 (moderate tea and high coffee intake), 5 (high tea and moderate coffee intake), 6 (high tea and coffee intake) with moderate intake referring to 0.1 – 3.0 cups per day while intake of >3 cups per day was considered as high.

Even though we had information on decaffeinated coffee, it was not separately analyzed since the numbers were too small for a meaningful analysis.

Ascertainment of breast cancer cases and follow-up of the cohort

The outcome of interest in this study was the occurrence of first, primary invasive breast cancer. Data on diagnosis of breast cancer was obtained from the Netherlands Cancer Registry, which

holds a standardized computerized register of cancer patients. This database was directly linked to the EPIC-NL cohort using patient's names after obtaining their consents. Information on vital status and participant movements were made available through linkage with the municipal administration registries. The Morgen cohort was censored on 1st January, 2004 while the Prospect cohort was censored on 1st January, 2007.

Statistical analysis

Cox proportional hazards analysis was used to examine the association between coffee and tea consumption and the incidence of breast cancer. Crude hazard ratios (HR) with 95% confidence intervals were calculated for each coffee or tea intake category with the moderate consumers as reference. The HRs were further stratified to two BMI categories which has been reported an effect modifier.[19] A cut off point of 25 kg/m² was used to distinguish between normal and overweight women based on the WHO criteria. No separate analysis was carried out for premenopausal breast cancer subtypes as the number of premenopausal breast cancer cases was too small. Assessment of the estrogen receptor (ER) and progesterone receptor (PR) status was done in about 330 patients with breast cancer and we analyzed the ER+/PR+ tumours separately. However, the numbers of ER+/PR- and ER-/PR- tumours were relatively small to allow for further subgroup analysis.

Coffee and tea consumption were expected to be strongly associated with many lifestyle characteristics that could confound associations with breast cancer. In order to optimize confounder adjustment and avoid large Cox models, we first calculated propensity scores.[31-33] We used a logistic regression model to estimate the probability of drinking coffee for each participant as predicted by their age at recruitment, smoking status (never, past, current), educational status (low, intermediate, high), BMI, alcohol intake, energy intake, fat and fiber intake adjusted for energy (using nutrient residual model[34]), tea intake, physical activity level (inactive, moderately inactive, moderately active, active), ever use of oral contraceptives (yes, no), presence of hypercholesterolemia (yes, no), cohort (Prospect, Morgen), family history of breast cancer (yes, no), age at menarche, and parity. We also calculated the predicted probability of drinking tea for each participant using a similar logistic regression model, which instead adjusted for coffee intake. The resulting propensity score (i.e. predicted probability) distributions for all participants were divided into quintiles and sufficient overlap of lifestyle characteristics by coffee and tea intake (yes/no) was evaluated as a pre requisite in propensity score modeling.[31] These propensity scores were considered as proxy for lifestyle of participants and subsequently added into the Cox regression model for adjustment of confounders.

The follow up time was calculated from the date of enrolment into the study to the date of breast cancer diagnosis. Participants who during follow-up developed other type of cancers were censored on the date of diagnosis. Other participants were censored upon loss to follow up, at death or at the end of follow up. The Cox proportional hazards assumption was examined by visually inspecting log-minus-log plots with no deviations detected.

Since using propensity scores alone would not help in identifying which covariates contributed most as confounders in this study, we proceeded to identify such important covariates

***Table 1**. Relation of Coffee and Tea Consumption with Selected Demographic, Lifestyle and Breast Cancer Risk Characteristics in 27 323 Participants*

	Daily coffee consumption					
	0 cup	0.1-1.0cups	1.1-2.0 cups	2.1-3.0 cups	3.1-5.0 cups	>5 cups
No of participants	1368	4667	3709	3896	7782	5901
Age (years)	50.1	55.0	54.5	54.6	54.6	52.7
High educational level (% [n])	21.8 (297)	18.7 (870)	23.3 (863)	22.1 (860)	16.6 (1285)	13.4 (791)
Tea intake (cups/day)	5.0	3.0	3.0	2.0	2.0	1.0
Soft drink intake (cups/day)	0.077	0.066	0.067	0.069	0.065	0.072
BMI (kg/m²)	24.9	25.1	25.0	25.0	25.0	26.0
Low physical activity (% [n])	10.4 (142)	9.8 (458)	8.4 (310)	7.7 (299)	6.9 (534)	9.0 (529)
Current smoker (% [n])	17.8 (244)	20.9 (974)	20.9 (774)	23.4 (911)	26.4 (2052)	44.4 (2616)
Alcohol intake (g/week)	2.2	14.2	24.1	29.0	29.7	26.2
Total energy intake (kcal/day)	1747	1730	1806	1818	1830	1857
Saturated fat intake (g/day)*	31.5	32.0	32.6	33.0	33.6	34.4
Fiber intake (g/day)*	22.1	23.6	23.6	23.5	23.6	23.6
Ever use of oral contraceptives (% [n])	81.2 (1109)	72.2 (3360)	74.2 (2746)	72.9 (2838)	70.6 (5485)	74.5 (4388)
Breast cancer in 1st degree relative (% [n])	7.1 (96)	9.9 (458)	9.5 (350)	10.2 (393)	11.3 (871)	10.1 (588)
Post menopausal (% [n])	33.8 (462)	64.5 (3009)	65.6 (2433)	67.4 (2626)	73.3 (5708)	67.0 (3953)
Ever use of post menopausal hormone (% [n])	12.7 (126)	20.3 (840)	21.6 (716)	21.9 (775)	21.2 (1531)	20.0 (1095)
Age at menarche (years)	13	13	13	13	13	13
Parity (number of children)	2	2	2	2	2	2

All continuous variables are expressed as median while the categorical variables are expressed as percentages .

* Energy adjusted values

	Daily tea consumption					
	0 cup	0.1-1.0cups	1.1-2.0 cups	2.1-3.0 cups	3.1-5.0 cups	>5 cups
No of participants	2281	7462	5707	3336	5268	3269
Age (years)	53.1	52.3	53.8	54.9	56.4	54.8
High educational level (% [n])	7.4 (168)	14.8 (1105)	16.1 (916)	19.7 (656)	22.3 (1171)	29.1 (950)
Coffee intake (cups/day)	4.5	3.6	3.6	2.7	2.7	1.5
Soft drinks intake (cups/day)	0.077	0.092	0.077	0.060	0.053	0.040
BMI (kg/m²)	26.0	25.5	25.1	25.0	25.0	24.9
Low physical activity (% [n])	13.6 (311)	9.3 (692)	8.1 (461)	7.4 (248)	6.1 (322)	7.3 (238)
Current smoker (% [n])	50.3 (1144)	36.8 (2742)	26.7 (1524)	20.6 (687)	16.9 (889)	17.9 (585)
Alcohol intake (g/week)	17.0	24.2	23.9	24.4	23.9	21.9
Total energy intake (kcal/day)	1751	1827	1813	1813	1828	1785
Saturated fat intake (g/day)*	34.1	33.7	33.2	33.1	32.9	32.5
Fiber intake (g/day)*	22.8	22.8	23.3	23.9	24.3	24.6
Ever use of oral contraceptives (% [n])	69.2 (1577)	77.6 (5777)	73.2 (4175)	71.4 (2375)	69.2 (3640)	72.9 (2382)
Breast cancer in 1st degree relative (% [n])	10.1 (228)	9.5 (699)	10.9 (618)	9.8 (324)	10.6 (553)	10.3 (334)
Post menopausal (% [n])	67.3 (1536)	58.7 (4381)	67.6 (3856)	69.4 (2316)	74.2 (3907)	67.1 (2195)
Ever use of post menopausal hormones (% [n])	18.1 (384)	20.1 (1323)	21.7 (1128)	20.9 (634)	20.5 (994)	21.3 (620)
Age at menarche (years)	13	13	13	13	13	13
Parity (number of children)	2	2	2	2	2	2

All continuous variables are expressed as median while the categorical variables are expressed as percentages.
* Energy adjusted values

by dropping them one at a time and examining the changes in adjusted HRs as compared to the crude value. We did this for age, family history of breast cancer, age at menarche, parity, smoking, physical activity, education and dietary exposures (combined intake of alcohol, total energy, saturated fat, fiber, and coffee for tea mutually).

Two-tailed p-values <0.05 and 95% confidence intervals for HR not including 1 were considered as statistically significant. All statistical analyses were performed using SPSS for Windows version 16.0 (SPSS Inc., Chicago, USA).

Results

During an average of 9.6 years of follow up, a total of 681 incidents of first invasive primary breast cancers were diagnosed among our study cohort of 27 323 women. Out of these, only 53 cases were pre menopausal breast cancers (i.e. diagnosed before the age of 50 years), therefore, making it impossible for further meaningful analysis. The median age of this cohort at recruitment was 52.6 years with an age range of 20 to 70 years. Median coffee intake was 3.1 cups / day and median tea intake was 2 cups / day. Overall, median BMI was 25.0 kg /m² and about 10% of women reported a positive history of breast cancer in a first degree relative. Baseline characteristics of participants according to coffee / tea consumption are shown in Table 1. Many risk factors for breast cancer, including lifestyle characteristics, were associated with coffee and tea intake.

Prior to adjustment, coffee intake increased the risk of breast cancer in consumers by more than twofold as compared to non consumers (crude HR; 2.25, 95% CI; 1.30-3.90). However, following adjustment, this association attenuated and was not significant (adjusted HR; 1.17, 95% CI; 0.65-2.12). Table 2 shows the breast cancer risk across various categories of coffee intake where no significant association was observed in the overall, or BMI specific groups. Restricting the analysis to only post menopausal breast cancer cases (i.e. diagnosed after the age of 50 years) also resulted in similar results despite additionally adjusting for use of postmenopausal hormones (results not shown).

Tea intake was neither associated with risk of breast cancer in the crude analysis nor in the adjusted analysis (Table 3). The results did not change with either stratification to BMI status or restricting analysis to postmenopausal women.

When coffee and tea intakes were combined, the Cox analysis across the different categories did not show any significant association with the risk of breast cancer (results not shown).

Estrogen receptor (ER)/Progesterone receptor (PR) status was assessed in about 48% of breast cancer patients. Among them, 192 were ER+/PR+, 51 were ER+/PR-, and 45 were ER-/PR-. Overall, there was no association between coffee or tea intake and risk of breast cancer among the patients with ER+/PR+ tumour. Adjusted HR for coffee consumers versus non consumers was 1.18, 95% CI; 0.37-3.78, while adjusted HR for tea consumers versus non consumers was 1.35, 95% CI; 0.77-2.39.

Since there was a significant attenuation in risk of breast cancer in relation to coffee consumption following adjustment with the propensity scores, we proceeded to identify which

Table 2. *Coffee Consumption and Risk of Breast Cancer Stratified by BMI Status*

Daily coffee intake	**n**	**0 cup**	**0.1-1.0 cups**	**1.1-2.0 cups**	**2.1-3.0 cups**	**>5 cups**	**>5 cups**
No. of participants	27 323	1368	4667	3709	3896	5901	5901
Total breast cancers							
No. of cases	681	13	110	108	100	152	152
Crude HR		0.47	1.00	1.23	1.00	1.06	1.06
(95%CI)		(0.27-0.84)		(0.94-1.62)	(0.75-1.32)	(0.83-1.37)	(0.83-1.37)
Adjusted HR		0.86	1.00	1.20	0.93	0.94	0.94
(95%CI)†		(0.47-1.59)		(0.90-1.60)	(0.69-1.25)	(0.72-1.24)	(0.72-1.24)
Women with BMI < 25 kg/m²							
No. of breast cancer cases	313	8	44	52	52	62	62
Adjusted HR		1.22	1.00	1.37	1.11	1.09	1.09
(95%CI)†		(0.53-2.80)		(0.88-2.13)	(0.71-1.75)	(0.71-1.68)	(0.71-1.68)
Women with BMI > 25 kg/m²							
No. of breast cancer cases	368	5	66	56	48	90	90
Adjusted HR		0.62	1.00	1.12	0.83	0.84	0.84
(95%CI)†		(0.24-1.57)		(0.76-1.65)	(0.55-1.24)	(0.59-1.20)	(0.59-1.20)

HR – Hazard Ratio CI – Confidence Interval

† Adjusted to propensity score (based on age, smoking status, educational status, BMI, alcohol intake, energy intake, energy adjusted saturated fat intake, energy adjusted fiber intake, tea intake, physical activity level, ever use of oral contraceptives, presence of hypercholesterolemia, family history of breast cancer, age at menarche, parity and cohort)

Table 3. *Tea Consumption and Risk of Breast Cancer Stratified by BMI Status*

Daily tea intake		**0 cup**	**0.1-1.0 cups**	**1.1-2.0 cups**	**2.1-3.0 cups**	**3.1-5.0 cups**	**>5 cups**
No. of participants	27 323	2281	7462	5707	3336	5268	3269
All women							
No. of breast cancer cases	681	53	195	146	83	128	76
Crude HR		0.84	1.00	0.97	0.91	0.87	0.86
(95%CI)		(0.61-1.15)		(0.78-1.21)	(0.70-1.18)	(0.69-1.10)	(0.65-1.13)
Adjusted HR		0.74	1.00	0.93	0.90	0.83	0.83
(95%CI)†		(0.52-1.05)		(0.74-1.17)	(0.68-1.19)	(0.65-1.06)	(0.62-1.11)
Women with BMI < 25 kg/m²							
No. of breast cancer cases	313	21	93	53	41	67	38
Adjusted HR		0.63	1.00	0.72	0.80	0.86	0.68
(95%CI)†		(0.36-1.10)		(0.51-1.03)	(0.53-1.20)	(0.60-1.21)	(0.45-1.05)
Women with BMI > 25 kg/m²							
No. of breast cancer cases	368	32	102	93	42	61	38
Adjusted HR		0.85	1.00	1.13	1.01	0.80	1.03
(95%CI)†		(0.54-1.33)		(0.84-1.54)	(0.69-1.48)	(0.56-1.13)	(0.69-1.54)

HR – Hazard Ratio CI – Confidence Interval

† Adjusted to propensity score (based on age, smoking status, educational status, BMI, alcohol intake, energy intake, energy adjusted saturated fat intake, energy adjusted fiber intake, coffee intake, physical activity level, ever use of oral contraceptives, presence of hypercholesterolemia, family history of breast cancer, age at menarche, parity and cohort

covariate contributed to this effect. We found that dietary exposures in combination contributed most to the change in breast cancer risk among coffee consumers, followed by age, age at menarche and parity. Family history of breast cancer, smoking, alcohol and physical activity did not contribute to the change in risk among the coffee drinkers.

In order to avoid spurious reverse associations, we restricted our analyses to breast cancer cases occurring after 2 years of follow up. It did not materially change the observed HRs (not shown).

Discussion

We found no statistically significant association between coffee and tea consumption with risk of breast cancer. These results were similar for lean and overweight women as well as when restricting analysis to postmenopausal breast cancers.

The strength of our study is its prospective nature, the relatively large sample size involving 27 323 women, as well as solid confounder adjustment which accounted for the risk factors for breast cancer and various lifestyle related variables, summarized to a single propensity score and subsequently adjusted for. Even though most of the previous prospective studies adjusted for multiple confounders mainly age, risk factors of breast cancer, smoking (except in 1 study[16]), and total energy intake, many did not adjust for other important nutritional variables such as fiber intake (except 2 studies[13,16]), saturated fat intake, alcohol intake (except 4 studies[13-16]), or mutually adjusted coffee for tea intake since these beverages are inversely correlated (except 2 studies[13,14]). Even if these variables are solely not capable of changing the hazard ratios for developing breast cancer drastically, they may in combination confound the association between coffee or tea intake and risk of breast cancer.

Since the measurement of coffee and tea intake was done at baseline only, we are uncertain about the effects of participants subsequently changing their pattern of coffee / tea consumption. However, this would only pose a problem if change in coffee or tea consumption occurred selectively in a particular group of participants (i.e. those subsequently developing breast cancer or vice versa) but this is highly unlikely. Anyhow, we attempted to deal with this by excluding those with prevalent cancer at baseline and censoring participants with cancer at the time of their diagnosis that may have induced change in their dietary habits.

Even though we did not have information on the type of tea consumed by our study population, we are aware that the percentage of green tea consumption is very low in the Western population where black tea consumption is dominant. Since there was no information on history of prior benign breast disease, we were unable to incorporate this risk factor of breast cancer into our present analysis. We also did not have genetic information e.g. BRCA1 or BRCA2 mutations.

Findings of previous epidemiological studies on the association of coffee consumption with breast cancer risk, however, have been inconsistent and even contradictory, possibly due to issues of study design and methodology. Following the WCRF report in 2007, two large prospective cohort studies revealed that there is no association between the consumption of these beverages and risk of breast cancer.[15-16] Our study is therefore valuable since it further adds concrete and

valid evidence to this finding. However, a recent meta analysis of 18 studies showed a weak inverse association between coffee and tea intake and risk of breast cancer where the pooled RR for the highest versus lowest coffee consumption level was 0.95 (0.90-1.00).[35] Anyhow, it is possible that misclassification of coffee consumption may have occurred in this analysis due to variation in measurement of coffee or tea intake among studies which probably diluted the observed effects towards the null value.

Even though animal and cellular studies seem to show either a protective[23-25] or harmful[21,22] effect of coffee and tea in relation to breast cancer, we were not able to demonstrate this in humans most probably due to higher doses of coffee / tea constituents used in laboratory studies or due to differences in causal factors of cancer in humans and animals.[36] It may also be possible that the counter effect between various constituents in these beverages leaves no net effect in humans.

From this study, it seems that the association between coffee and tea intake with risk of breast cancer is actually strongly confounded by lifestyle, especially with coffee where a significant crude HR of 2.25 (95% CI 1.30-3.90) comparing consumers against non consumers was substantially reduced to 1.17 (0.65-2.12) after adjustment for lifestyle factors. In fact, this effect of adjustment indicates that the coffee (or tea) drinking associated lifestyle seems important in respect to breast cancer. It is very likely that the various lifestyle determinants have acted synergistically in the causal pathway of breast cancer as suggested from the effect brought about by adjustment with the propensity score.

As for premenopausal breast cancers, we could not draw any conclusion since the number of cases was too small to perform a meaningful analysis. Therefore, we would need a bigger sample to capture any associations between coffee or tea intake and the risk of breast cancer among premenopausal women.

In conclusion, our findings support the view that coffee and tea consumption are not related to the risk of breast cancer in women.

