Prognostic Factors and Survival of Breast Cancer Patients in the National Cancer Institute, Thailand

การศึกษาปัจจัยในการพยากรณ์และการรอดชีพของผู้ป่วยมะเร็งเต้านม ณ สถาบันมะเร็งแห่งชาติ

Warangkana Chantarasuk (วรางคณา จันทรสุข)* Dusit Sujirarat (ดุสิต สุจิรารัตน์)**
Aronrag Cooper Meeyai (อรุณรักษ์ คูเปอร์ มีใย)*** Arkom Chaiwerawattana (อาคม ชัยวีระวัฒนะ)****

ABSTRACT

The study design was a retrospective cohort study, which aimed to study the 5-years survival rate and significant prognosticating factors of breast cancer treated at the National Cancer Institute of Thailand. There were 537 breast cancer patients whose status was followed until December 31, 2007. The overall survival rate at five years was 73.7%. There were nine factors which had significant differences in the survival time. Stage, combination of ER, PR, and HER2 status and treatment methods were associated with survival rate of breast cancer patients. A combination of ER, PR, and HER2 status was the most significant prognosticating factor for survival. Thus, woman at high risk of the breast cancer should be screened. The results of this study provide useful information for planning screening early stage of breast cancer and for planning breast cancer treatment.

บทคัดย่อ

ระเบียบวิจัยเป็นการศึกษาแบบย้อนหลังเพื่อหาการรอดชีพและปัจจัยการพยากรณ์โรคของผู้ป่วยมะเร็งเต้านมที่มารับรักษา ณ สถาบันมะเร็งแห่งชาติ ผู้ป่วยมะเร็งเต้านม 537 คนได้รับการติดตามจนถึง 31 ธันวาคม พ.ศ. 2550 อัตรารอดชีพ 5 ปี เท่ากับ ร้อยละ 73.7 พบปัจจัย 9 ปัจจัย ที่สัมพันธ์ต่อระยะเวลาการรอดชีพ สถานะรวมของ ER, PR และ HER2 เป็นปัจจัยพยากรณ์โรคที่สำคัญที่สุดต่อการรอดชีพ ดังนั้น ผู้หญิงที่มีความเสี่ยงสูงต่อการเป็นมะเร็งเต้านมควรได้รับการคัดกรองโรค ผลการศึกษานี้เป็นประโยชน์ในการวางแผนการตรวจคัดกรองในระยะเริ่มต้นของโรคมะเร็งเต้านมและวางแผนการรักษาผู้ป่วยมะเร็งเต้านม

Key Words: Survival time, Prognostic factors, Breast cancer

คำสำคัญ: อัตราการรอดชีพ ปัจจัยการพยากรณ์โรค มะเร็งเต้านม

* *Student, Master of Science (Public Health) in Infectious Diseases and Epidemiology, Faculty of Public Health, Mahidol University*

** *Associate Professor, Department of of Epidemiology, Faculty of Science, Faculty of Public Health, Mahidol University*

*** *Assistant Professor, Department of of Epidemiology, Faculty of Science, Faculty of Public Health, Mahidol University*

**** *National Cancer Institute of Thailand*

Introduction

Cancer is public health world's problem. World Health Organization had expected the increase in cancer deaths from 7.4 million in 2004 to 11.8 million in 2030. The highest causes of death from cancers each year are lung cancer, stomach cancer, liver cancer, colon cancer and breast cancer.

