Prevalence of Human Papillomavirus Infection in Breast Cancer Cells from Thai Women

Jarunya Ngamkham1*, Anant Karalak2, Akrom Chaiwerawattana3, Adisak Sornprom3, Somchai Thanasutthichai1,3, Saowakorn Sukarayodhin1, Maneerut Mus-u-Dee2, Krittika Boonmark1, Thainsang Phansri1, Nattapon Laochan1

Abstract

Breast cancer is the leading female cancer worldwide and is the most frequently diagnosed in Thai women. Its potential etiologic has not been clearly identified. Several recent reports could detect human papillomavirus (HPV) infection in breast cancer or benign breast lesions. HPV infection considered suggests being one of many risk factors for cancer development. The aim of this study was to determine the frequency of HPV infection in both breast cancer and benign breast lesion/tumor tissues. Seven hundred samples from Thai women were collected during 2013-2015 and statistically correlation between HPV infection, sociodemographic and histopathological parameters were also analyzed. HPV DNA detection and genotyping were performed by polymerase chain reaction and enzyme immunoassay, respectively. The results demonstrated that mean age of the patients were 41.76±12.53 years and 52.73±11.68 years for benign breast lesions/tumor and breast cancer samples, respectively. HPV DNA was detected in 25/700 (3.57%) samples, in which 10/350 (2.857%) from benign breast lesion/tumor samples and 15/350 (4.285%) from breast cancer samples. HPV 16 is the predominant types of this study, follow by HPV 33, 18, 35, 52. Most of HPV type detection samples belong to the high risk types, except 1/25 sample could be detected low risk type; HPV 6 which was presented as co-infection with the other high risk type. From sociodemographic and histopathological correlation analysis, all of studied parameters such as breast cancer history, hormone receptors status etc. did not show statistically significant correlated with HPV infection (P>0.05). In conclusion, the low frequency detection in this study suggests that HPV did not play the main important role for breast cancer development and represented highly controversial, but it may be causative agents of only a relative small proportion of all breast cancer or non-malignant breast lesion and it is the interesting data for further study in virus-associated cancer.

Keywords: Human papillomavirus- benign breast lesions/tumor- breast cancer- Thai women

Introduction

Breast cancer is the leading cause of malignant disease among women worldwide and is the most frequently diagnosed cancer in Thai women with age standardized incidence rate (ASR) of 26.4 per 100,000 Thai women (Khuhaprema et al., 2013). While the worldwide ASR of breast cancer is 43.1 per 100,000 women and the trend of incidence rate has strongly increased over the past few years, although many countries have been implement breast cancer control and primary screening program for reducing the incidence and mortality rates of this cancer (International Agency for Research on Cancer, 2012; Ferlay et al., 2010). Several epidemiologic studies reported many risk factors that have been related with the pathogenesis of breast cancer, including environmental pollutants, sex-steroid hormone, alcohol consumption, cigarette smoking, family history, life style factors, viral infection etc, but the molecular mechanism associated with cancer development is still poorly understood (de Villier et al., 2008; Trentham-Dietz et al., 2000; Band et al., 2002; Sangrajrang et al., 2013). Recent studies have been detected some types of viruses such as mouse mammary tumor virus (MMTV), Epstein Barr virus (EBV) and human papillomavirus (HPV) in benign breast tumor and cancer tissues and suggested that they might be involved in the pathogenesis of breast cancer progression, however their mechanism is still highly controversial and unclear (Lawson et al., 2006; Lawson, 2009; zur Hausen, 2009; Parkin, 2006; Khan et al., 2008; Gillison et al., 2003), especially human papillomavirus which is the major etiology of cervical cancer (ICO Information Center on HPV and Cancer, 2014; zur Hausen, 2002; Joshi et al., 2012).

Persistent high risk HPV infection is the major causally related to cervical cancer and is also associated with other
Materials and Methods

Specimen and Data collection

All breast cancer and benign breast tumor tissues were collected from newly diagnosed patients with histologically confirmed at the National Cancer Institute, Thailand during the period between November 2013 and May 2015. A total of 350 breast cancer cases and 350 benign breast tumor cases were recruited for analysis of HPV infection and all of biopsy were collected directly from the physician and pathologist in chilled 10 mM Tris-HCl solution and stored at -20 °C until further processing.

A questionnaire was used for obtained information on sociodemographic, life-style/genetic related factors, etc from the participants. Face to face interviews were done by trained researcher and all of clinical information were taken form their clinical records.

This research was reviewed and approved by Ethic Committee of National Cancer Institute, Thailand, based on Declaration of Helsinki and Good Clinical Practice. Informed consent was acquired and obtained from all participants before being enrolled in this study.