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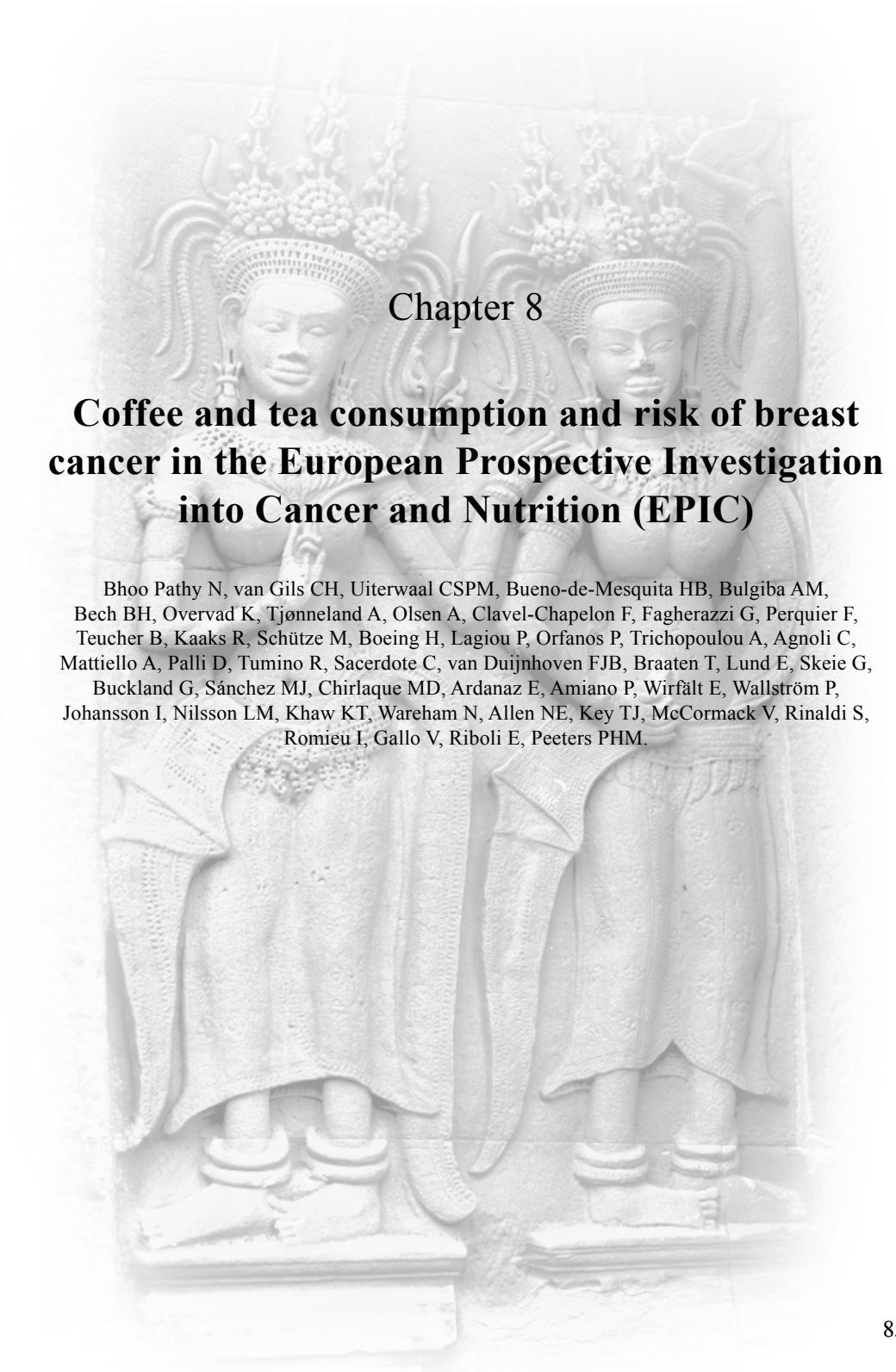

Chapter 8

Coffee and tea consumption and risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC)

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Abstract

Background

In 2007, the World Cancer Research Fund concluded that there is insufficient evidence to make definitive conclusions on the association between coffee and tea consumption and breast cancer.

Methods

The association between coffee (total, caffeinated, decaffeinated) and tea intake and risk of breast cancer was investigated among 335,868 women in the European Prospective Investigation into Nutrition and Cancer cohort. Participants completed a dietary questionnaire in 1992–2000 and were followed-up for breast cancer. Cox proportional hazards models were used to adjust for breast cancer risk factors. As the volume and concentration of coffee and tea intake varied substantially by country, we used country-specific categories for analyses.

Results

By 2007, 7482 primary invasive breast cancers were diagnosed in 2,943,491 person-years of follow-up. Caffeinated coffee intake was marginally associated with a lower risk of breast cancer: hazard ratio (HR) 0.89; 95%CI: 0.79-1.00, for high consumption (upper quartile) versus no consumption; $P_{\text{linear trend}} = 0.04$. Decaffeinated coffee consumption was associated with a higher risk of breast cancer (HR: 1.17; 95% CI: 1.05-1.30), for above median consumption versus no consumption; $P_{\text{linear trend}} = 0.01$. In non-consumers of decaffeinated coffee, there was no association between caffeinated coffee consumption and risk of breast cancer. Among low consumers of caffeinated coffee, HR for high intake versus no intake of decaffeinated coffee was 1.18 (95% CI: 1.02-1.37). Total coffee or tea consumption was not associated with breast cancer risk.

Conclusion

In this study, caffeinated coffee intake was associated with a marginally lower risk of breast cancer, whereas decaffeinated coffee consumption seems to be associated with an increased risk of breast cancer. These associations have never been reported and need to be substantiated in further studies.

Introduction

Biological evidence has fuelled the idea that components of coffee or tea such as caffeine, polyphenols, and diterpenes might be implicated in carcinogenesis. In 2007, the World Cancer Research Fund concluded that for the association between coffee and tea intake and pre- and postmenopausal breast cancer, evidence did not allow for definite conclusions.[1]

Case-control studies have shown contradictory findings[2] probably due to issues of study design and methodology such as selection and information bias. Most large prospective studies report no association between coffee or tea intake and risk of breast cancer.[3-10] A meta-analysis including 25,250 breast cancer cases from Europe, United States and Japan reported an association close to unity; HR: 0.95; 95%CI: 0.90-1.00, for highest versus lowest coffee consumption categories.[2] However, a Norwegian prospective study of 14,593 participants had shown that coffee consumption was protective in lean women only (Incidence rate ratio[IRR]: 0.5; 95% CI:0.3-0.9), while it increased the risk in obese women; IRR: 2.1; 95% CI: 0.8-5.2, *p* for interaction with BMI=0.02.[11] A recent prospective study in Sweden found that drinking boiled coffee was associated with a significantly lower risk of breast cancer (HR: 0.52; 95% CI: 0.30-0.88, comparing >4 versus <1 occasions/day).[12]

According to legislation in European Union, decaffeinated coffee has caffeine content reduced to 0.1% or less in roasted coffee beans, and to 0.3% or less in instant coffee [http://www.cosic.org/decaffeinated-coffee]. Studies investigating the association between decaffeinated coffee intake and breast cancer are scarce as well as contradictory; with one cohort[6] and a case-control[13] study reporting no significant association, and another case-control study reporting an inverse association; odds ratio(OR): 0.84 (95%CI 0.72-0.98).[14] Therefore, we set out to determine the association between coffee (total, decaffeinated and caffeinated) and tea consumption with risk of breast cancer in female participants of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.[15]

Methods

EPIC is an ongoing multi-center prospective cohort study designed to investigate nutrition and cancer. It consists of 521,448 males and females (mostly aged 25-70 years), to be followed-up for cancer incidence and cause-specific mortality for several decades. There are 23 EPIC centers in 10 European countries i.e. Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, and United Kingdom. Details have been described elsewhere.[15]

Study Participants

This study pertains to female participants of the EPIC cohort. At enrolment between 1992 and 2000, information on habitual diet in the preceding year was collected through a questionnaire in most countries. Lifestyle questionnaires were used for information on education, reproductive history, use of oral contraceptives and hormone therapy, family history, past medical history, physical activity and history of consumption of alcohol and tobacco.[15]

All participants gave written and oral informed consent. The study was approved by the International Agency for Research on Cancer (IARC)'s ethical review committee and by the local ethical committees at the participating centers.

Exposure assessment

Diet was assessed using country-specific questionnaires designed to capture local dietary habits and to provide high compliance;[15] namely self-administered semi-quantitative food-frequency questionnaires (± 260 food items), dietary history questionnaires (>600 food items) administered by interviews, and semi-quantitative food-frequency questionnaire combined with a food record. Further details on questionnaires and their validation are described elsewhere.[16,17] The intake of coffee and tea was reported as number of cups consumed per day, week, or month; the exact structure of the questions varied slightly by center and questionnaire. Total consumption in milliliter per day (ml/day) was calculated for each center. Due to variation in questionnaire design, complete information on the type of coffee consumed (caffeinated or decaffeinated) was only available for centers from Germany, Netherlands, United Kingdom, and Sweden (Malmo only). Information on tea intake was not available in Norway.

To improve comparability across centers, dietary intake was calibrated by a 24 -hour dietary recall method common to all centers, in a random sub-sample of 8% of the cohort at baseline.[18] Face-to-face 24-hour recall interviews were done using a computerized program (EPIC-SOFT) developed ad hoc, to adjust for systematic and random intra-individual error and between-center errors.

Ascertainment of Breast Cancer Cases

The outcome of interest was first incident of primary invasive breast cancer (coded using International Classification of Diseases for Oncology, Second Edition [ICD-O-2] as C50.0-C50.9). Follow-up was based on linkage with population cancer registries in Denmark, Italy, Netherlands, Norway, Spain, Sweden and the United Kingdom. In France, Germany and Greece, combined methods including health insurance records, cancer and pathology registries, and active follow-up through participants and next-of-kin were used.

This analysis included data on cancer cases recorded in the central database at IARC until March, 2007. Censoring dates for each center were established depending on the dates at which cancer registries were considered complete (varying from December, 2002 to December, 2006). For Germany and Greece, the end of follow-up was considered to be the last known contact, date of diagnosis, or date of death, whichever came first. Loss to follow-up was <6% across centers.

Statistical Analysis

Any prevalent cancers at recruitment were excluded a priori leaving 345,995 women. Exclusion of participants with incomplete dietary / non-dietary information, and poorly completed questionnaires based on their ratio of energy intake (EI) versus energy expenditure (ER) i.e. EI/ER in the bottom 1% or top 1% of the cohort (n=10,127), left 335,868 women.

Analyses of caffeinated and decaffeinated coffee consumption only included women for whom the information on type of coffee intake was complete and available i.e all participants from Germany, Netherlands, and United Kingdom, and part of the participants from France (n=47 600), Italy (n=11 374), and Sweden (n = 14 114); (N=180,188). Norway was excluded from the analysis of tea intake (n=300,641). Since coffee and tea intake differed significantly by country in terms of concentration and volume, country specific quantiles for these beverages were estimated based on distribution of intake within each country, after excluding the non consumers. Based on the above categorization, we had 5 categories of intake for total coffee, caffeinated coffee and tea consisting of non consumers, and the quartiles in consumers to which we refer as: low, moderately low, moderately high, and high. Since decaffeinated coffee intake was relatively uncommon, we only had 3 categories; no intake, below median (low) intake, and above median (high) intake.

Multivariable Cox regression was used to examine the association between coffee or tea consumption (independent variable) and risk of breast cancer (dependent variable). Time at entry was age at recruitment, and exit time was age at diagnosis with breast cancer as first tumor, death, emigration, loss to follow-up, or end of follow-up. All analyses were stratified by age at recruitment in 1-year categories to account for possible departures from proportionality of hazards, and by centers to control for differences in recruitment or follow-up procedures, and questionnaire design. We studied consumption of coffee and tea both as categorical and continuous (increment of 100ml/day) variables. For categorical analysis, the non consumers were taken as the reference category. To test for linear trends $P_{\text{linear trend}}$ the categories were entered as a continuous term in the Cox model. Likelihood ratio tests were applied between nested models to assess for possible interaction (effect modification) with any variables.

Crude hazard ratios (HR) with 95% confidence intervals were calculated for each intake category compared to the reference. We adjusted for age at menarche (categorical: never, <12, 12-14, >15 years), ever use of oral contraceptives (yes/no), age at first delivery (categorical: nulliparous, <20, 20–29, 30–39, ≥40 years), ever breastfed (yes/no), menopausal status at recruitment (categorical: premenopausal, postmenopausal, perimenopausal, surgical menopause), ever use of postmenopausal hormones (yes/no), smoking status (categorical: never, past, current), educational level (categorical: none, primary school, technical/professional school, secondary school, university), physical activity level based on Cambridge Physical Activity Index[19] (categorical: inactive, moderately inactive, moderately active, active), alcohol intake (continuous), height (continuous), weight (continuous), energy intake from fat source (continuous), energy intake from non-fat source (continuous), total saturated fat intake (continuous), total fiber intake (continuous) and coffee for tea mutually (continuous). Tea intake of Norwegians was set to zero (as consumption is generally very low), when adjusting analyses of total coffee intake. To disentangle effects of caffeinated and decaffeinated coffee consumption, analyses were mutually adjusted. We additionally estimated the effect of caffeinated coffee among non-consumers of decaffeinated coffee. The effect of decaffeinated coffee was also estimated among low consumers of caffeinated coffee, whom were defined as non-consumers or those being in the lowest tertile of caffeinated coffee consumption. These

two categories were combined as the number of non consumers was too low for a meaningful analysis.

Since pre- and postmenopausal breast cancers are often considered as diseases with different etiologies, specific Cox models were fitted. As data on menopausal status at diagnosis were lacking, breast cancers occurring before the median menopausal age of 49 years were considered premenopausal. In the premenopausal model, women aged ≥ 49 at baseline were excluded leaving 135 428 women. Exit time was age at diagnosis of breast cancer as the first tumor (before turning 49 years), or turning 49 years, death, emigration, loss to follow-up, or end of follow-up. Analyses of postmenopausal breast cancers (breast cancers diagnosed at age ≥49 years), were similar to the main model but with premenopausal breast cancers excluded, leaving 335 023 women.

Since a previous prospective study found that body mass index (BMI) might modify the association between coffee intake and risk of breast cancer,[11] we included the interaction term 'consumption of coffee or tea multiplied by BMI (both continuous)' in the model, and tested for interaction.

To assess heterogeneity of estimates across countries, we introduced an interaction term; 'countries multiplied by beverage intakes' (total coffee: 10 countries, tea: 9 countries, caffeinated coffee / decaffeinated coffee: 4 countries) into the model. In the 43% of women with available information on family history of breast cancer, analyses with and without adjustment for family history were performed. To preclude reverse causation by preclinical disease influencing coffee and tea consumption, we repeated the analysis excluding the first two years of follow-up.

Calibration

Linear regression calibration was done,[20] with 24-hour dietary recall measurements being regressed on dietary questionnaire values for coffee (total, caffeinated, decaffeinated) and tea consumption, to obtain predicted intake values (further referred to as calibrated values). In the calibration models, the same covariates as in the Cox regression models described above were included. Additionally, data were weighted by day of the week and season of the year on which the 24-hour dietary recall was obtained.

Cox regression models were then fitted with continuous calibrated values (100ml/day) to obtain the measurement error-corrected (de-attenuated) HR estimates. To account for additional variability introduced by the calibration model, the standard errors of the de-attenuated coefficients were corrected through bootstrap sampling (10 repetitions).

Two-tailed p-values <0.05 and 95% confidence intervals (CI) for HR not including 1 were considered statistically significant. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

Results

Table 1 shows median daily consumption of coffee (total, caffeinated, decaffeinated) and tea by country. Median total coffee intake ranged from 90 ml/day in Italy to 900 ml/day in

***Table 1**. Coffee and Tea Intake[1] of Participants According to Country*

Country	Participants, N	Follow-up, person-years	Breast cancer, N	Total coffee		Caffeinated Coffee[2]		Decaffeinated Coffee[2]		Tea[3]	
				Non-consumers, %	Consumers ml/day	Non-consumers, %	Consumers ml/day	Non-consumers %	Consumers ml/day	Non-consumers %	Consumers ml/day
Denmark	28 736	215 967	822	5	900 (200-1300)	-	-	-	-	11	200 (7-900)
France	68 050	741 203	2 454	15	280 (70-657)	29	260 (70-600)	85	143 (10-490)	41	214 (15-725)
Germany	27 915	227 268	456	4	392 (106-784)	9	300 (96-750)	75	53 (20-471)	23	53 (2-450)
Greece	15 019	108 486	114	8	140 (33-341)	-	-	-	-	47	0 (0-34)
Italy	30 498	257 243	674	11	92 (37-190)	30	90 (30-180)	89	11 (3-60)	45	43 (5-150)
Netherlands	26 520	228 947	564	5	500 (250-875)	5	450 (63-720)	5	70 (25-338)	8	238 (34-645)
Norway	35 227	210 300	468	9	420 (120-780)	-	-	-	-	-	-
Spain	24 857	241 319	316	11	113 (3-307)	-	-	-	-	95	114 (29-314)
Sweden	26 381	271 071	679	4	400 (150-775)	4	450 (150-900)	100	-	56	89 (1-625)
United Kingdom	52 665	441 686	935	3	380 (4-857)	6	190 (2-855)	18	2 (2-475)	2	475 (2-1140)
Total	335 868	2 943 491	7 482	9	300 (48-870)	6	338 (2-855)	38	38 (2-475)	33	190 (4-855)

[1] Median (10^{th}- 90^{th} percentile) for beverage consumption is only calculated among consumers

[2] Including only those with complete information on type of coffee intake, which are all participants from Germany, Netherlands, and United Kingdom, and part of the participants from France (n=47 600), Italy (n=11 374), and Sweden (n = 14 114).

[3] Information on tea intake is not available for participants from Norway.