Globally, Breast cancer is the most frequently diagnosed and leading cause of cancer death among women. (American cancer society, 2011) In 2008, it is estimated the new breast cancer cases of 1.3 million new cases and 458,503 deaths. (Globalcan, 2008)

In Thailand, most common cancer among women are breast cancer, cervix uteri cancer and colon cancer. Breast cancer is the most common of cancer among Thai women. (The national cancer institute of Thailand, 2007) The estimated incidence rate is 20.5 per 100,000 women. Although the incidence rate is low in Thailand when comparing to other countries in Southeast Asia, but it has been increasing over the past few years. (Bray F, 2004)

Breast cancer is a disease in which malignant (cancer) cells form in the breast tissues, which is made up of glands for milk production, called lobules, and the ducts that connect lobules to the nipple. The remainder of the breast is made up of fatty, connective, and lymphatic tissue. (American Cancer Society, 2010) Invasive breast carcinoma is a group of malignant epithelial tumors characterized by invasion of adjacent tissues and a marked tendency to metastasize to distant sites. (Fattaneh, 2003)

Breast cancer survival rates are vary greatly worldwide, ranging from 80% in North America, Sweden, and Japan to around 60% in middle-income countries and below 40% in low-income countries. (Coleman, 2008) The low survival rates in developing countries are explained mainly by the lack of early detection programmes, resulting in a high proportion of women presenting with late-stage disease, as well as by the lack of sufficient diagnosis and treatment facilities. (American Institute for Cancer Research, 2012) Furthermore, the important factors related survival rate are educational background, alcohol intake and smoking. (Fujino, 2008)

Many factors relate to the survival rate of breast cancer such as types of tumor, stage, aggressiveness, treatments, and genetic makeup. This study aimed to determine the factors affecting the survival rate of breast cancer patients at the National Cancer Institute of Thailand.

Objectives of the study

To study the 5-years survival rate and significant prognosticating factors of breast cancer treated at the National Cancer Institute of Thailand.

Methodology

The information was collected from existing medical record of breast cancer patients. Those information contains the 5-years survivor, age at diagnosis (years), reimbursement system, Body Mass Index (at diagnosis), stage (at diagnosis), grade, classification of tumor of breast cancer, ER (Estrogen Receptor) status, PR (Progesterone Receptor) status, HER2 (Human epidermal growth factor receptor 2) status, and treatment methods of breast cancer patients in the National Cancer Institute of Thailand during October 2002 to September 2003. Final status of patients was determined from three sources: medical record review, telephone interview and data from Population Registration Database Ministry of Interior. Kaplan-Meier method was used to analyze the survival

rate of breast cancer patients. The log-rank test was used to test statistical significance of the differences between survival curves. Cox's regression was used to determine of each associated factor with survival time and compute hazard ratio (HR), p-value and 95% confidence interval (95%CI).

Results

There were 537 breast cancer patients whose status was followed until September 2007 – August 2008, from medical records, telephone interviews and the Population Registration Database, Ministry of the Interior.

Most of the breast cancer patients (38.5 %) aged 40-49. The median age of patients was 47 years (minimum 22 and maximum 81 years). There were four stages of breast cancer found in this study. Most case were in stage IIA, followed by stage IIB, stage I, stage III and stage IV. Combination of ER, PR, and HER2 status of patients were found as followed; 131 cases were ER+PR+HER2- group, 69 cases were ER+PR+HER2+, 66 cases were HER2- and (ER+ or PR+) group, 47 cases were HER2+and (ER+ or PR+) group, 119 cases were triple negative group and 105 cases were ER- PR- HER2+ group. Breast cancer patients were treated with surgery and another treatment, such as, chemotherapy, radiotherapy, hormonal therapy, or the combination of them. In this study, the patients' treatment methods were found as followed; 94 cases had only chemotherapy, 120 cases had chemotherapy and hormonal therapy, 60 cases had chemotherapy and radiotherapy, 107 cases had chemotherapy and hormonal therapy and radiotherapy, 60 cases only hormonal therapy, 16 cases hormonal therapy and radiotherapy, and 12 cases only radiotherapy.

Of all 537 breast cancer patients, 141 patients had died. The overall proportions of patients surviving at 5-years were 73.7%.