DNA preparation

Cellular DNA from freshly breast cancer and benign breast tumor biopsies were prepared using QIAamp DNA Mini kit (QIAGEN, England) according to manufacturer’s instruction and the quality of extracted DNA was evaluated by polymerase chain reaction (PCR) technique with β-globin primers; sense 5'-ACA CAA CTG TGT TCA CTA GC-3' and anti-sense 5'-GAA ACC CAA GAG TCT TCT CT-3' (Jacob et al., 1996). A total volume of 25 µl PCR reaction containing 0.4 µM of each primer, 2.5U Taq polymerase, 200 nM of dNTP mixed solution, 1.5 mM MgCl₂, and 5 µl extracted DNA. The amplification was performed under the cyclic program; initial denaturation step of 94 °C, 5 min, followed by 40 cycles of 94 °C, 1 min; 60 °C, 1 min; 72 °C for 1 min and final extension at 72 °C for 5 min in the last step by using GeneAmp 9700 thermal cycler (Applied Biosystemic, USA). PCR product of tested DNA was visualized on 2% agarose gel electrophoresis in transilluminator (SYNGENE, England).

Detection of HPV DNA and genotype

The specimen from patients which showed β-globin positive were continued investigate HPV DNA and genotyping by using polymerase chain reaction with general primers; GP5+ (5'-TTT GTT ACT GTG GTA GTA ACT-3') and biotin GP6+ (5'-GAA AAA TAA ACT GTA AAT CAT ATT C-3') and enzyme-immunoassay (EIA) methods, respectively according to Jacob et al. (1997; 2000) protocol. Briefly, 50 µl of PCR reaction was prepared by mixing 0.4 µM of each primer, 2.5U Taq polymerase, 200 nM of dNTP mixed solution, 1.5 mM MgCl₂, and 10 µl extracted DNA. The temperature profile used for HPV DNA amplification were started with an initial denaturation at 94 °C for 5 min, 40 cycles of 94 °C for 1 min, 38 °C for 2 min and 72 °C for 1.30 min. The final extension step was performed at 72 °C for 4 min. The samples which presented HPV DNA positive were used for identifying HPV genotype with specific HPV oligoprobes that categorized as high risk types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 59, 66, 58 and 68) and low risk types (HPV6, 11, 26, 34, 40, 42, 43, 44, 53, 54, 55, 57, 61, 70, 71, 72, 73, 81, 82, 83, 84 and 89). Specfic probe sequences and protocol are described by Jacob et al. (1997; 2000) The protocol was initial by adding 5 µl PCR products and 50 µl freshly prepared of 1xSSC, 0.5% Tween20 solution to each well of streptavidin-coated microplate (Roche, Germany) and incubated at 37 °C for 60 min. And then unbound biotinylated PCR products were removed by three times washing with freshly prepared of 1xSSC, 0.5% Tween 20 solution. Each type of specific oligoprobes that were labeled with digoxigenin was added into each well to allow hybridization and incubated at 37 °C for 60 min, and then unbound particles were eliminated. Specifically bound digoxigenin-labeled probe was detected by adding conjugate solution (Roche, Germany) and p-Nitrophenyl phosphate (pNpp) substrate (Sigma, USA), respectively. The optical density; 405 nm and 620 nm, were measured at 60 min and 16-24 hours.

Statistical analysis

Normally distributed parameters were expressed as the
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Discussion

Breast cancer is the leading female cancer and common cause of cancer death worldwide, including Thailand. Numerous reports have evaluated the association between breast cancer pathogenesis, risk factors; such as cigarette smoking, alcohol consumption, body mass index, viral infection, obesity etc to investigate the major etiology for breast cancer developing (Li et al., 2011; Ekpanyaskul et al., 2010; Trentham-Dietz et al., 2000; Sangrajrang et al., 2013; Lawson et al., 2006). A recent studies found different high risk HPV types infection, that is the well-known etiology of genital abnormal lesions and cancer, in breast cancer tissues, especially HPV 16, 18 and 33 (Amarante et al., 2009; Kan et al., 2005; Wang et al., 2012; Khan et al., 2008; Li et al., 2011; Zur Hausen, 2009). The frequency and type distribution of HPV in breast cancer was different in each studies and represented great variation with the ranging from 0%-86% (Wang et al., 2012; Hedau et al., 2011; de Cremoux et al., 2008), whereas several HPV type distribution studies did not investigate HPV in normal breast or benign tumor tissues (Joshi et al., 2012; Choi et al., 2007).