***Table 2**. Distribution of Risk Factors According to Levels of Consumption of Coffee (total, caffeinated and decaffeinated) and Tea*

	Total	Coffee (total)		Coffee Caffeinated [1]		Coffee Decaffeinated [1]		Tea[2]	
		No intake	High intake[3]	No intake	High intake[3]	No intake	High intake[4]	No intake	High intake[3]
Number of participants	335 868	26 839	69 609	24 694	34 305	96 526	37 323	99 940	34 610
Age at recruitment [mean (years)]	51	51	50	53	50	53	50	52	52
Familial breast cancer (%)[5]	8.3	7.6	7.8	8.3	9.2	8.1	10.4	7.5	9.3
Age at menarche (% <12 yrs)	15	15	17	17	16	15	17	16	15
Oral contraceptive use (% ever)	59	52	61	57	71	61	70	54	67
Nulliparity (%)	4.1	3.1	4.1	1.7	3.8	3.7	3.9	2.9	3.0
Age at first delivery (%< 20 yrs)[6]	12	7	11	9	12	11	9	15	7
Breastfed (% ever)	71	71	72	66	67	70	62	73	67
Postmenopausal (%)	43	44	38	47	41	49	41	48	46
Menopausal hormone use (% ever)	26	25	26	29	29	32	24	27	31
Education (% university)	24	23	22	26	28	28	29	23	33
Smokers (% ever)	32	29	55	29	53	38	46	39	42
Physically inactive[7] (%)	25	33	23	28	19	23	17	27	17
BMI [mean(kg/m²)]	25.0	24.7	25.2	24.1	25.0	24.4	24.7	25.1	24.1
Tea[2] [median(ml/day)]	29	86	3	150	14	15	238	-	-
Coffee[8] [median(ml/day)]	290	-	-	0	0	250	175	203	150
Alcohol [median(g/day)]	3.6	1.3	4.2	2.2	6.0	5.2	4.4	4.1	5.2
Total energy [mean(kcal/day)]	1 932	1 954	2 008	2 038	2 022	2 024	1 920	1995	2003
Total saturated fat [mean(g/day)]	29.4	29.6	31.1	31.9	32.9	32.9	28.6	30.9	31.3
Total fiber [mean(g/day)]	22.1	22.8	22.1	23.0	21.8	21.5	23.6	21.9	23.7

[1] Including only those with complete information on type of coffee intake, which are all participants from Germany, Netherlands, and United Kingdom, and part of the participants from France (n=47 600), Italy (n=11 374), and Sweden (n = 14 114).
[2] Excluding participants from Norway (n=300 641)
[3] High intake is defined as highest quartile within consumers of total/ caffeinated coffee and tea
[4] High intake is defined as above median intake within consumers of decaffeinated coffee
[5] In first degree relative (available for 43% of women)
[6] Only for parous women
[7] Using Cambridge physical activity index
[8] For caffeinated coffee categories, median decaffeinated coffee intake is given and vice versa

Denmark while tea intake was close to 0 ml/day in Greece, Spain and Sweden and 475 ml/day in United Kingdom. Of 180,188 women with complete information on type of coffee intake, 42.5% drank both caffeinated and decaffeinated coffee, 43.7% drank caffeinated coffee exclusively, 3.8% drank decaffeinated coffee exclusively, while 10.0% were non-consumers.

The mean age at recruitment was 51 years (Table 2) with 43% of participants being postmenopausal. Based on BMI classification by WHO, 58% of participants were normal weight, 29% overweight and 13% obese. All risk factors for breast cancer that we studied were associated with coffee and tea intake, e.g. age at first delivery, use of oral contraceptives and menopausal hormone. Lifestyle related factors such as smoking, physical activity, and intake of alcohol, saturated fat and fiber were also related to coffee and tea consumption. During an average 8.9 years of follow-up, 7482 first incidences of primary invasive breast cancer were observed among 335,868 women, contributing 2,943,491 person-years of observation. Of these, 839 were premenopausal breast cancers.

Tables 3-7 show the numbers of participants, person-years, cases, and estimated HRs for each category of coffee (total, caffeinated, decaffeinated intake) and tea intake. For analysis of beverages as continuous value (per 100ml increment), the observed and calibrated HRs were identical. We only presented the latter.

Total coffee consumption was not associated with breast cancer risk. Multivariable HR comparing high coffee intake to no intake was 0.92 but not statistically significant (refer Table 3). HR by subgroups of pre- and postmenopausal breast cancer were also in the direction of unity: HR per 100 ml increase in coffee intake was 1.01 (95% CI: 0.98-1.04) for premenopausal breast cancer, and 0.99; (95% CI: 0.98-1.00) for postmenopausal breast cancer. There was no interaction with BMI; p for likelihood ratio test =0.30. Results were similar when the above analysis was repeated in the 180,188 women whose type of coffee intake was known (multivariable HR for high total coffee intake versus no intake = 0.89; 95% CI: 0.73-1.09).

High intake of caffeinated coffee was associated with 11% lower risk of breast cancer compared to no intake (multivariable HR: 0.89; 95% CI: 0.79-1.00) with a p value for linear trend test of 0.04 (Table 4). On the other hand, high consumption of decaffeinated coffee was associated with a 17% (HR: 1.17; 95% CI: 1.05%-1.30%) higher breast cancer risk, when compared to no intake of decaffeinated coffee; $P_{\text{linear trend}} = 0.006$ (Table 5). The risk estimates associated with both types of coffee intake with risk of breast cancer were the same for premenopausal and postmenopausal breast cancer (not shown). While there was no interaction between caffeinated coffee intake and BMI ($p = 0.08$), there was significant interaction between decaffeinated coffee intake and BMI ($p = 0.02$). Decaffeinated coffee intake was not associated with breast cancer in lean or overweight women (not shown). However, among obese women, high decaffeinated coffee intake was associated with 57% (HR: 1.57; 95%CI: 1.11-2.23) increased risk of breast cancer compared to no intake. In women reporting not to consume decaffeinated coffee, there was no association between caffeinated coffee consumption and risk of breast cancer (Table 6). Whereas, among women reporting low intake of caffeinated coffee, the HR was 1.18 (95% CI: 1.02-1.37) for high

Table 3. *Total Coffee Consumption and Risk of Breast Cancer in 335 868 Participants*

Daily coffee intake	Total	No intake	Low intake[1]	Moderately low intake[1]	Moderately high intake[1]	High intake[1]	*Ptrend*	Per 100mls
No. of participants	335 868	26 839	87 715	71 692	80 013	69 609		
Person years	2 943 491	243 815	752 071	635 596	700 886	611 123		
No. of breast cancer cases	7 482	630	1 844	1 620	1 856	1 532		
Crude Hazard Ratio [2]		1.00	1.01	1.00	1.02	0.97	0.48	1.00
(95% Confidence Interval)			(0.92-1.11)	(0.91-1.10)	(0.93-1.11)	(0.88-1.07)		(0.99-1.00)
Adjusted Hazard Ratio [3]		1.00	0.98	0.98	0.99	0.92	0.14	0.99
(95% Confidence Interval)			(0.89-1.08)	(0.88-1.08)	(0.90-1.09)	(0.83-1.02)		(0.98-1.00)

[1] Cut-off points are based on country specific quartiles of overall coffee intake after exclusion of non-consumers.
[2] Stratified by study center and age at recruitment
[3] Stratified by study center and age at recruitment, and adjusted for age at menarche, ever use of oral contraceptives ,age at first delivery, breastfeeding, menopausal status, ever use of postmenopausal hormones, smoking, education, physical activity level, alcohol intake, height, weight, energy intake from fat source, energy intake from non-fat source, total saturated fat intake, total fiber intake, and tea intake

Table 4. *Caffeinated Coffee Consumption and Risk of Breast Cancer in 180 188 Participants* [1]

Daily caffeinated coffee intake	Total	No intake	Low intake[2]	Moderately low intake[2]	Moderately high intake[2]	High intake[2]	*Ptrend*	Per 100mls
No. of participants	180 188	24 694	43 878	44 432	32 849	34 335		
Person years	1 652 838	241 476	396 027	399 202	302 282	313 851		
No. of breast cancer cases	4 364	717	1 033	968	838	808		
Crude Hazard Ratio [3]		1.00	1.03	0.92	1.00	0.94	0.13	0.99
(95% Confidence Interval)			(0.93-1.14)	(0.83-1.02)	(0.90-1.11)	(0.84-1.04)		(0.98-1.00)
Adjusted Hazard Ratio [4]		1.00	1.01	0.91	0.97	0.89	0.04	0.98
(95% Confidence Interval)			(0.90-1.12)	(0.81-1.02)	(0.86-1.09)	(0.79-1.00)		(0.97-0.99)

[1] Including only those with complete information on type of coffee intake, which are all participants from Germany, Netherlands, and United Kingdom, and part of the participants from France (n=47 600), Italy (n=11 374), and Sweden (n = 14 114).

[2] Cut-off points are based on country specific quartiles of caffeinated coffee intake after exclusion of non-consumers

[3] Stratified by study center and age at recruitment

[4] Stratified by study center and age at recruitment, and adjusted for age at menarche, ever use of oral contraceptives, age at first delivery, breastfeeding, menopausal status, ever use of postmenopausal hormones, smoking, education, physical activity level, alcohol intake, height, weight, energy intake from fat source, energy intake from non-fat source, total saturated fat intake, total fiber intake, tea intake and decaffeinated coffee intake.

Table 5. *Decaffeinated Coffee Consumption and Risk of Breast Cancer in 180 188 Participants* [1]

Daily decaffeinated coffee intake	Total	Non consumers	Low consumers [2]	High consumers [2]	*Ptrend*	Per 100mls
No. of participants	180 188	96 526	46 239	37 423		
Person years	1 652 838	930 632	396 312	325 894		
No. of breast cancer cases	4 364	2 653	875	836		
Crude Hazard Ratio [3]		1.00	1.13	1.16	0.007	1.02
(95% Confidence Interval)			(1.01-1.26)	(1.04-1.28)		(1.00-1.04)
Adjusted Hazard Ratio [4]		1.00	1.13	1.17	0.006	1.02
(95% Confidence Interval)			(1.00-1.26)	(1.05-1.30)		(1.00-1.05)

[1] Including only those with complete information on type of coffee intake, which are all participants from Germany, Netherlands, and United Kingdom, and part of the participants from France (n=47 600), Italy (n=11 374), and Sweden (n = 14 114).

[2] Cut-off points are based on country specific median values of decaffeinated coffee intake after exclusion of non-consumers

[3] Stratified by study center and age at recruitment

[4] Stratified by study center and age at recruitment, and adjusted for age at menarche, ever use of oral contraceptives, age at first delivery, breastfeeding, menopausal status, ever use of postmenopausal hormones, smoking, education, physical activity level, alcohol intake, height, weight, energy intake from fat source, energy intake from non-fat source, total saturated fat intake, total fiber intake, tea intake and caffeinated coffee intake.

Table 6. *Combined Coffee Intake and Risk of Breast Cancer in 180 188 Participants* [1]

Caffeinated coffee \ Decaffeinated coffee		No consumption	Low Consumption[2]	High consumption[2]
Low consumption[3]	No. of participants (%)	29 206 (16.2)	16 291 (9.0)	15 625 (8.6)
	Crude HR (95%CI)	1.00	1.21 (1.04-1.40)	1.17 (1.02-1.34)
	Adjusted HR (95%CI)[4]	1.00	1.30 (1.11-1.53)	1.18 (1.02-1.37)
Medium consumption[3]	No. of participants (%)	36 705 (20.4)	22 168 (12.3)	12 907 (7.2)
	Crude HR (95%CI)	0.98 (0.89-1.08)	1.08 (0.93-1.25)	1.12 (0.96-1.31)
	Adjusted HR (95%CI)[4]	1.01 (0.91-1.12)	1.09 (0.93-1.28)	1.18 (0.99-1.40)
High consumption[3]	No. of participants (%)	30 615 (17.0)	7 780 (4.3)	8 891 (4.9)
	Crude HR (95%CI)	0.98 (0.89-1.09)	1.01 (0.83-1.22)	1.09 (0.91-1.31)
	Adjusted HR (95%CI)[4]	1.00 (0.89-1.12)	0.90 (0.73-1.12)	1.11 (0.91-1.35)

[1] Including only those with complete information on type of coffee intake, which are all participants from Germany, Netherlands, and United Kingdom, and part of the participants from France (n=47 600), Italy (n=11 374), and Sweden (n = 14 114).
[2] The cut-off values are based on country specific medians of decaffeinated coffee Intake after excluding the non-consumers.
[3] The cut-off values are based on country specific tertiles
[4] Stratified by study center and age at recruitment, and adjusted for age at menarche, ever use of oral contraceptives ,age at first delivery, breastfeeding , menopausal status, ever use of postmenopausal hormones, smoking, education, physical activity level, alcohol intake, height, weight, energy intake from fat source, energy intake from non-fat source, total saturated fat intake, total fiber intake, and tea intake.

***Table** 7. Tea Consumption and Risk of Breast Cancer in 300 641 Participants* [1]

Daily coffee intake	Total	No intake	Low intake[2]	Moderately low intake[2]	Moderately high intake[2]	High intake[2]	*Ptrend*	Per 100mls
No. of participants	300 641	99 940	52 870	57 063	56 158	34 610		
Person years	2 733 191	950 426	472 007	497 941	497 992	314 825		
No. of breast cancer cases	7 014	2 330	1 190	1 286	1 311	897		
Crude Hazard Ratio [3]		1.00	1.05	1.05	1.04	1.03	0.47	1.00
(95% Confidence Interval)			(0.96-1.13)	(0.97-1.13)	(0.96-1.12)	(0.95-1.12)		(0.99-1.01)
Adjusted Hazard Ratio [4]		1.00	1.03	1.03	0.99	0.97	0.44	0.99
(95% Confidence Interval)			(0.95-1.12)	(0.94-1.11)	(0.91-1.08)	(0.88-1.06)		(0.98-1.00)

[1] Excluding Norway
[2] Cut-off points are based on country specific quartiles of tea intake after exclusion of non-consumers.
[3] Stratified by study center and age at recruitment
[4] Stratified by study center and age at recruitment, and adjusted for age at menarche, ever use of oral contraceptives, age at first delivery, breastfeeding, menopausal status, ever use of postmenopausal hormones, smoking, education, physical activity level, alcohol intake, height, weight, energy intake from fat source, energy intake from non-fat source, total saturated fat intake, total fiber intake, and coffee intake

intake versus no intake of decaffeinated coffee (Table 6). To exclude residual confounding by caffeinated coffee in this subgroup, we additionally adjusted for its intake (ml/day), and found that the HR remains materially unchanged (1.12; 95%CI: 0.95-1.32).

After adjustment for confounders, tea consumption was not associated with risk of breast cancer (Table 7). HR per 100 ml increase in tea intake was 1.01 (95% CI: 0.98, 1.04) for premenopausal breast cancer, and 0.99 (95% CI: 0.98, 1.00) for postmenopausal breast cancer. No interaction was observed between tea intake and BMI (p=0.20).

There was significant heterogeneity between countries for the association between caffeinated coffee intake and breast cancer; p<0.001, but not for other beverages. When analysis was split by country, caffeinated coffee intake in Italy and Netherlands were associated with non-significantly increased risk for breast cancer as opposed to other countries (Figure 1). When we excluded these countries, the association between high caffeinated coffee intake and breast cancer was marginally stronger; HR: 0.84 (95% CI: 0.74-0.96).

To assess the robustness of our results, we also analyzed beverage intake using quintiles based on the overall cohort, instead of country specific quintiles, but this did not materially change any of our findings. None of the associations were significantly altered when family history of breast cancer was included in analyses, or when we analyzed follow-up experience after 2 years of recruitment into the study (not shown).

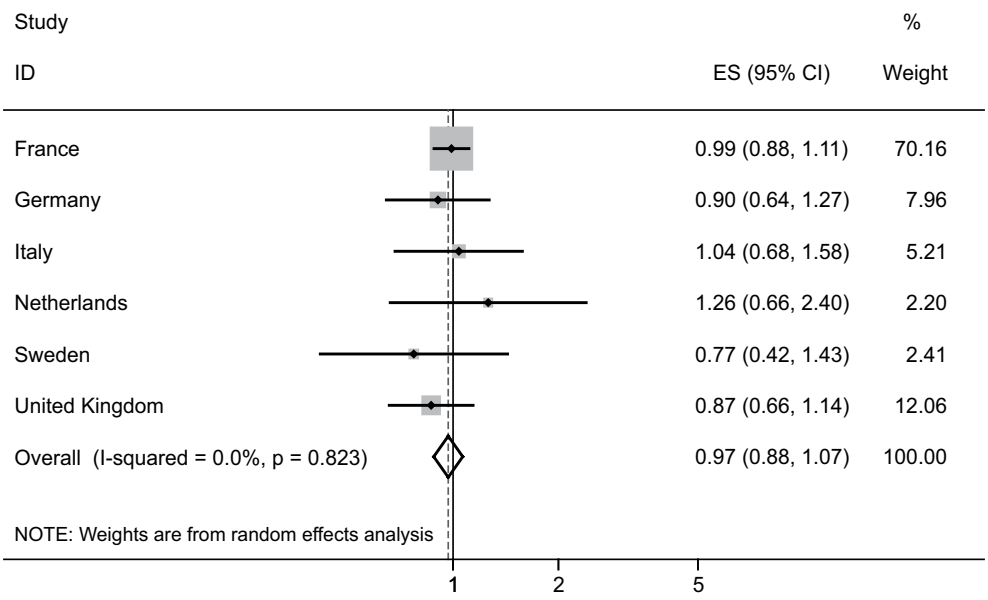

Figure 1. *Caffeinated coffee intake and risk of breast cancer by country*

ES = Effect size is based on hazard ratio comparing consumers versus non consumers, adjusted for age at menarche, ever use of oral contraceptives, age at first delivery, breastfeeding, menopausal status, ever use of postmenopausal hormones, smoking, education, physical activity level, alcohol intake, height, weight, energy intake from fat source, energy intake from non-fat source, total saturated fat intake, total fiber intake, tea intake and decaffeinated coffee intake

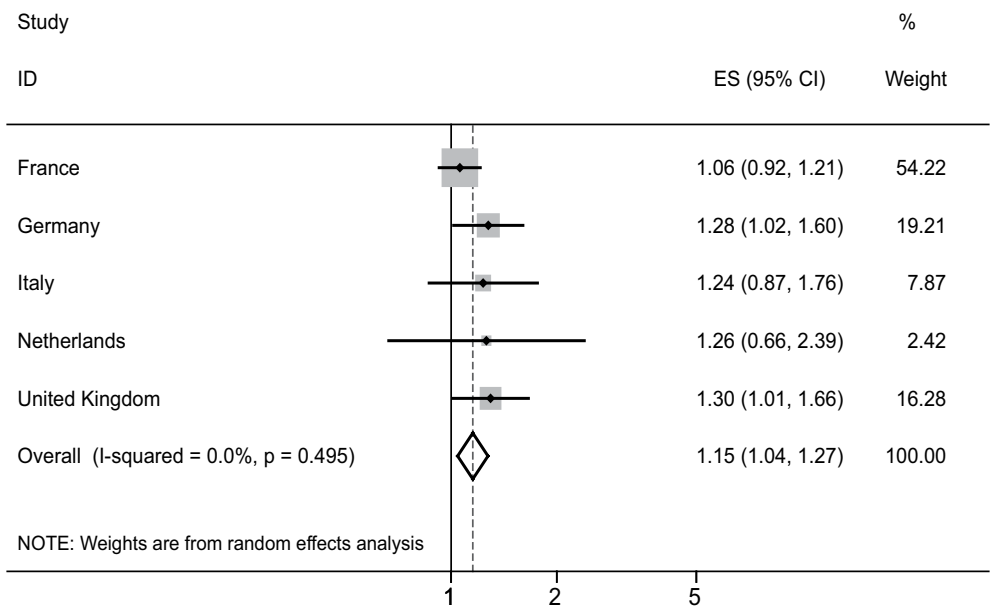

Figure 2. *Decaffeinated coffee intake and risk of breast cancer by country*

Sweden is not included as there was no consumer of decaffeinated coffee
ES = Effect size is based on hazard ratio comparing consumers versus non consumers, adjusted for age at menarche, ever use of oral contraceptives, age at first delivery, breastfeeding, menopausal status, ever use of postmenopausal hormones, smoking, education, physical activity level, alcohol intake, height, weight, energy intake from fat source, energy intake from non-fat source, total saturated fat intake, total fiber intake, tea intake and caffeinated coffee intake

Discussion

Caffeinated coffee intake seemed to be marginally associated with a lower risk of breast cancer. Conversely, decaffeinated coffee consumption was associated with a modestly increased risk of breast cancer. Neither total coffee nor tea intake was associated with breast cancer risk.