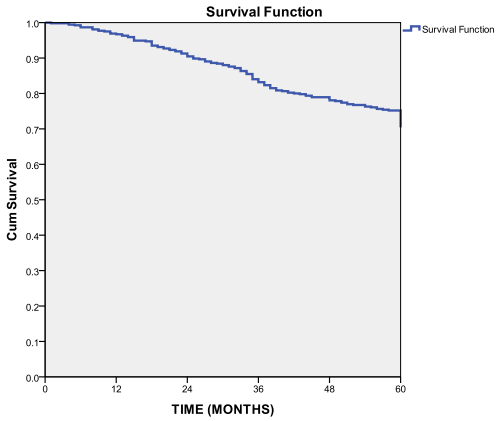

Fig 1 The overall survival curves of the breast cancer patients.

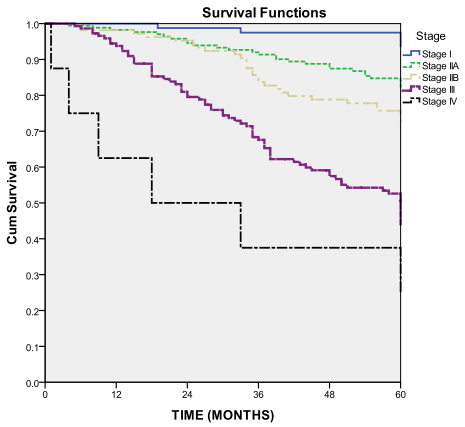

Fig 2 Survival curves of breast cancer by stage.

There were 9 factors which had significant difference in the survival time; occupation, reimbursement status, education, stage, node status, ER status, PR status, treatment methods, and Combination of ER, PR, and HER2 status. (Table 1)

Table 1 Univariate analysis of survival of breast cancer patients followed characteristic, prognostic factors and treatments by Log-rang test.

Variable	P-value
Occupational	.001
Reimbursement	<.001
Education	.002
Stage	<.001
Node status	<.001
ER status	<.001
PR status	<.001
Treatment methods	<.001
Combination of ER, PR, and HER2 status.	<.001

Cox's Proportional Hazard Model (unadjusted) among stage I, IIA, and IIB showed the risk of death of breast cancer patients who were triple negative and ER-PR-HER2+ were 3.19 times (95% CI, 1.445-7.065, p = 0.004) and 3.06 times (95%CI, 1.364 – 6.864, p = 0.007) higher patients than who were ER+PR+HER2-, respectively. In the other hand, patients who were other group were not significantly associated with survival time.

Identical in the multivariable analysis (adjusted), among stage I, IIA, and IIB showed the risk of death of breast cancer patients who were triple negative and ER-PR-HER2+ were 2.95 times (95% CI, 1.299-6.719, p = 0.01) and 3.79 times (95%CI, 1.584 – 9.089, p = 0.003) higher patients than who were ER+PR+HER2-, respectively. In the other hand, patients who were other group were not significantly associated with survival time. In addition, among stage III and IV showed the risk of death of breast cancer patients who were HER2+ and (ER- or PR-) and ER-PR-HER2+ were 2.92 times (95% CI, 1.135- 7.518, p = 0.026) and 3.07 times (95%CI, 1.513 – 6.218, p = 0.002) higher patients than who were ER+PR+HER2-, respectively. In the other hand, patients who were other group were not significantly associated with survival time.

Discussion and Conclusions

This study showed that the overall survival of breast cancer patients at 5-years was 73.7%, which less than the overall 5-years survival from 18 SEER geographic areas in 2002-2008 (89.0%). Five-year survival by race was: 90.3% for white women and 77.7% for black women. (Howlader, 2009) It was higher from one of the study in Thailand. The study conducted in Thailand, at Maharaj Hospital located in northeast of Thailand. The overall observed survival rates of 1, 3 and 5 years were 83.3%, 59.9% and 42.9%, respectively.(Poum, 2012) In addition, in 2010, the study conducted at Srinagarind Hospital, Thailand, the overall five-year survival rate was 63%. The overall five-year survival rate in stage I, II, III and IV were 100%, 85%, 39% and 9% respectively. (Aphinives, 2010)