Previous studies have lacked statistical power for subgroup analysis.[2,10] We attempted to study coffee intake and pre- and postmenopausal breast cancers in a previous study within the Dutch EPIC sub-cohort but this was hampered by low number of cases.[10] Even though it is conceivable that different patterns in tea and coffee consumption exist among premenopausal and postmenopausal women, possibly driven by lifestyle and medical history, we observed no difference between pre and postmenopausal associations in the current study.

A potential limitation is that although similar types of dietary questionnaires were used in the EPIC centers, questions were tailored to local dietary habits.[15] Possible center specific, systematic over- or underestimation of dietary intakes, were dealt with by stratifying Cox models by centers and intake calibration.[18] The calibration method assumes that any bias in the 24-hour dietary recall is independent of that of dietary questionnaires, but a positive correlation between individual errors in dietary questionnaires and 24-hour dietary recalls

has been reported.[21] Even though coffee and tea intakes were measured only at baseline, analysis of participants in the EPIC sub-cohort of Umea, with repeated measures taken 10 years apart, showed that coffee habits are stable over time.[22] However, the single measurement of consumption in our study may not have been done in the etiologically relevant time period with respect to breast cancer risk, therefore diluting the observed associations. We neither had information on the type of tea, coffee/tea brewing methods nor the beverage concentration which may be associated to their caffeine content. We therefore used country specific categories of consumption to address this limitation.

Our null finding for the association between total coffee intake and risk of breast cancer corroborates with most of the previous prospective studies[3-10] and meta-analysis.[2] It seems that the finding may be a net result of sub-associations whereby caffeinated and decaffeinated coffee intakes seem to be associated with opposite effects. This further leads to the recommendation that future studies in populations consuming both types of coffee should explicitly analyze caffeinated and decaffeinated coffee intake separately.

We hypothesize that the marginally lower risk of breast cancer observed in association with caffeinated coffee intake may be due to the indirect role of caffeine. It was recently found that caffeine intake was inversely associated with luteal levels of estrogens in premenopausal consumers, possibly by mediating alterations of sex hormones.[23] It is well established that estrogen plays an important role in breast carcinogenesis.[24] Caffeine may also directly protect against breast cancer through its antioxidant effect.[25,26] Other examples of potentially protective substances in coffee are polyphenols such as lignans,[27] flavonoids, and catechines, as well as coffee specific diterpenes such as cafestol and kahweol.[28]

Decaffeinated coffee consumption has not been reported to be associated with higher breast cancer risk before.[6,13,14] Although our study included a larger number of decaffeinated coffee consumers than previous studies and allowed for extensive confounder adjustment, our finding needs to be interpreted cautiously and warrants further investigation. Previous studies have suggested that decaffeinated coffee consumers may be unique in terms of lifestyle or medical history.[29,30] Decaffeinated coffee intake is related to illness in some persons but to a healthy lifestyle in others.[29] Therefore, distinguishing genuine decaffeinated coffee effects from decaffeinated coffee preference effect is important.[30] It is therefore conceivable that the screening behaviour of consumers of decaffeinated coffee may have contributed to the apparent increase in breast cancer incidence in this subgroup. This is however unlikely to have influenced our results to a great extent as carcinomas in situ were not included in our study. Although the observed increased breast cancer risk among decaffeinated coffee consumers may be partially attributed to the above aspects, other hypotheses warrant exploration.

In this study, decaffeinated coffee intake was associated with increased risk of breast cancer, among low consumers of caffeinated coffee. Furthermore, increasing intake of caffeinated coffee seems to dilute the association of decaffeinated coffee intake and breast cancer. These seem to suggest that caffeine counteracts the effect of a particular agent (exposure) in decaffeinated coffee. This however needs further investigation. Furthermore, the European process, which dominates the specialty coffee industry, uses solvents to extract caffeine from

green coffee beans, such as methylene chloride and ethyl acetate.[31] Use of methylene chloride had generated some health concerns as its residues may be retained in decaffeinated coffee.[32] In 1999, IARC had classified methylene chloride as possibly carcinogenic to humans.[33] Pharmacokinetic studies have shown that it may be preferentially deposited in adipose tissue where the amount of absorption correlated highly with degree of obesity and body weight.[34,35] This may partially explain the observed interaction between BMI and decaffeinated coffee intake in our study.

A meta-analysis on the association of green tea and black tea intake, with breast cancer risk had found no overall protective effect of black tea (pooled OR = 0.98; 95% CI = 0.88–1.09).[36] This is in accordance with our findings since black tea is the predominantly consumed type of tea in Europe.[36] Possibly explaining this lack of association is that black tea contains relatively lower amount of caffeine compared to coffee, and up to 10-fold reduction in catechin levels compared with green tea, which had been inversely associated with breast cancer.[36]

In our large prospective study, caffeinated coffee intake seems to be marginally associated with lower risk of breast cancer. Consumption of decaffeinated coffee appears to be associated with an increased risk of breast cancer, particularly in heavier women. Total coffee or tea intake is not associated with breast cancer incidence. Since the associations between caffeinated and decaffeinated coffee intakes and risk of breast cancer have never been reported, results have to be interpreted cautiously and we propose that this study is further replicated.

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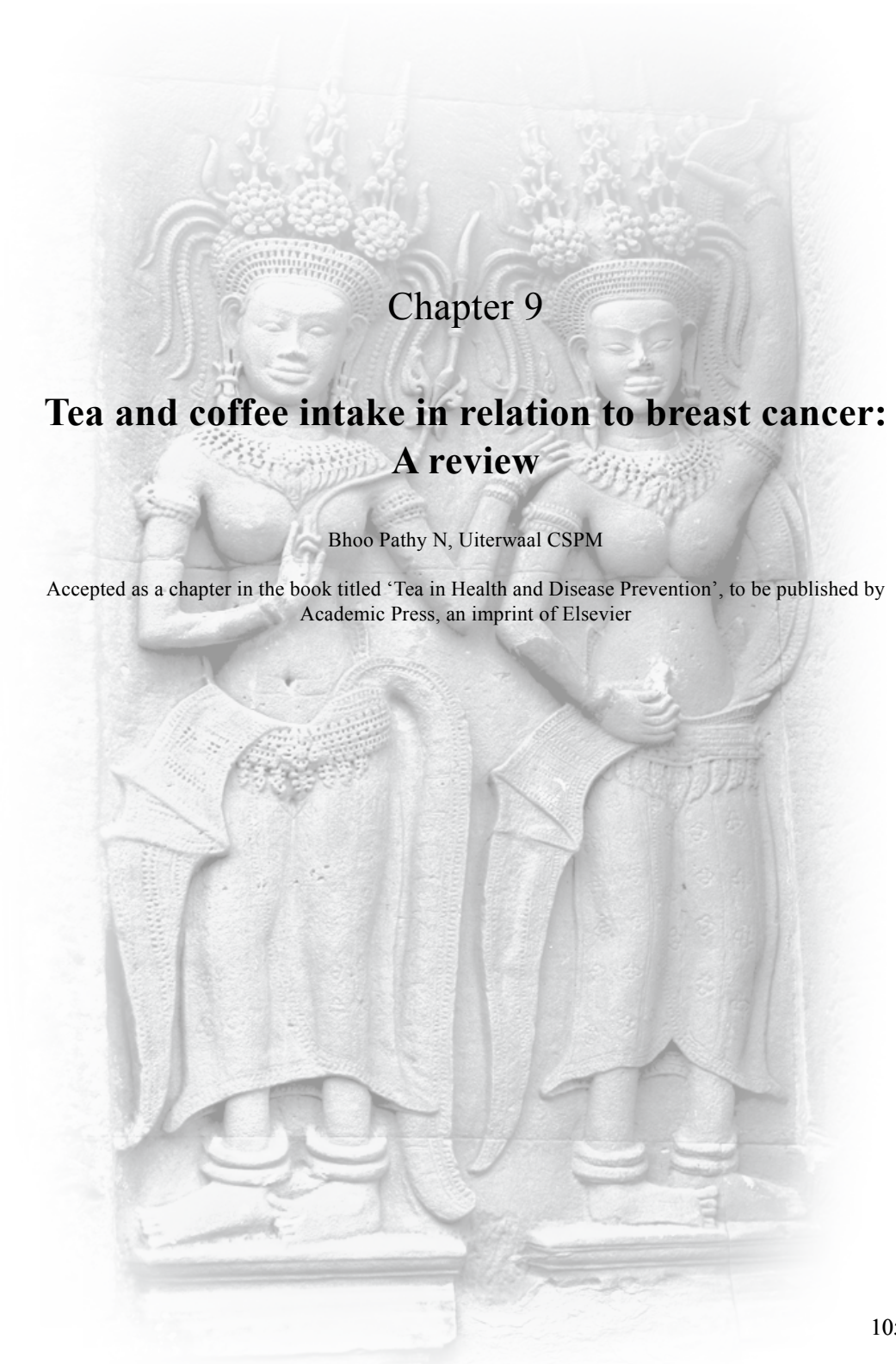

Chapter 9

Tea and coffee intake in relation to breast cancer: A review

Bhoo Pathy N, Uiterwaal CSPM

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Abstract

Tea and coffee are the most popular and widely consumed beverages worldwide, rendering them as relevant daily dietary exposures. Breast cancer on the other hand comprises 23% of all female cancers making it by far the commonest cancer in women. The idea that tea and coffee intake may be implicated in breast carcinogenesis was coined based on a complex body of scientific evidence. If tea and coffee intake were causally implicated in breast carcinogenesis, they would have a potentially large impact on the overall burden of breast cancer around the globe. Epidemiological studies have suggested that green tea consumption may be associated with lower risk of breast cancer and recurrence. Black tea, oolong tea and coffee intake do not seem to be associated with breast cancer incidence, although evidence to date is still considered inconclusive. Studies investigating the associations between tea and coffee intake and breast cancer should continue by employing cutting edge methodology to deal with previous challenges in the field.

Introduction

Breast cancer comprises 23% of all female cancers. Its incidence and mortality vary by world region, whereby the incidence is generally high in developed regions (> 80 per 100,000 person years), and low in developing regions (<40 per 100,000 person years).[1] Recent studies have also found that the incidence of breast cancer had been escalating in an alarming trend over the past few decades in developing countries.[2] International variations in breast cancer incidence, evidence from studies of migrants, and rapid rise in cancer rates within specific populations, in combination suggest that environmental exposures, and lifestyle related behaviours may be crucial in the etiology of breast cancer.[3] Dietary intake has been hypothesized to play a major role in carcinogenesis as there seem to be strong correlations between cancer rates and national per capita intake of nutrients from ecological studies.[4] It has been estimated that 30% of all cancer occurrence is related to diet[5] and therefore may provide an avenue for cancer prevention by adjustments of dietary intake.

In the past three decades, a multitude of epidemiological studies have embarked on investigating the association between tea and coffee consumption and the risk of breast cancer. The sparked interest in studying these associations is largely attributed to the public health implication of the potential findings. The fact that coffee and tea are the most popular and widely consumed beverages worldwide renders them relevant daily dietary exposures. On the other hand, breast cancer is by far the commonest cancer in women. The fact that currently established risk factors in conjunction only explain some 10-15% of breast cancer incidence further highlights the importance of studying the effects of tea and coffee consumption on breast cancer from a preventive perspective.

Tea and Coffee Constituents

While there are three major types of tea in the world comprising black tea, green tea and oolong tea, there are two main types of coffee i.e. caffeinated coffee and decaffeinated coffee. Tea and coffee are complex mixtures of various chemical compounds. In order to compare tea and coffee in relation to breast cancer, it is pertinent to compare the constituents in these beverages that may potentially influence the association with breast cancer risk. Furthermore, the constituents in these beverages may vary by differences in the manufacturing and preparation of the various types of tea and coffee.[6,7] Below are some of the common as well as beverage specific constituents of tea and coffee that may be of special interest with respect to cancer occurrence in general.

Catechins, which belong to the flavonoid class are found in abundance in fresh tea leaves. When tea leaves go through oxidation, catechins get converted into theaflavins, and thearubigins. Green tea which goes through minimal oxidation contains the highest content of catechins, while black tea which goes through prolonged oxidation has much lower catechin levels but higher levels of theaflavins, and thearubigins.[8] Oolong tea which is subjected to moderate oxidation lies somewhere in between. Catechins are however absent in coffee.[9]

The caffeine content in black tea (177-303 mg/l) is approximately half that of brewed coffee (306-553 mg/l). Black tea however has higher caffeine content than green tea (40-211 mg/l) or oolong tea.[10] Chlorogenic acids are esters which are found in abundance in coffee and have strong antioxidant activities in vitro. However, they are metabolized extensively in vivo, mainly before they enter the circulation into compounds with lower antioxidant activity.[11] Although tea also contains chlorogenic acid, the levels are notably lower than in coffee.

Cafestol and kahweol are two coffee specific diterpenes. These substances are found in unfiltered coffee (e.g. boiled coffee) as oil droplets or floating fines. However, they are only found in trace amounts in filtered coffee as they are largely retained by the paper filter.[12]

Tea And Coffee Constituents And Breast Cancer: Evidence From Basic Research

Basic research has fuelled the idea that components of tea and coffee might be implicated in breast carcinogenesis. Among others, these drinks contain caffeine, a purine alkaloid belonging to a group collectively recognized as methylxanthines. The hypothesis that these beverages may be associated with breast cancer risk was coined about two decades ago, following the finding that caffeine facilitates development of fibrocystic breast disease,[13] which in turn was shown to be a risk factor for breast cancer.[14] On the other hand, a recent finding has suggested that caffeine intake was inversely associated with luteal levels of estrogens in premenopausal consumers.[15] It has been well established that estrogen plays a promotional role in breast carcinogenesis.[16] Caffeine had also been shown to inhibit invasiveness and metastatic capabilities of tumor cells. In vivo studies in spontaneous transgene induced mammary tumor models found that chronic exposure to caffeine suppressed metastasis.[17]

Tea and coffee are also rich in polyphenolic compounds such as flavonoids, lignans and chlorogenic acid.[18] Catechines which belong to the flavonoid class were found to be potent inhibitors of growth in MCF-7 breast cancer cell lines.[19] Experiments in carcinogen-induced rodent models, found that mice that received lifelong catechines and theaflavins survived longer and had smaller mammary tumors.[20] Further experiments using healthy mice models, showed that administration of green tea delayed the onset of spontaneous mammary cancer and suppressed tumor growth by 40% compared to mice controls fed with tap water.[21] Both flavonoids and lignans are members of a diverse group called phytoestrogens. Their structural properties, which are similar to estradiol, enable them to bind to estrogen receptors. Eventhough they weakly mimic endogenous estrogens, they may also act as estrogen antagonists.[22] Chlorogenic acid and caffeic acid which are common coffee polyphenols were found to inhibit DNA methylation in in-vitro studies. As DNA methylation may contribute to breast carcinogenesis, these coffee polyphenols may potentially protect against cancer.[23] Coffee specific diterpenes have also been associated with anticarcinogenic activities in animal models and in-vitro studies whereby they seem to reduce the genotoxicity of several carcinogens.[24]

Tea And Coffee Intake In Relation To Breast Cancer: Evidence From Epidemiological Studies

Over the past few decades, numerous studies have been conducted to investigate the association between tea and coffee intake and risk of breast cancer. In 2007, the World Cancer Research Fund (WCRF) concluded in its report that for the association between premenopausal and postmenopausal breast cancer with dietary exposures like tea and coffee intake, the data were of too low quality, too inconsistent, and the number of studies too small to allow for definite conclusions to be reached.[25] To date, approximately twelve studies investigating the association between green tea intake and breast cancer risk,[26] and more than 15 studies on black tea intake and breast cancer risk[27-29] have been published. One study had investigated the association between oolong tea intake and risk of breast cancer.[30] Meanwhile, more than 20 studies have reported on the association between coffee intake and risk of breast cancer in the last twenty five years.[29,31-33]

Two cohort studies conducted in Japan and five case control studies in China, Singapore and United States, which had assessed the role of green tea in breast cancer prevention, were included in a recent meta-analysis[26] (Figure 1). Pooled analysis of the case control studies had suggested a modest protective effect of green tea against breast cancer (pooled relative risk: 0.89; 95%CI:0.81-0.98), while the cohort studies showed a non statistically significant protective effect (pooled relative risk: 0.85; 95%CI:0.65-1.22). It is likely that the non significant pooled relative risk from the cohort studies is due to inclusion of only 2 studies. Based on these findings, it seems that green tea consumption may be associated with a modest lowering in risk of breast cancer. This study also investigated the association between green tea intake and risk of breast cancer recurrence. Pooled analysis of two cohort studies from Japan with more than 1000 patients showed that drinking more than 3 cups of green tea was associated with approximately 30% reduction in breast cancer recurrence compared to non-consumers (summary relative risk: 0.73; 95%CI: 0.56-0.96). Therefore, it has been suggested that green tea intake may protect against breast cancer recurrence in breast cancer survivors.[26]

The association between black tea consumption and breast cancer incidence had been studied extensively in many countries. A meta-analysis of 13 studies which were conducted in Asia (Japan, Israel), Europe (Sweden, Netherlands, Finland, Denmark, Italy) and America (United States), found that there is no overall protective effect of black tea on breast cancer risk (summary odds ratio: 0.98; 95%CI: 0.88-1.09)[27] (Figure 2). However, analysis restricted to cohort studies seemed to suggest that black tea consumption may have a promotional effect on breast carcinogenesis (summary odds ratio: 1.15; 95%CI: 1.02-1.31). In contrast, pooled analysis of the case control studies seemed to show a very modest protective effect of black tea consumption against breast cancer (summary odds ratio: 0.91; 95%CI: 0.84-0.98) (Table 1). Based on the contradicting findings, it was concluded that current epidemiological data do not support the hypothesis that black tea protects against incidence of breast cancer.

A prospective cohort study in Japan investigated the association between oolong tea intake and risk of breast cancer in more than 40 000 women. Based on this study, it seems

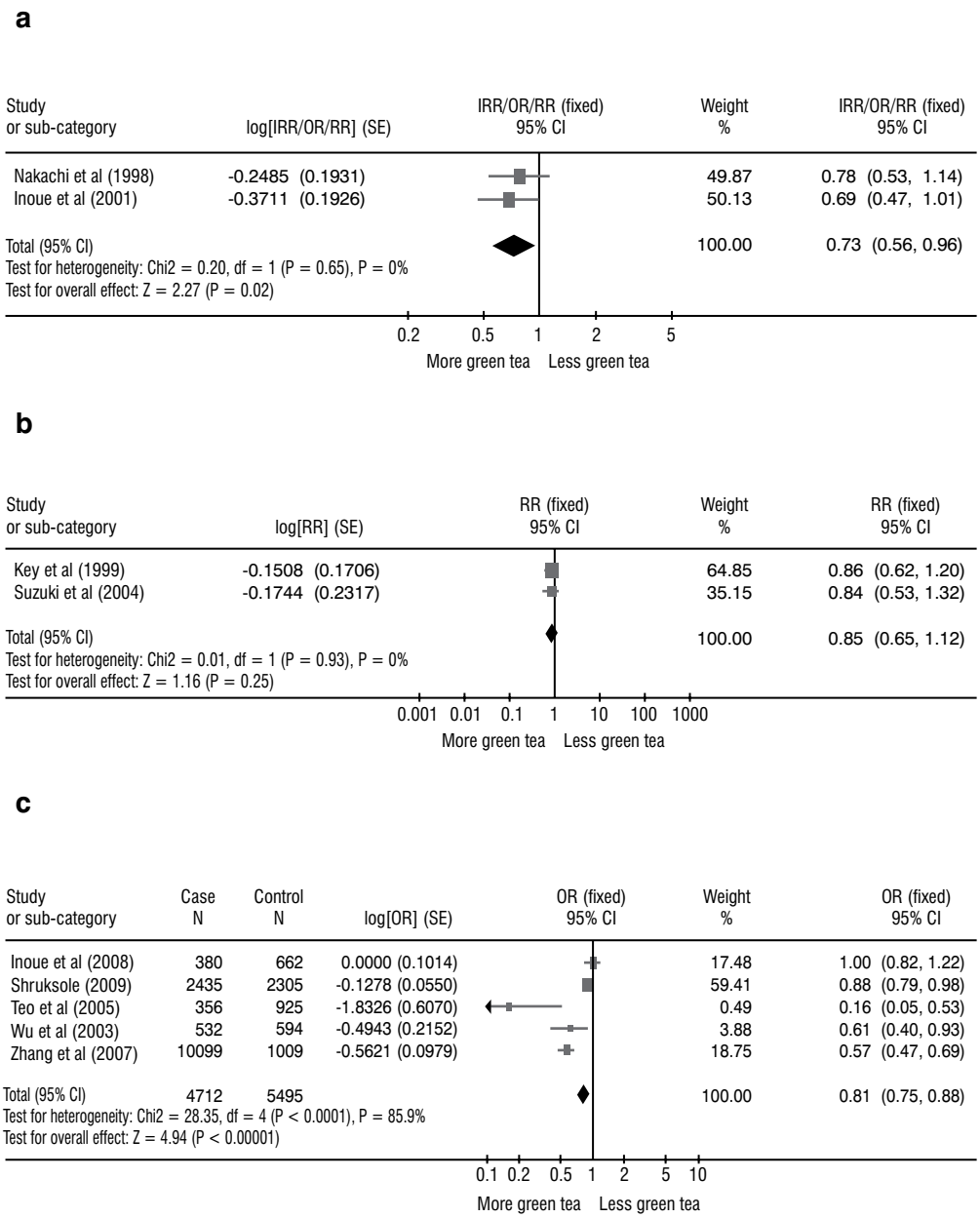

Figure 1. *Meta-analysis of green tea consumption and breast cancer by design of study*

a Meta-analysis of studies of breast cancer recurrence; **b** Meta-analysis of cohort studies of breast cancer risk; **c** Meta-analysis of case–control studies of breast cancer risk

Risk estimates from studies assessing the association between high green tea consumption and breast cancer. Squares indicate study-specific risk estimates; horizontal lines indicate 95% confidence intervals; diamonds indicate pooled relative risk estimate.

Source: Ogunleye et al. Green tea consumption and breast cancer risk or recurrence: a meta-analysis. Breast Cancer Res Treat 2010 (Reproduced with permission from Springer Link)

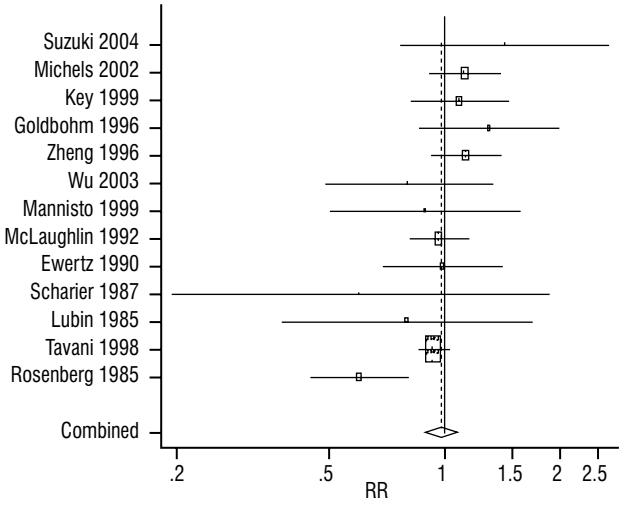

Figure 2. *Pooled results for association between high black tea consumption and risk of breast cancer.*

RR: relative risk
Risk estimates from studies assessing the association between high black tea consumption and breast cancer risk. Squares indicate study-specific risk estimates; horizontal lines indicate 95% confidence intervals; diamond indicates combined relative risk estimate.
Source: Sun et al. Green tea, black tea and breast cancer risk: a meta-analysis of epidemiological studies. Carcinogenesis 2006. (Reproduced with permission from Oxford Journals)

that oolong tea intake of one or more cup daily is not associated with risk of breast cancer (hazard ratio: 0.98; 95%CI: 0.74-1.30).[30]

Between 1985 and 2010, more than 20 studies have been conducted to investigate the role of coffee in relation to breast cancer risk. To date, only two studies have found any significant association. A prospective study of 14,593 participants conducted in late 1980's in Norway had shown that coffee consumption was protective only in lean women (Incidence rate ratio[IRR]: 0.5; 95% CI:0.3-0.9), while it increased the risk in obese women; IRR: 2.1; 95% CI: 0.8-5.2.[34] However, a meta-analysis that included 9 cohort and 9 case control studies from Europe, United States and Japan with a total of 25,250 breast cancer cases reported an association close to unity between coffee intake and breast cancer, whereby the pooled relative risk was 0.95 (95%CI: 0.90-1.00) (Table 2 and Figure 3).[32] Following this study, a few more prospective studies did not show any association between coffee intake and breast cancer risk,[29,35] except a recent prospective study in Sweden which showed that drinking boiled coffee was associated with a significantly lower risk of breast cancer (HR: 0.52; 95% CI: 0.30-0.88, comparing >4 versus <1 occasions/day).[33] Therefore, there seems to be no association between regular coffee intake and risk of breast cancer.

In conclusion, green tea intake may confer a modest protection against risk of breast cancer and recurrence. However, more prospective cohort studies investigating the association between green tea consumption and breast cancer are required to further strengthen the evidence. It seems that neither black tea, oolong tea nor coffee intake is associated with risk of breast cancer, although evidence to date is still considered inconclusive.

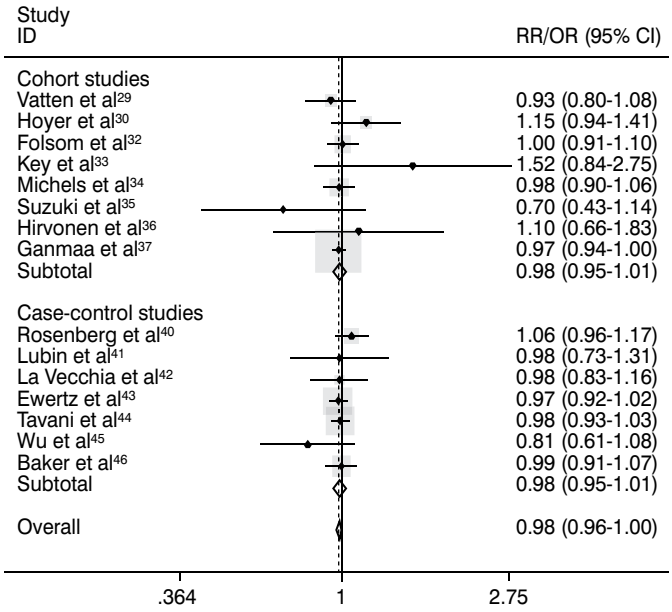

Figure 3. *Association between high coffee consumption and breast cancer risk.*

RR: relative risk; OR: odds ratio

Risk estimates from cohort and case-control studies assessing the association between high coffee consumption (highest vs non/lowest) and breast cancer risk. Squares indicate study-specific risk estimates (size of square reflects the study-statistical weight [ie, inverse of variance]); horizontal lines indicate 95% confidence intervals; diamonds indicate summary relative risk estimate with its corresponding 95% confidence interval.

Source: Tang et al. Coffee consumption and risk of breast cancer. Am J Obstet Gynecol 2009. (Reproduced with permission from Elsevier)

Sources Of Inconsistencies Between Studies On Black Tea And Coffee In Relation To Breast Cancer

Study design

Previous studies on tea and coffee and breast cancer have either used case control or (prospective) cohort designs. Both designs can produce valid and mutually consistent results when performed well and each play an equally important role in medical research. Accurate and timely measurement of exposure (i.e. tea and coffee intake), and outcome (i.e. breast cancer) are an equal challenge to both designs.

The case control studies on black tea (and coffee) have shown contradictory findings, which may have arisen due to methodological issues such as selection and recall bias. Genuine case control studies are prone to selection or recall bias. Particularly, identifying and enrolling the appropriate controls may be challenging, and recall bias is inherently difficult to be captured whereby the cases and controls may recall their exposures differentially. It should be however remarked that some meta-analyses of tea and coffee in relation to breast cancer have categorized nested case control studies as case control studies, apparently to allow pooling of results.[26] However, nested case control studies are case control analyses

Table 1. *Characteristics and Summary Estimates of Studies on Black Tea Consumption and Breast Cancer Risk.*

Study	Design	Study period	Population	No. of cases/no. of non-cases	No. of levels	Lowest exposure level	Highest exposure level	Percent in lowest, highest levels	RR (95% CI) for highest versus lowest level
Cohort studies									
Suzuki 2004	Cohort	1984–1997	Japan	222/34?782	3	Never	Daily	NA	1.44 (0.77–2.69)
Michels 2002	Cohort	1987–1997	Sweden	1271/57?765	5	?1 cup/week	4 + cups/day	32%, 8%	1.13 (0.91–1.40)
Key 1999	Cohort	1969–1993	Japan	342/34?332	3	?1 cup/week	5 + cups/day	62%, 15%	1.10 (0.82–1.48)
Goldbohm 1996	Cohort	1986–1990	Netherlands	507/1376	6	<1 cup/day	5 + cups/day	11%, 19%	1.31 (0.86–1.99)
Zheng 1996	Cohort	1986–1993	USA	1015/10?056	4	Never/monthly	2 + cup /day	58%, 9%	1.14 (0.92–1.41)
Summary OR: all cohort studies									1.15 (1.02–1.31)
Summary OR: cohort studies excluding the two Japanese studies									1.15 (1.00–1.33)
Population-based case–control (PCC) studies									
Wu 2003	PCC	1995–1998	USA	501/593	3	Non-drinkers	>87.5 ml/day	22%, 11%	0.81 (0.49–1.34)
Mannisto 1999	PCC	1990–1995	Finland	310/454	5	0	>150 g/day	20%, 20%	0.89 (0.50–1.57)
McLaughlin 1992	PCC	1982–1984	USA	1617/1617	2	Never	Ever	21%, 79%	0.97 (0.81–1.16)
Ewertz 1990	PCC	1983–1984	Denmark	1474/1322	5	0	5 + cups/day	17%, 7%	0.99 (0.69–1.42)
Scharier 1987	PCC	1973–1980	USA	1510/1882	6	0	5 + cups/day	33%, 0.6%	0.60 (0.20–1.90)
Lubin 1985	PCC	1975–1979	Israel	804/804	4	0	4 + cups/day	28%, 10%	0.80 (0.40–1.80)
Summary OR: PCC studies									0.94 (0.81–1.09)
Hospital-based case–control (HCC) studies									
Tavani 1998	HCC	1983–1994	Italy	5882/5399	2	No	?1 cup/day	21%, 79%	0.94 (0.85–1.03)
Rosenberg 1985	HCC	1975–1982	USA	2645/1476	4	0	5 + cups/day	55%, 6%	0.60 (0.50–0.90)
Summary OR: HCC studies									0.77 (0.50–1.19)
Summary OR: all case–control studies									0.91 (0.84–0.98)

RR: relative risk; OR: odds ratio; CI: confidence interval
Source: Sun et al. Green tea, black tea and breast cancer risk: a meta-analysis of epidemiological studies. Carcinogenesis 2006. (Reproduced with permission from Oxford Journals)

Table 2. *Summary Risk Estimates from Meta-analysis of Coffee Consumption and Breast Cancer Risk*

Study	Studies, n	Cases, n	RR (95% CI)	Heterogeneity test		
				Q	*P*	I^2 (%)
Highest vs lowest consumption						
All studies	18	25,250	0.95 (0.90-1.00)	13.86	.677	0.0
Study design						
All cohort studies	9	9426	0.95 (0.88-1.02)	7.30	.505	0.0
All case-control studies	9	15,824	0.95 (0.87-1.04)	6.56	.585	0.0
Hospital-based case-control studies	4	11,158	0.98 (0.88-1.09)	2.75	.431	0.0
Population-based case-control studies	5	4666	0.87 (0.73-1.03)	2.33	.674	0.0
Study population						
Europe	8	9894	0.95 (0.86-1.06)	3.55	.829	0.0
United States	7	13,983	0.94 (0.87-1.01)	4.82	.567	0.0
Asia	3	1373	0.92 (0.64-1.33)	4.83	.090	58.6
Increment of 2 cups/day						
All studies a	15	21,884	0.98 (0.96-1.00)	12.09	.599	0.0
Study design						
All cohort studies	8	7987	0.98 (0.95-1.01)	7.40	.388	5.5
All case-control studies	7	13,897	0.98 (0.95-1.01)	4.50	.609	0.0
Hospital-based case-control studies	4	11,158	0.99 (0.96-1.03)	2.10	.551	0.0
Population-based case-control studies	3	2739	0.96 (0.92-1.01)	1.49	.474	0.0
Study population						
Europe	7	9584	0.98 (0.95-1.01)	3.14	.791	0.0
United States	5	10927	0.99 (0.95-1.02)	5.01	.287	20.1
Asia	3	1373	0.98 (0.69-1.41)	3.93	.140	49.1

CI, confidence interval; RR, relative risk.
[a] Three studies were excluded because they reported only 2 quantitative exposure categories
Source: Tang et al. Coffee consumption and risk of breast cancer. Am J Obstet Gynecol 2009. (Reproduced with permission from Elsevier)

conducted within cohorts for efficiency reasons. In nested designs, reported intakes of tea (or coffee) are taken at baseline, and therefore independent of disease occurrence, such that selection bias and recall bias are not major issues. The primary reason for the nested design is to attain efficiency for instance, with respect to expensive genetic testing, rather than inexpensive measurements of tea and coffee intake.[36]

Results from large cohort studies on tea and coffee exposure and breast cancer are considered inconclusive. Cohort designs are based on census, accounting for outcome on all cohort members, whereby selection bias and recall bias are less of a problem. However, selective loss to follow-up and presence of confounders are still threats to valid outcome estimations, and may partially explain the inconsistencies of results between the

previous studies. Furthermore, some cohort studies had obtained repeated assessment of exposure among the participants[30,37] while some assessed exposures only at baseline.[29] Using cumulative average of the repeated dietary measurements may not be the optimum method to capture diet-disease associations, as additional systematic measurement error may further distort the associations.[38] In cohort studies where only a single baseline assessment of the beverage intake is taken, it remains questionable whether measurements were indeed taken during the etiologically relevant time period with respect to breast cancer risk.

Measurement of tea and coffee intake

A majority of previous epidemiological studies have used food frequency questionnaires (FFQ) as the tool to measure dietary intake of tea and coffee. Despite being convenient and involving relatively lower cost of data processing compared to food diaries and dietary recalls, FFQs are prone to substantial error.[38] FFQs tend to be subjected to systematic bias where participants may over-report drinks they believe to be healthy (e.g. green tea) and under-report drinks they believe to be unhealthy (e.g. coffee). Since FFQs require participants to recall food items that they have consumed over a specified time period, they rely on the memory of participants. Therefore, it is possible that measurement errors pertaining to use of FFQ have attenuated a modest relative risk for breast cancer associated with tea or coffee intake, to null.[38]

Processing and preparation of tea and coffee / Bioavailability of constituents

Most previous studies did not have adequate information on the type of tea or coffee intake, their concentration, as well as the method of preparation. It may be possible that different subtypes of tea / coffee may in fact have opposing effects such that studying overall beverage intake results in dilution of any plausible association with breast cancer. Furthermore, addition of other food items into beverages e.g. milk into tea may counteract the beneficial effects of tea, as observed in a study investigating tea intake and risk of cardiovascular disease.[39] Method of brewing may also result in changes in the chemical composition of tea/ coffee [6,7] and most epidemiological studies were not designed to address this issue. Different constituents of tea or coffee may have different bioavailability, such as cholorogenic acids which are known to be metabolized extensively in the body to less active compounds.[11] To further complicate the problem, inter-individual variation in metabolic differences may also alter bioavailability of tea and coffee constituents.