Stage at diagnosis had relationship with the risk of death by breast cancer. Analysis showed the five-year survival rate of breast cancer patients with stage I, stage IIA, stage IIB, stage III and stage IV were 94.3%, 84.5%, 74.8%, 50.76%, 25.0%, respectively. The stage was significantly associated with survival time ($p < 0.001$). When compared with stage I, the risk of death of breast cancer patients is higher than stage IIA, stage IIB, stage III and stage IV were 3.01 times (95%CI, 1.163-7.798, p=0.023), 4.9 times (95% CI, 1.892 – 12.693, p=0.001), 12.26 times (95%CI, 4.951- 30.342 , p<0.001) and 25.15 times (95%CI, 7.672 -82.448 , p < 0.001) respectively. Patients who

were diagnosed at a higher stage demonstrated a poor prognosis for survival time. These results were consistent with previous findings in many studies. (Lee JH, 2007 and Gajalakshmi, 1997) The most important component was disease stage at diagnosis, as this would affect both the treatment received and survival. Improving the completeness of staging information would enhance future analyses. More advanced stage during the diagnosis could reflect a more aggressive form of disease.

Many studies showed ER/PR status was the most significant factors in the prognosis of overall survival. While this study showed the combination of ER, PR, and HER2 status was significantly associated with survival time ($p < 0.001$). The five-year survival rate of breast cancer patients with ER+PR+HER2+, ER+PR+HER2-, HER2+ and (ER+ or PR+) group, HER2- and (ER+ or PR+) group, Triple negative group and ER-PR-HER2+ group were 88.4%, 84.0%, 72.3%, 75.8%, 64.7%, 61.0%, respectively similar to several studies (Fredholm, 2009). The risk of death from breast cancer patients who had triple negative and ER-PR-HER2+ were 2.95 times (95% CI, 1.299-6.719, $p = 0.01$) and 3.79 times (95%CI, 1.584 – 9.089, $p = 0.003$) higher patients than those who were ER+PR+HER2-. In the other hand, the other group of patients was not significantly associated with survival time. On the contrary, ER/PR status was not significantly associated with survival. (Tao MH, 2006)

Cox's Proportional Hazard Model (unadjusted) among stage I, IIA, and IIB showed the risk of death of breast cancer patients who were triple negative and ER-PR-HER2+ were 2.54 times (95% CI, 1.265-5.120, $p = 0.009$) and 2.93 times (95%CI, 1.464 – 5.878, $p = 0.002$) higher patients than who were ER+PR+HER2-. In the other hand, patients who were other group were not significantly associated with survival time. Identical in the multivariable analysis (adjusted), among stage I, IIA, and IIB showed the risk of death of breast cancer patients who were triple negative and ER-PR-HER2+ were 2.95 times (95% CI, 1.299- 6.719, $p = 0.01$) and 3.79 times (95% CI, 1.584 – 9.089, $p = 0.003$) higher patients than who were ER+PR+HER2. In the other hand, patients who were other group were not significantly associated with survival time. In addition, among stage III and IV showed the risk of death of breast cancer patients who were HER2+ and (ER- or PR-) and ER-PR-HER2+ were 2.92 times (95% CI, 1.135- 7.518, $p = 0.026$) and 3.07 times (95%CI, 1.513 – 6.218, $p = 0.002$) higher patients than who were ER+PR+HER2-, respectively. Moreover, this study showed the treatment was not significantly associated with survival time among stage III and stage IV.