Confounding by lifestyle or health related behaviors

Dietary intake is influenced by a complex of other factors such as lifestyle, socioeconomic status, risk of chronic diseases etc. A previous study had suggested that tea- or coffee-drinking associated lifestyles may be important in respect to breast cancer.[29] Table 3 shows the association of socio-demographic and lifestyle characteristics, with tea and coffee intake in a cohort of Dutch women.[29] Therefore, studies investigating tea and coffee intake

***Table 3**. Association between Tea and Coffee Intake and Socio-demographic and Lifestyle Characteristics in a Cohort of 27 323 Dutch Women*

Daily tea consumption	**0 cup**	**0.1–1.0 cups**	**1.1–2.0 cups**	**2.1–3.0 cups**	**3.1–5.0 cups**	**>5 cups**
High educational level (%)	7.4	14.8	16.1	19.7	22.3	29.1
Coffee intake (cups/day)	4.5	3.6	3.6	2.7	2.7	1.5
BMI (kg/m²)	26.0	25.5	25.1	25.0	25.0	24.9
Low physical activity (%)	13.6	9.3	8.1	7.4	6.1	7.3
Current smoker (%)	50.3	36.8	26.7	20.6	16.9	17.9
Alcohol intake (g/week)	17.0	24.2	23.9	24.4	23.9	21.9
Total energy intake (kcal/day)	1751	1827	1813	1813	1828	1785
Saturated fat intake (g/day) [a]	34.1	33.7	33.2	33.1	32.9	32.5
Fiber intake (g/day) [a]	22.8	22.8	23.3	23.9	24.3	24.6
Ever use of oral contraceptives (%)	69.2	77.6	73.2	71.4	69.2	72.9
Daily coffee consumption	**0 cup**	**0.1–1.0 cups**	**1.1–2.0 cups**	**2.1–3.0 cups**	**3.1–5.0 cups**	**>5 cups**
High educational level (%)	21.8	18.7	23.3	22.1	16.6	13.4
Tea intake (cups/day)	5.0	3.0	3.0	2.0	2.0	1.0
BMI (kg/m²)	24.9	25.1	25.0	25.0	25.0	26.0
Low physical activity (%)	10.4	9.8	8.4	7.7	6.9	9.0
Current smoker (%)	17.8	20.9	20.9	23.4	26.4	44.4
Alcohol intake (g/week)	2.2	14.2	24.1	29.0	29.7	26.2
Total energy intake (kcal/day)	1747	1730	1806	1818	1830	1857
Saturated fat intake (g/day) [a]	31.5	32.0	32.6	33.0	33.6	34.4
Fiber intake (g/day) [a]	22.1	23.6	23.6	23.5	23.6	23.6
Ever use of oral contraceptives (%)	81.2	72.2	74.2	72.9	70.6	74.5

a Energy adjusted values

Source: Bhoo Pathy et al. Coffee and tea intake and risk of breast cancer. Breast Cancer Res Treat 2010. (With permission from SpringerLink)

in relation to breast cancer have to be meticulous in collecting data on such confounders, and adopt a multivariable approach during data analysis.

Furthermore, tea and coffee intake seem to be inversely related to one another whereby as tea intake increases, coffee intake reduces.[29] While tea intake is often associated with healthy behaviors, coffee intake somehow seems to be inversely associated with these behaviors. It is therefore often very difficult to disentangle the beverage effect from the beverage-preference effect,[40] as not all factors can be measured objectively such as psychosocial factors (e.g. health beliefs).

Others

Even though animal and cellular studies seem to show promising results, most epidemiological studies were unable to demonstrate significant findings in humans. This is probably due to a combination of higher doses of tea / coffee constituents used in laboratory studies, and the controlled environment in which the animals / cell lines are experimented with. It may also be that there are intrinsic differences in causal factors of cancer in humans and animals. Furthermore, as tea and coffee are complex mixtures of chemicals, it may be that the counter effect between various constituents in these beverages leaves no net health effect in humans.[29]

Future Directions

As results from case-control studies and particularly large cohort studies have been inconclusive, we may have to identify ways to improve the methodology of such studies. Problems related to measurement of exposure maybe partially dealt with by using other instruments to measure tea / coffee intake such as food diaries, or dietary recalls. In recent years, more innovative dietary measurement instruments have been introduced such as internet based assessments, use of digital cameras and cell phones.[41] However, they may be more costly and unable to capture the preparation or concentration of tea or coffee intake. Alternatively, traditional methods can be revised to address their limitations; FFQs that incorporate information on the type, preparation and concentration of beverage can be used to measure tea and coffee intake, and this data may further be calibrated with computer based dietary recalls[42] or biomarker studies.[38] Calibration of dietary intake measurements allows the evaluation of the accuracy of tea and coffee measurements in these cohort studies.[43]

Recent development in nutritional epidemiology includes an increasingly attractive option of using biomarkers as proxies of dietary intake and nutrition status. A nutritional biomarker may be generically defined as any biological specimen that is an indicator of nutritional status with respect to intake or metabolism of dietary constituents.[44] It has been argued that using nutritional biomarkers may be a more direct measure of nutritional status after absorption and metabolism in vivo. Furthermore, using nutritional biomarkers allows us to measure dietary exposure in a less subjective manner than self reports, and may compensate for measurement errors introduced by dietary questionnaires.[45]

The challenge however lies in identifying specific biomarkers for tea or coffee intake which may allow objective measurement of exposure to these beverages. The selected biomarkers have to produce valid estimates and this essentially depends on their ability to reflect actual exposure.[45] Nutritional biomarkers may be used as either proxy indicator of dietary tea and coffee intake, or means of validating such intake as measured by conventional dietary instruments (e.g. FFQ).[44] Some of the biomarkers that have been studied in relation to coffee and tea intake in the recent years are phenolic acids (e.g. 4-O-methylgallic acid (4OMGA) and isoferulic acid), flavonoids (e.g. catechin), and mammalian lignans (e.g. enterodiol).[46,47] These biomarkers however require much further research to establish their reliability and validity, and this process needs substantial resources in terms of time and cost.

Clinical trials assessing the effectiveness of tea or coffee intake in primary or secondary prevention of breast cancer may seem to be an excellent solution to address the methodological challenges faced in non-experimental studies (prospective cohort or case control studies). It has to be however noted that green tea has been extensively studied in many clinical trials as possible chemopreventive agent for other types of cancer such as oral, liver, and prostate malignancies, but results remain inconclusive.[48] Some possible reasons to explain the null findings, include limitations in methodology as characterized by lack of randomization, blinding, or placebo-control, as well as small sample sizes leading to low power to detect modest associations. Another issue is that it is in fact difficult to randomize to lifestyle behaviors such as tea and coffee intake for long term. In cardiovascular disease research, there have been only short-term randomized trials to study surrogates of cardiovascular disease risk such as blood pressure, cholesterol, etc, but this seems rather problematic with breast cancer as there are no established biomarkers for early disease.

Implications Of Tea Or Coffee As Etiologic Factors In Breast Cancer

If tea and coffee intake were causally implicated in breast carcinogenesis, they have a large potential impact on the overall burden of breast cancer around the globe. Since these exposures are modifiable, this may provide (economically) feasible opportunities to direct primary and secondary prevention of breast cancer for instance by adjusting tea or coffee intake habits. However, current evidence on the causality of tea and coffee intake is still considered as an insufficient basis for preventive measures. Therefore, studies investigating the associations between tea and coffee intake and breast cancer should continue by employing cutting edge methodology to deal with previous challenges in the field.

Conclusion

In conclusion, consumption of green tea may be associated with a lower risk of breast cancer, as well as recurrence in breast cancer survivors. Current evidence however does

not support any association between black tea, oolong tea, and coffee intake with risk of breast cancer.

Summary Points:

1. Tea and coffee which are common dietary exposures have been implicated in breast carcinogenesis, fuelled by evidence from basic research.
2. Tea specific constituents such as catechins, as well as other tea / coffee constituents such as caffeine, and chlorogenic acids have generally been found to be protective against breast cancer in in-vivo and in-vitro studies.
3. Epidemiological studies seem to suggest that green tea is associated with lower risk of breast cancer and cancer recurrences, whereas black tea, oolong tea, and coffee are not associated with risk of breast cancer.
4. Problems related to methodology such as weaknesses in study design, error in measurement of tea/ coffee intake, confounding by lifestyle factors, identifying different types and preparation of beverages, etc continue to complicate non-experimental studies investigating tea and coffee intake in relation to breast cancer.
5. Improved methodology in epidemiological studies may aid to further strengthen the current evidence and improve our understanding of the association between tea and coffee intake with breast cancer.

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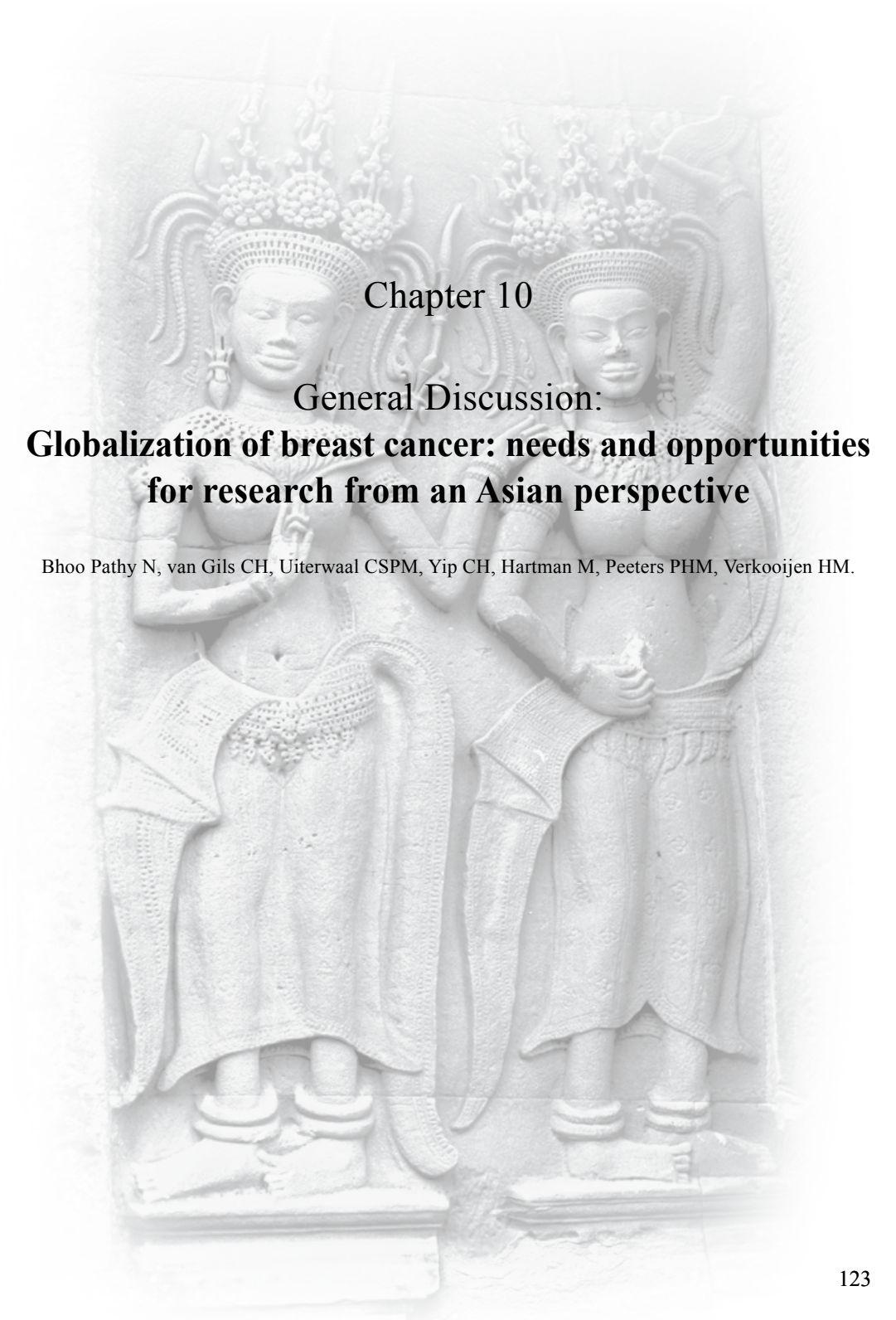

Chapter 10

General Discussion:
Globalization of breast cancer: needs and opportunities for research from an Asian perspective

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Preamble

In the past few decades, Asia has seen rapid economic growth resulting in among others, increasing life expectancies, declining mortality from infectious diseases and westernization of lifestyles. With these developments comes a price whereby breast cancer incidences are increasing in Asian populations. Breast cancer rates have increased by up to 30% over the last 10 years in China and India, whereas in Japan, Korea and Singapore, incidence rates have doubled or even tripled in the past few decades.[1] For instance, in Singapore, the age-standardized incidence rate (ASR) of breast cancer had increased from 20.2 per 100,000/year between 1968 and1972,[2] to 54.9 per 100,000/year between 1998 and 2002.[3] It is therefore conceivable that in the relatively near future, the majority of breast cancer patients will be of Asian ethnicity.

Breast Cancer Research: Do We Need To Adopt Or Adapt Western Knowledge In Asia, Or Do We Need A Different Research Question?

With the globalization of breast cancer, we are now faced with the urgent need to study it in Asian women who were in the past relatively understudied. It has been common practice among both researchers and clinicians to superimpose findings from studies conducted in Western populations onto other ethnic groups.

Whether this practice is appropriate needs to be considered for each of the domains of medical research: etiology, diagnosis, prognosis and intervention. Central to this issue is that Asian women are in many aspects very different from Western women. Clearly, Asian ethnicities, genetic backgrounds, socio-economic profiles, lifestyles, diets, cultures, health beliefs, and even life expectancies are substantially different from those of western women, and each of these may play a distinct role in breast cancer incidence and prognosis.

Etiological Breast Cancer Research

Western derived knowledge on etiology may not be always valid in other populations. As an example, low parity (or nulliparity) had been established as a risk factor for breast cancer based on research in Caucasian women.[4,5] However, studies in African American women have found that increasing levels of parity are associated with lower postmenopausal, but higher premenopausal breast cancer risks,[6,7] whereas in Chinese women, there was no association between parity and risk of premenopausal breast cancer.[8]

In the instances when aetiological factors are valid in either Western or Asian (other) populations, exposure levels may be different and therefore the relevance or (population) attributable risks may substantially be different between populations. As an example, studying the association of coffee and tea with breast cancer may be equally valid in both populations as these beverages are popular and widely consumed worldwide, although types and preparations may differ. In contrast, even though alcohol consumption had been consistently shown to be associated with increased breast cancer risk in Caucasian women,

the prevalence of alcohol consumption is still low in many if not most Asian women and will currently have a smaller relative contribution to breast cancer incidence.[9]

There may also be other etiological factors in breast cancer that are different in Asian women. For instance, Asian women may have different genetic make-up that could in interaction with local exposures constitute distinct pathophysiology. Therefore, it may not seem all that far-fetched to replicate for instance the European Prospective Investigation into Cancer and Nutrition (EPIC) in Asia, as it allows for distinct etiologic studies in Asians, and for international comparisons of heterogeneous populations. In Malaysia, one such study is the Malaysian Cohort Study.[10] This cohort is part of the Asian Cohort Consortium which is an international collaboration between countries including China, India, Japan, Malaysia, Singapore, South Korea, Taiwan, and the USA, which was started in 2005. The aim of this consortium is to study the interaction of genes, environment and lifestyle in causing diseases. Similarly, the Singapore Chinese Health Study is a prospective study which aims to investigate the association between diet with cancer risk and other health outcomes.[11] The results from studies conducted within these cohorts will be able to more accurately depict the current lifestyle practices among Asians, and answer questions which are unique to Asian populations.

Diagnostic And Prognostic Breast Cancer Research

Diagnostic and prognostic breast cancer research is descriptive in nature. In diagnostic breast cancer research the purpose is to, among women clinically suspected of having breast cancer, accurately predict the presence of breast cancer using patient's clinical characteristics, and test results. Ultimately, such research should allow estimation of absolute risks for disease presence given the combined predictors for individual women. In prognostic breast cancer research the purpose is to, among women with diagnosed breast cancer, accurately predict relevant outcomes of breast cancer using combined patient, disease and treatment characteristics for individual women. However, both types of research strongly depend on care settings, on patient characteristics, and on the availability of and access to diagnostic / prognostic tests.

A majority of the Asian countries either fall into the middle or low income categories, and it has been recognized that in these settings, interactions between health system and patient-related barriers have contributed to delayed breast cancer presentation and poor survival.[12] In the recent years, there have been various calls for the introduction of population based mass screening mammography in Asian women.[13] However, there is no evidence that breast cancer screening via mammography would be effective in the Asian setting as Asian women generally have denser breast tissue which may obscure detection of early and small breast tumors.[14] Furthermore, a study conducted among the Chinese women in Hong Kong had described population based mammographic screening in Asian populations as misappropriation of resources, given the currently low breast cancer incidence among our women.[13] In the United States and Europe, it was found that 838 women must be screened

annually for 6 years to prevent one breast cancer death,[15] and this number is expected to be much higher in Asia where breast cancer incidences are lower.[13] Based on these premises, it would seem wiser to channel the available resources in low and middle income Asian countries to improve the awareness and encourage women with breast lumps / symptoms to seek early treatment.[16]

Prognostic research findings from Western countries may also be not readily inferred to Asia, as the outcome of breast cancer depends on a multitude of factors ranging from genetic, clinical and histological predictors to social predictors. For example, 'Adjuvant! Online' is a free online prognostic calculator for women breast cancer which was developed in the United States based on data from the Surveillance, Epidemiology and End Results registry.[17] Since its introduction, Adjuvant! Online has gained wide recognition among clinicians as a tool to aid patient counseling and clinical decision making in the management of women with early breast cancer following receipt of loco-regional treatment.[18] However, a recent study conducted in a multiethnic Asian setting found that Adjuvant! Online significantly overestimated survival in Asian women with breast cancer [unpublished]. The model was shown to be overoptimistic across most subgroups of patients especially in those aged less than 40 years at diagnosis, and of Malay ethnicity. It was further concluded that Adjuvant! Online in its current form may not be suitable for use in Asian women with breast cancer, as it may overestimate survival in a substantial number of patients. The example of Adjuvant! Online illustrates the peril of directly adopting a clinical prediction rule developed in another population to an Asian population. Therefore, it is essential that such prognostic models are validated in Asian patients, and it may even be necessary to adapt an existing prediction rule to improve its utility in Asian settings.

Intervention Research In Breast Cancer

Interventions and treatments that have been found to be effective in Caucasian populations may not always be effective in Asian women. For instance, observational studies conducted in Western settings have found that surgical removal of the primary breast tumor may have a positive impact on survival of women presenting with metastatic breast cancer at initial diagnosis. However, there is an uncertainty whether breast surgery is associated with a survival advantage in Asian women with stage IV breast cancer at initial presentation. In Western settings, a substantial proportion of women with breast cancer undergo so-called metastatic work-up, leading to the detection of small, asymptomatic, often solitary metastases. In most Asian countries, systematic work-up for detection of asymptomatic metastatic lesions is rare due to limited resources. Therefore, distant metastases are mostly detected due to symptoms and more likely to involve multiple sites compared to affluent settings. Therefore, the impact of an intervention such as breast surgery on survival of patients with metastatic breast cancer in these two different settings may not be the same and one can only validly assess the impact of breast surgery in the Asian patients by replicating a similar study from the West.

There are also issues with regards to generalizing findings from clinical trials conducted in Western settings to Asian populations. A recent review studying the differences in toxicity and clinical outcome following treatment with anticancer drugs had highlighted that there may be ethnic differences in tolerability and response to hormonal treatment and cytotoxic chemotherapy in breast cancer.[19] Therefore, anticancer drugs may have to be tested in multiethnic Asian populations before claims on the potential benefits of the new treatment can even be made. For instance, the China's State Food and Drug Administration requires that local pharmacokinetic studies must be conducted in Chinese patients, and a minimum of 100 Chinese patients per arm must be included in international Phase III trials, before a new drug could be approved for marketing in China.[20]

The Impact Of Breast Cancer Research In Asia

Performing cancer research in Asia is not merely about gaining new knowledge but much more than that. It is of prime importance that research findings are judiciously translated into clinical practice, and guide policy makers to perform health transformation and realigning their funding priorities. With the rapid industrialization of most Asian countries, breast cancer will be soon one of the leading causes of death replacing infectious diseases, and it is crucial that the governments in developing Asian countries are prepared to deal with this. It has been estimated that 1.7 million women will be diagnosed with breast cancer in 2020, with most cases originating from the developing countries.[21] Experts have warned that most of these nations will not be prepared to face the crisis as they do not have the infrastructure in place to prevent cancer, diagnose it early, or provide long-term treatment.[22]

The currently reported low incidence of breast cancer in Asian countries should not be used as an excuse for non –action.[12] Labeling breast cancer as 'low-priority'[23] is not going to benefit any nation and affirmative actions have to be taken immediately. It also seems that the creation of awareness that breast cancer is a treatable disease not only has to be directed at the public, but also at policy-makers in Asia. While some international expert groups such as the Breast Health Global Initiative[12] and CanTreat International[22] have been lobbying to improve cancer prevention and control in developing countries, Asian governments also need to proactively take actions to combat cancer. Central to this issue, would be to convince the policy makers in this region that breast cancer is a growing public health threat in Asian countries.

Areas for action in breast cancer prevention should be ideally multifaceted, and therefore include primary, secondary and tertiary prevention. Thus, health care systems should be groomed to not only promote the prevention of breast cancer incidences, but also to detect it early, and ensure that women are offered access to adequate treatment as well long term follow-up, and palliative care when necessary. The aim of this approach is to improve the survival rates and quality of life of Asian patients with breast cancer.

A crucial step therefore would be to quantify the extent of cancer related problems in Asia. Therefore, cancer registries are essentially needed in Asian countries to facilitate health service planning and policy-making, by providing valuable information about the local population. Ideally, every country should set up a population based cancer registry which is enriched with demographic, clinical, pathological and treatment data. However, when resources are lacking, hospital based cancer registries may be used as stepping stones in establishment of population based registries.

The formation of the Singapore-Malaysia Hospital Based Breast Cancer Registry was a first step in realizing the above mission.[24] To date, this registry covers patients from two academic hospitals from Singapore (National University Hospital) and Malaysia (University Malaya Medical Centre) and includes approximately 6000 patients. Over the past two years, members of the Singapore-Malaysia Breast Cancer Working Group have performed various studies among others determining the prognostic factors of survival in Asian women following breast cancer,[25,26] as well as validate prognostic classification systems such as Lymph Node Ratio[27] and Adjuvant! Online in Asian women [unpublished]. Further studies to answer important questions that have the potential to influence clinical practice and also health related policies in Asian region are also currently underway. It is expected that the Singapore-Malaysia Breast Cancer Working Group will be able to spread its wings to other South East Asian countries such as Indonesia, and Thailand in the near future. Ultimately, it is hoped that this working group will substantially contribute to breast cancer research in Asia. Their findings can be used by local policy makers to set up systems to face the daunting challenges (to be) imposed by breast cancer in the not too distant future.

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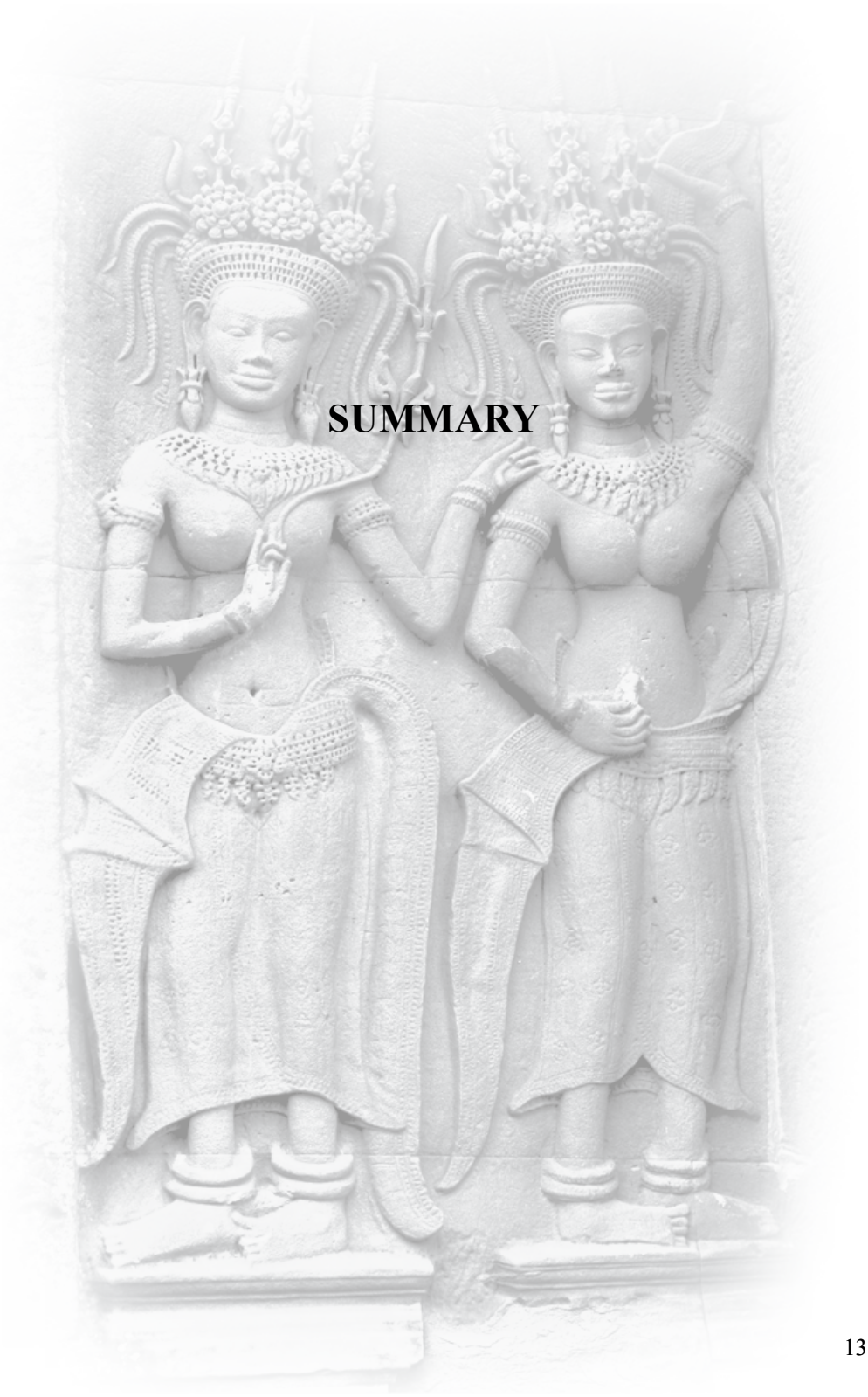

SUMMARY

Introduction

Breast cancer results in significant mortality and morbidity across the globe. In Asia, the burden of breast cancer is increasing at an alarming rate. However, there seems to be a paucity of studies to answer important questions pertaining to breast cancer in Asian settings. This thesis therefore presents some new knowledge on breast cancer in Asian women.

Asia

In **Chapter 2**, we described the setting-up of the Singapore-Malaysia Breast Cancer Registry (SMBCR) as well as the clinical and pathological tumor characteristics, treatment patterns, and outcomes of breast cancer among our cohort of Southeast Asian women. The results of this study indicate that the presentation of breast cancer of women in Asian settings may indeed be different from the Caucasian/Western settings. Approximately 50% of the women in our study were diagnosed before the age of 50 years. This is in contrast to the Western settings where breast cancers in women aged younger than 50 years accounts for about 23% of the total breast cancer incidence. Asian women also presented with larger tumors, and 10% of them had metastatic breast cancer at initial presentation as opposed to 3%–6% in the Western settings. The overall mastectomy rates in our population were higher, whereas breast conserving surgery rates for early stage breast cancer were lower than in the West. Our chemotherapy administration rates were also higher than countries like Sweden, United Kingdom and USA. While the 5-year overall survival rates for patients with early breast cancer (stage 0 and I) were comparable with patients from affluent settings, patients with more advanced stages had worse 5-year overall survival rates. A multi-sectoral approach aiming at early detection and effective management may reduce the burden of breast cancer in Asia.

As a significant proportion of patients with breast cancer in Asia present with metastatic disease at diagnosis, in **Chapter 3**, we evaluated the impact of breast surgery on survival of these patients by performing a historical cohort study. This is based on a growing body of evidence from observational studies from Western settings suggesting that surgery of the primary breast tumor may have a positive impact on survival. Since the surgeons' decision 'to operate or not to operate' is influenced by the underlying prognosis of the patient whereby those who are deemed fit or those with limited metastatic involvement are more likely to receive surgery, whereas those who appear ill or have concurrent illness are less likely to be selected for surgery, we used propensity score analysis to minimize the bias associated with patient selection. Of 375 patients presenting with metastatic breast cancer to the University Malaya Medical Center (UMMC), Malaysia between 1993 and 2008, 139 (37.1 per cent) underwent surgery. Two-year survival was significantly higher in women subjected to surgery compared to those without surgery. Breast surgery was associated with 28% (hazard ratio (HR): 0.72, 95%CI: 0.56 to 0.94) lower risk of mortality, after adjustment for patient and tumor characteristics, metastatic profile and treatment. Therefore, breast surgery seems to be associated with a survival advantage in women presenting with metastatic breast cancer at diagnosis, in resource-limited Asian settings.

Many recently published studies have investigated the prognostic value of new biomarkers in breast cancer by using data from cancer registries. These registries often span long periods whereby the biomarkers may not have been assessed routinely in the initial phase. Particularly of concern is that a number of recently published studies have performed complete case analyses (while disregarding potential biases). In **Chapter 4**, using Human epidermal growth factor receptor 2 (HER2) as an example, we found that in the early years after its introduction, testing for HER2 status in UMMC was significantly associated with prognosis of the patients, as predicted by their age and disease profile. This finding shows that performing naive complete case analysis on registry based data when studying the prognostic value of a newly introduced biomarker may potentially lead to invalid conclusions.

Adjuvant! Online is a free web-based tool which predicts the 10-year breast cancer outcomes and efficacy of adjuvant therapy in patients with early breast cancer. In **Chapter 5**, we validated this program in a multi-ethnic cohort of Asian women. For the entire cohort, Adjuvant! Online predicted 10 year survival was significantly higher than the observed 10 years survival by 6.7% (95%CI: 3.0-10.4%, $p<0.001$). The model was especially overoptimistic in women under 40 years and of Malay ethnicity, where survival was overestimated by approximately 20% ($p<0.001$) and 15% ($p=0.003$) respectively. Adjuvant! Online however is capable of discriminating between good and poor survivors; area under the receiver operating characteristic curve = 0.73. We therefore suggest that the model needs further adaptation prior to use in the Asian setting.

In **Chapter 6**, we described the study evaluating the impact of ethnicity on survival after breast cancer in the multi-ethnic region of South East Asia. Data from the SMBCR was used. Of 3883 patients, a majority were Chinese (75%), followed by the Malays (16%) and Indians (9%). Malay patients presented at a significantly younger age, with larger tumors, and at later stages than women of other ethnicities. They also seemed to have a more aggressive tumor biology compared to other races, as evidenced by their higher risk of axillary lymph node involvement with similar tumor size. Five year overall survival was not significantly different between the Chinese (72.4%; 95%CI: 70.4%-74.4%) and Indian (65.3%; 95%CI: 59.4%-71.1%) patients, but was substantially lower in Malay patients (47.4%; 95%CI: 42.7%-52.1%). Compared to the Chinese, Malay ethnicity was associated with 60% higher risk of all cause mortality (HR: 1.60; 95%CI: 1.44-1.77), independent of patient profile, TNM stage, tumor characteristics and treatment. Indian ethnicity was also associated with a modest increase in mortality risk (HR: 1.16; 95%CI: 1.03 -1.32). The underlying reasons to explain the ethnic disparities in survival especially in the Malays may include variations in tumor biology, psychosocial and cultural factors, treatment responsiveness and lifestyle after diagnosis of breast cancer.

Europe

Lifestyle is increasingly being implicated as an etiologic and prognostic factor in breast cancer. In **Chapter 7**, we investigated the association of coffee and tea consumption with the risk of breast cancer among women in EPIC-NL cohort, a population-based prospective cohort in Netherlands with 27 323 participants. Exposure was measured by a validated food frequency

questionnaire and outcome verified by linkage with the Netherlands Cancer Registry. In approximately 10 years of follow-up, 681 invasive primary breast cancers were diagnosed. Compared to no intake, coffee consumption increased the risk of breast cancer by more than twofold as compared to non consumers (HR; 2.25, 95% CI; 1.30-3.90). This association did not hold after multivariate adjustment which resulted in a HR of 1.17, 95% CI; 0.65-2.12. In fact, this effect of adjustment indicated that the coffee (or tea) drinking associated lifestyle seems important in respect to breast cancer. In this study, we concluded that coffee and tea consumption are not related to the risk of breast cancer in women.

In **Chapter 8**, we extended the above study in the European Prospective Investigation into Cancer and Nutrition which includes 335,868 participants from 10 European countries. This was in light of not being able to study some specific subgroups such as premenopausal breast cancers, and distinguishing between intake of caffeinated and decaffeinated coffee in our earlier study. A total of 7482 primary invasive breast cancers were diagnosed in about 10 years of follow-up. Caffeinated coffee intake was marginally associated with a lower risk of breast cancer; hazard ratio (HR) 0.89; 95%CI: 0.79-1.00, for high consumption versus no consumption, whereas decaffeinated coffee consumption was associated with a higher risk of breast cancer (HR: 1.17; 95% CI: 1.05-1.30), for above median consumption versus no consumption. Tea and total coffee intake were not associated with breast cancer. The null finding for the association between total coffee intake and risk of breast cancer may be a result of dilution; whereby caffeinated and decaffeinated coffee intakes seem to be associated with opposite effects. However, since the associations between caffeinated and decaffeinated coffee intakes and risk of breast cancer have never been reported, results have to be interpreted cautiously.

In **Chapter 9**, we first discussed the underlying mechanisms by which coffee and tea constituents may be associated with breast carcinogenesis. We also reviewed the epidemiological evidence on the association between coffee and different types of tea consumption in relation to breast cancer. Previous studies seem to suggest that green tea is associated with lower risk of breast cancer and cancer recurrences, whereas black tea, oolong tea, and coffee are not associated with risk of breast cancer. Problems related to methodology such as weaknesses in study design, error in measurement of tea/ coffee intake, confounding by lifestyle factors, identifying different types and preparation of beverages, etc continue to complicate non-experimental studies investigating tea and coffee intake in relation to breast cancer. Improved methodology in epidemiological studies may aid to further strengthen the current evidence and improve our understanding of the association between tea and coffee intake with breast cancer.

General

There is good reason to believe that Western derived knowledge on breast cancer may not be always applicable to other populations such as in Asia. In **Chapter 10**, we had discussed this sentiment along the four domains of medical research i.e. etiologic, diagnostic, prognostic, and intervention research. As Asian ethnicities, genetic backgrounds, socio-economic profiles,

lifestyles, diets, cultures, health beliefs, and even life expectancies are substantially different from those of western women, it may not seem far-fetched to replicate etiologic studies from the Western settings in Asia, be it on a large (e.g. European Prospective Investigation Into Cancer and Nutrition) or small scale (hospital based). It is also felt that diagnostic and prognostic studies findings (or prediction rules) which are 'setting sensitive' must be validated in Asian women before recommending it for use in clinical settings in Asia. Importantly, interventional research findings from Caucasian populations must also be carefully interpreted. There is often a need to replicate interventional studies in Asia for a variety of reasons among others, differences in host factors such as tumor biology, response to treatment, and also health beliefs which can influence treatment acceptance and adherence.

SAMENVATTING

Inleiding

Borstkanker is wereldwijd een van de belangrijkste oorzaken van morbiditeit en sterfte onder vrouwen. Hoewel incidentie van en sterfte aan borstkanker in Azië in snel tempo stijgen, zijn er maar weinig studies die zich specifiek richten op oorzaak en uitkomst van borstkanker in de Aziatische setting. Dit proefschrift verschaft nieuwe inzichten ten aanzien van borstkanker in Aziatische vrouwen.