The efficacy of therapy for breast cancer patients varies widely among individuals. This study showed the five-year survival rate of breast cancer patients with CT only, CT+HT, CT+RT, CT+HT+RT, HT only, HT+RT and RT only were 78.7%, 67.5%, 48.3%, 83.2%, 90%, 68.8%, 66.7%, 73.5%, respectively. There was significant difference in the survival time of patients by treatment methods. ($p < 0.001$) According to the standard treatment practice at the National Cancer Institute of Thailand, which follows the clinical guideline of the National Comprehensive Cancer Network (NCCN), patients with early stage of breast cancer were usually treated by surgery or radiation, and patients in the advanced stage will received concurrent chemotherapy or combine therapies. However, in practice, those criteria were not applied to all the patients in the study; it was also depending on the patients' and relatives'

preference. There were patients who refused to undergo surgery and preferred to be treated by best supportive care. The results of this study shows that treatment type was significantly associated with survival time of breast cancer patients (p =0.001) similar to other studies. However, this result was not consistent with other studies.

Conclusion

Stage, combination of ER, PR, and HER2 status and treatment methods were associated with survival rate of breast cancer patients. The five years overall survival in this study was within standard survival rate. A combination of ER, PR, and HER2 status was the most significant prognosticating factor for survival. Thus, woman at high risk of the breast cancer should be screened. The results of this study provide useful information for planning breast cancer treatment and research in Thailand.

Acknowledgements

I wish to express my sincere gratitude and deep appreciation to my major advisor, Associate Professor Dusit Sujirarat, for his valuable advice, supervision, guidance, constructive criticism, and tremendous assistance throughout my study. I also want to thank my co-advisors, Assistant Professor Aronrag Cooper Meeyai and Dr. Arkom Chaiwerawattana for valuable advice in improving this thesis.

I also thank staff at The National Cancer Institute Thailand for the support and assistance throughout the study.

References

American cancer society. Global cancer facts & figures 2nd edition. Atlanta American cancer society; 2011.

Globalcan. Globocan Cancer Fact Sheets: Breast Cancer. globocan; 2008.

The national cancer institute of Thailand. Cancer in Thailand. The national cancer institute of Thailand; 2007.

Bray F, McCarron P, Parkin DM. The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res. 2004;6 (6):229-39.

American Cancer Society. Breast Cancer Facts & Figures. American Cancer Society 2009-2010.

Fattaneh A.T., Peter D. World Health Organization Classification of tumours Pathology and Genetics of Tumours of the Breast and Female Genetal Organ. World Health Organization, 2003.

Coleman MP et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol; 2008, 9, 730–56.

Fujino Y, Mori M, Tamakoshi A, Sakauchi F, Suzuki S, Wakai K, et al. A prospective study of educational background and breast cancer among Japanese women. Cancer Causes Control. 2008 Nov;19 (9):931-7.

Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2009

Poum A, Kamsa-ard S, Promthet S. Survival rates of breast cancer: a hospital-based study from northeast of Thailand. Asian Pac J Cancer Prev. 2012;13(3):791-4.

Aphinives P, Punchai S, Vajirodom D, BhudhisawasdiV. five-year survival in Srinagarind Hospital, Thailand. Source Breast cancer Department of Surgery, Faculty of Medicine, KhonKaen University, KhonKaen, Thailand. J Med Assoc Thai. 2010 Mar;93 Suppl 3:S25-9.

Lee JH, Yim SH, Won YJ, Jung KW, Son BH, Lee HD, et al. Population-based breast cancer statistics in Korea during 1993-2002: incidence, mortality, and survival. J Korean Med Sci 2007; 22(Suppl): S11-6.

Gajalakshmi CK, Shanta V, Swaminathan R, Sankaranarayanan R, Black RJ. A population-based survival study on female breast cancer in Madras, India. Br J Cancer 1997; 75: 771-5.

Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H. Breast cancer in young women: poor survival despite intensive treatment. PloS one. 2009;4(11):e7695.

Tao MH, Shu XO, Ruan ZX, Gao YT, Zheng W. Association of overweight with breast cancer survival. American journal of epidemiology. 2006 Jan 15;163 (2):101-7.