Azië

Hoofdstuk 2 beschrijft de totstandkoming van de Singapore Maleisische Borstkanker registratie (Singapore-Malaysia Breast Cancer Registry, SMBCR) en geeft een overzicht van klinische kenmerken, tumorkarakteristieken, behandelingspatronen van en overleving na borstkanker in een cohort van borstkankerpatiënten in Zuidoost Azië. Dit hoofdstuk laat zien dat borstkanker zich in Aziatische vrouwen op een andere manier manifesteert dan in Westerse vrouwen. In tegenstelling tot Westerse populaties, waar minder dan een kwart van alle borstkankerpatiënten jonger is dan vijftig jaar, wordt ongeveer de helft van de Aziatische borstkankerpatiënten gediagnosticeerd voor het vijftigste levensjaar. Aziatische patiënten presenteren zich ook met grotere tumoren, en bij 10% van de patiënten worden, op het moment van het stellen van de diagnose, metastasen op afstand gevonden. In de Westerse setting is dit percentage 3-6%. Aziatische vrouwen worden vaker behandeld met mastectomie, en vrouwen met kleine (stadium 1) tumoren worden minder vaak borstbesparend geopereerd. In Azië wordt borstkanker vaker behandeld met adjuvante chemotherapie dan bijvoorbeeld in Zweden, het Verenigd Koninkrijk en de Verenigde Staten. Patiënten met vroege tumoren (*in situ* carcinomen en stadium 1) hebben overlevingskansen die vergelijkbaar zijn met die van Westerse vrouwen, maar patiënten met vergevorderde ziekte (Stadium 3 en 4) hebben een beduidend slechtere vijfjaarsoverleving. Om de desastreuze effecten van borstkanker in Azië te controleren, is een strategie nodig, die zowel gericht is op vroegere opsporing van borstkanker, als op effectievere behandeling.

Een aanzienlijk deel van de Aziatische borstkankerpatiënten heeft op het moment dat de diagnose gesteld wordt al metastasen op afstand. **Hoofdstuk 3** beschrijft een historische cohort studie, waarin geëvalueerd wordt of chirurgische verwijdering van de primaire borsttumor de overleving van patiënten met gemetastaseerde borstkanker kan verbeteren. De aanleiding voor deze studie was dat een reeks van observationele studies uit Westerse populaties heeft laten zien dat chirurgische verwijdering van de primaire tumor de overleving kan verbeteren. De beslissing van de chirurg om al dan niet over te gaan tot operatieve verwijdering van de tumor wordt mede beïnvloed door onderliggende prognostische factoren. Patiënten met bijvoorbeeld weinig comorbiditeit en beperkte uitbreiding van de ziekte hebben een grotere kans geopereerd te worden dan vrouwen met een minder goede algemene gezondheid en ongunstige tumorkenmerken. Met behulp van ‘propensity score’ analyse is in deze studie getracht deze zogenaamde confounding by indication bias te minimaliseren. Tussen 1993 en 2008 werden bij 375 vrouwen in het University Malaya Medical Center (UMMC, Maleisië) op het moment van diagnostiek van de primaire tumor ook metastasen op afstand gevonden. Bij 139 (37%) van deze vrouwen werd de

primaire tumor operatief verwijderd en hun tweejaars overleving was significant beter dan die van vrouwen bij wie de tumor niet operatief verwijderd was. Na correctie voor patiëntkenmerken, tumorkarakteristieken, aantal en type metastasen op afstand en andere behandelingsmodaliteiten door middel van 'propensity score' analyse, bleek dat chirurgie geassocieerd was met een 28% lagere sterfte (Hazard Ratio (HR): 0,72; 95% betrouwbaarheidsinterval (BI): 0,56-0,94). De conclusie van deze studie was dat ook in een 'limited resource setting' chirurgische verwijdering van de primaire tumor de overleving van vrouwen met metastasen op afstand op het moment van diagnose kan verbeteren.

Voor evaluatie van de prognostische waarde van nieuwe biomarkers voor borstkanker wordt vaak gebruik gemaakt van de gegevens van kankerregistraties. Deze registraties beslaan vaak lange periodes waarin de biomarkers, vooral in de beginfase, niet standaard bij iedere patiënt werden gemeten. Sommige recent gepubliceerde studies hebben de prognostische waarde van nieuwe biomarkers geanalyseerd aan de hand van 'complete case' analyse, geen rekening houdend met mogelijke introductie van bias. **Hoofdstuk 4** gebruikt het voorbeeld van de introductie van Human Epidermal Growth Factor Receptor 2 (HER2) om dit probleem te illustreren. In de eerste jaren na introductie in het UMMC was het uitvoeren van de HER2 test op zichzelf al geassocieerd met de overlevingskans gebaseerd op leeftijd en ziekteprofiel. Patiënten bij wie de test niet verricht was hadden ofwel een bijzonder goede, of juist een bijzonder slechte uitkomst. Deze bevinding benadrukt dat bij prognostisch onderzoek naar nieuwe biomarkers 'complete case' analyse van kankerregistratie data kan leiden tot onjuiste conclusies.

Adjuvant! Online is een gratis internet programma, dat zowel tienjaars overleving na borstkanker als het effect van adjuvante therapie voorspelt. **Hoofdstuk 5** beschrijft een validatie studie van dit programma in een multi-etnische Aziatische setting. Adjuvant! Online blijkt de tienjaars overleving na borstkanker in Aziatische patiënten te overschatten met gemiddeld 6.7% (95%BI: 3,0-10,4%; $p<0,001$). Vooral bij vrouwen jonger dan veertig jaar en bij vrouwen met een Malay etniciteit was Adjuvant!Online overoptimistisch en werd de tienjaars overleving met respectievelijk 20% ($p<0,001$) and 15% ($p=0,003$) overschat. Adjuvant! Online bleek redelijk in staat is goede en slechte overlevers van elkaar te onderscheiden, met een oppervlakte onder de Receiver Operating Characteristic curve van 0,73. Op basis van deze studie kan geconcludeerd worden dat Ajduvant! Online aangepast moet worden voordat het kan worden gebruikt in Azië.

De bevolking van Zuidoost Azië bestaat overwegend uit drie etniciteiten, i.e. de Chinese, Malay en Indiase etniciteit. **Hoofdstuk 6** beschrijft de associatie tussen etniciteit en overleving na borstkanker in Zuidoost Azië, gebruik makend van het SMBCR cohort. Malay patiënten werden op jongere leeftijd gediagnosticeerd, hadden grotere tumoren en meer vergevorderde ziekte dan vrouwen met een Chinese of Indiase etniciteit. Malay patiënten hadden ook een hoger risico op uitzaaiingen in de axillaire lymfklieren dan Chinese of Indiase vrouwen met primaire tumoren van vergelijkbare grootte. Dit suggereert dat tumoren in Malay patiënten zich agressiever gedragen dan tumoren in andere etnische groepen. De vijfjaars overleving was vergelijkbaar voor Chinese (72,4%; 95%BI: 70,4%-74,4%) en Indiase (65,3%; 95%BI: 59,4%-71,1%) patiënten, terwijl Malay patiënten een significant slechtere overleving lieten zien (47,4%; 95%BI: 42,7%-52,1%). Ook na correctie voor patiëntkarakteristieken, stadium, tumorkenmerken en behandeling bleef

Malay etniciteit geassocieerd met een verhoogd risico op overlijden (HR: 1,60; 95%BI: 1,44-1,77), Indiase etniciteit was geassocieerd met een marginaal verhoogd risico (HR: 1,16; 95%BI: 1,03-1,32). Verklaringen voor etnische verschillen in overlevingskansen na borstkanker zouden kunnen berusten op verschillen in tumorbiologie, psychosociale en culturele factoren, respons op chemotherapie en hormoontherapie en leefstijl na de diagnose.

Europa

Er komen steeds meer aanwijzingen dat leefstijl een rol speelt in het ontstaan en verloop van borstkanker. In **hoofdstuk 7** onderzochten we of de mate van koffie en thee consumptie de kans op het krijgen van borstkanker beïnvloedt. Dit onderzoek werd uitgevoerd in het zogenaamde EPIC-NL cohort, een Nederlands cohort met 27.323 vrouwelijke deelnemers. Koffie- en theeconsumptie onder de deelnemers werd vastgesteld met behulp van voedingsfrequentievragenlijsten. Om na te gaan of een deelneemster borstkanker ontwikkelde of niet werden de gegevens gekoppeld met die van de Nederlandse Kanker Registratie. In een periode van ongeveer 10 jaar, werden 681 vrouwen met invasief borstkanker gediagnosticeerd. In vergelijking met vrouwen die geen koffie drinken was de kans om borstkanker te krijgen meer dan twee keer zo hoog bij vrouwen die veel koffie drinken (HR: 2,25; 95%BI: 1,30-3,90). Na correctie voor confounders was dit effect niet langer zichtbaar, met een hazard ratio van 1,17; 95%BI: 0,65-2,12). De verdunning van dit effect na correctie voor confounders geeft aan dat leefstijlfactoren die samenhangen met koffie- en theeconsumptie belangrijk zijn voor de kans op borstkanker. De conclusie van deze studie was dat koffie- en theeconsumptie geen effect hebben op het borstkankerrisico bij vrouwen.

In **hoofdstuk 8**, breidden we de bovengenoemde studie uit tot het hele EPIC cohort (European Prospective Investigation into Cancer and Nutrition), met 335.868 vrouwelijke deelnemers uit 10 Europese landen. In tegenstelling tot bovengenoemd onderzoek waren we nu ook in staat in de analyses onderscheid te maken tussen verschillende subgroepen, bijvoorbeeld pre- en postmenopauzaal borstkanker, en ook tussen cafeïnehoudende en cafeïnevrije koffie. In een periode van ongeveer 10 jaar, werden 7.482 vrouwen met invasief borstkanker gediagnosticeerd. De consumptie van cafeïnehoudende koffie liet een zwak beschermend effect zien in relatie tot borstkanker (HR: 0,89; 95%BI: 0,79-1,00), voor vrouwen met een hoge consumptie, vergeleken met vrouwen die geen cafeïnehoudende koffie drinken. Cafeïnevrije koffie echter, liet een iets verhoogde kans op borstkanker zien (HR: 1,17; 95%BI: 1,05-1,30), voor een hoger dan mediane consumptie vergeleken met helemaal geen cafeïnevrije koffie). De consumptie van thee en de consumptie van de totale hoeveelheid koffie (zonder onderscheid tussen cafeïnehoudend en cafeïnevrij) waren beiden niet gerelateerd aan de kans op borstkanker. De afwezigheid van een relatie tussen de totale hoeveelheid koffie en de kans op borstkanker zou verklaard kunnen worden door het feit dat cafeïnehoudende en cafeïnevrije koffie tegengestelde effecten laten zien. Deze resultaten moeten echter voorzichtig geïnterpreteerd worden omdat deze effecten van cafeïnehoudende en cafeïnevrije koffie nog niet eerder in andere studies gerapporteerd zijn.

In **hoofdstuk 9** bespreken we allereerst de onderliggende mechanismen waardoor bestanddelen uit koffie en thee de ontwikkeling van borstkanker zouden kunnen beïnvloeden.

Vervolgens geven we een overzicht van de literatuur over de relatie tussen koffie en verschillende theesoorten en de kans op borstkanker. Eerder studies wijzen in de richting dat groene thee de kans op borstkankerrecidieven verlaagt, terwijl zwarte thee, oolong thee en koffie de kans op borstkanker niet beïnvloeden. Methodologische problemen zoals tekortkomingen in de studieopzet, meetfouten in koffie- en theeconsumptie, confounding door leefstijlfactoren en het niet kunnen onderscheiden van verschillende typen en bereidingswijzen van koffie en thee bemoeilijken de interpretatie van niet-experimentele studies op dit gebied. Verbeteringen in de methodologie van epidemiologische studies kunnen de bewijskracht verder versterken en meer inzicht geven in de relatie tussen koffie- en theeconsumptie en de kans op borstkanker.

Algemeen

Het is aannemelijk dat kennis over borstkanker, verworven in Westers onderzoek, niet altijd toepasbaar is op andere bevolkingsgroepen, zoals die in Azië. In **hoofdstuk 10**, bespreken we in hoeverre hiervoor nieuw onderzoek opgezet moet worden, voor ieder van de vier onderzoeksdomeinen in medisch-wetenschappelijk onderzoek, te weten: etiologie, diagnostiek, prognostiek en interventie. Aziatische etniciteiten, genetische achtergronden, sociaaleconomische profielen, leefstijlen, eetgewoonten, culturen, denkbeelden ten aanzien van gezondheid en zelfs levensverwachtingen verschillen aanzienlijk van die van Westerse vrouwen. Daarom lijkt het nuttig etiologische studies uit het Westen over te doen in Azië. Dit kan op grote schaal (vergelijkbaar met de European Prospective Investigation into Cancer and Nutrition) of op kleine schaal (bijvoorbeeld een ziekenhuis). Het lijkt ook belangrijk om bevindingen uit diagnostische en prognostische studies (ofwel predictieregels), die afhankelijk zijn van een specifieke setting, eerst te valideren in Aziatische vrouwen, alvorens deze te implementeren in de Aziatische klinische praktijk. Eveneens belangrijk is dat bevindingen uit interventieonderzoek bij Kaukasische bevolkingsgroepen voorzichtig worden geïnterpreteerd. Het zal vaak noodzakelijk zijn om deze studies te herhalen in Azië vanwege, onder andere, verschillen in tumorbiologie, response na behandeling, en ook in denkbeelden ten aanzien van gezondheid die de therapietrouw beïnvloeden.

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‘You’ll never walk alone’

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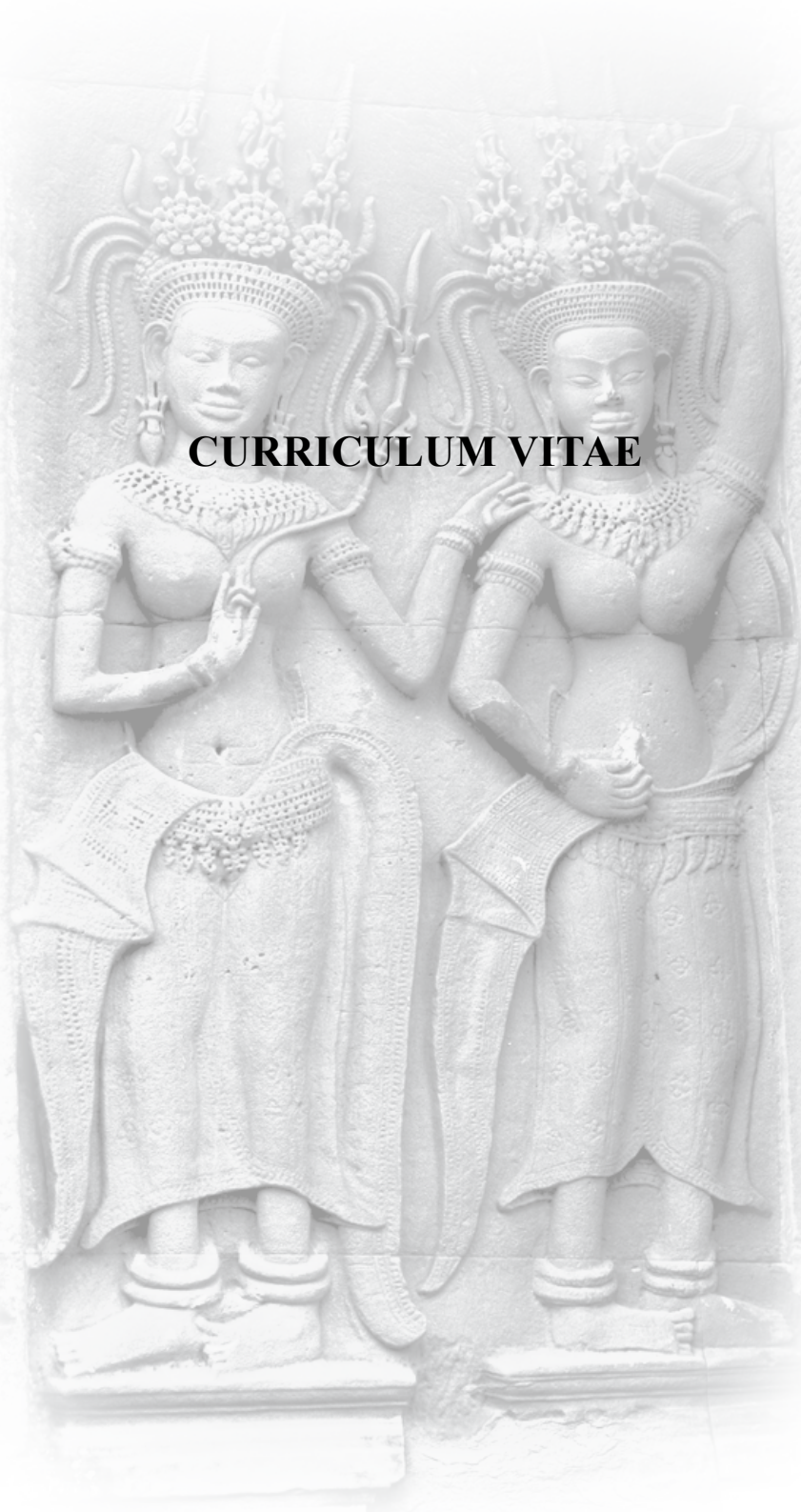
Ella pugalum iraivanukke…



CURRICULUM VITAE

Nirmala Bhoo Pathy was born on Aug 4th 1976 in Johor (Malaysia). After attending the Khir Johari Secondary School in Sg Sumun, Perak, she went to medical school in University of Malaya, and graduated with Bachelor of Medicine and Bachelor of Surgery (MBBS) in 2001. Following two years of internship in University Malaya Medical Centre, Nirmala Bhoo Pathy served as a medical and health officer in a rural health clinic in Hulu Langat District in Selangor (Malaysia). In 2006, she pursued her master's degree in public health in University of Malaya. Shortly after completion of her Master of Public Health (MPH) with distinction in 2008, Nirmala Bhoo Pathy was offered a scholarship from the European Union via the AsiaLink Clinical Epidemiology and Evidenced Based Medicine Program. In the context of this program, she was offered a PhD fellowship in clinical epidemiology in Utrecht University. In Sept 2008, Nirmala Bhoo Pathy started her doctoral training in Julius Center for Health Sciences and Primary Care in University Medical Center Utrecht, where she successfully completed her Master of Science in Clinical Epidemiology with cum laude. Following return to Malaysia in 2009, Nirmala Bhoo Pathy together with a group of epidemiologists, breast surgeons and oncologists from Singapore and Malaysia formed the Singapore-Malaysia Breast Cancer Working Group. A major part of her doctoral thesis is based on the work that was done with this group.