In this study, we found HPV positive breast cancer in 15/350 (4.285%) cases, that was slightly different from results of Mendizabal-Ruiz et al., (2009) and Choi et al., (2007) that found HPV frequency about 4.4% and 6.5% in Mexican and Korean women with breast carcinoma, respectively. But it was lower frequency than the report from a meta-analysis on HPV infection and sporadic breast carcinoma which was conducted by Li et al., (2011). Their results showed approximately 32.42% of the breast cancer with HPV positive were Asian women and 12.91% were in European and the result of Khan et al., (2008) that found HPV DNA in 21% of breast carcinoma in Japanese women. Additionally, 14/15 cases of breast cancer with mean and standard deviation (SD). Association between socio-demographic, clinic-pathological characteristic parameters and HPV infection status were analyzed using Chi-square test or Fisher’s Exact test and P-value less than 0.05 were accepted as statistically significant (P<0.05).

Results

The age of breast cancer and benign breast tumor patients recruited varied from 25-89 years (the mean age 52.73±11.68 years) and 18-73 years (the mean age 41.76±12.53 years), respectively. From histological diagnosis, 78.3% of all breast cancer patients were classified as invasive ductal carcinoma, followed by ductal carcinoma in situ (26/350; 7.4%), invasive lobular carcinoma/LIS (13/350; 13%), mucous carcinoma/malignant phylloides tumor/intraductal carcinoma (13/350, 13%) and other types (24/350; 6.9%), while fibroadenoma was the most frequent histological categorized of all benign breast tumor, accounting for 140/350 cases (40%), followed by fibrocystic disease/hyperplasia (116/350; 33.1), benign phylloides tumor (15/350; 4.3%), intraductal papilloma (8/350; 2.3%), respectively.

In this study, HPV DNA was detected by using polymerase chain reaction and enzyme immunoassay (PCR-EIA) technique, found that 15/350 (4.29%) cases and 10/350 (2.86%) cases of breast cancer group and benign breast tumor group, respectively could be detect HPV DNA in which 14/15 cases of breast cancer with HPV DNA were invasive ductal carcinoma and 1/15 cases was mucous carcinoma. While, the benign breast tumor tissues with presence HPV DNA consisted of 2, 4, 1 and 3 cases of fibroadenoma, fibrocystic disease/hyperplasia, intraductal papilloma and the mixed type cases, respectively, as presented in Table 2-3. The most frequency detected HPV genotype in breast cancer group and benign breast tumor was HPV 16, followed by HPV 35, 18, 52, 83 and 6 for breast cancer cases and HPV 33, 18, 35, 59 and 66 for benign breast tumor, as shown in Figure 1. Additionally, 4/15 of HPV positive-breast cancer cases and 2/10 of HPV positive-benign breast tumor cases contained multiple HPV types.

On the other hand, we also evaluated the association between HPV infection status and socio-demographic parameters in both of breast cancer and benign breast tumor groups, found that there were no significant difference between HPV infection status and all studied parameters of socio-demographic as shown in Table 1. As similar to the relationship between HPV infection status and clinic pathological characteristic, showed no significantly correlated in both of breast cancer and benign breast tumor (P>0.05), as shown in Table 2 and III, respectively.

Figure 1. Human Papillomavirus Type-Distribution I benign Breast Tumor (A) and cancer (B) samples from Thai women; included single and multiple HPV types.
HPV positive in this study were invasive ductal carcinoma as similar to the report of de Villier s., et al (2005) and Choi et al., (2006) found the frequency of high risk HPV DNA in invasive ductal carcinoma and invasive ductal carcinoma with adjacent intraductal papilloma, respectively higher than the other histological types. While, the result of HPV detection from benign breast tumor (10/350; 2.857%) in our finding was not different from the report of Sigaroodi et al., (2012) that found HPV DNA in 2.4% of Iran women with non-cancer breast tissues and a report from Tsai et al., (2005) investigated HPV infection in 2 out 44 (5%) cases in non-malignant tissues. Whereas, a study on HPV detection of women with non-malignant lesion using formalin – fixed tissues which was investigated by Heng et al., (2009) observed that 3/17 cases (18%) were HPV DNA positive.
Table 2. The Relationship between Clinicopathology Characteristics of Breast Cancer (n=350) and HPV Infection Status

| Characteristics                  | All cases | Benign | P   |
|----------------------------------|-----------|--------|-----|
|                                 | n (%)     | HPV positive n (%) | HPV negative n (%) |
| Menopausal status               |           |        | ----|
| Pre-menopause                   | 141 (40.3)| 9 (6.4) | 132 (93.6) |
| Post-menopause                  | 207 (59.1)| 6 (2.9) | 201 (97.1) |
| Unknown                         | 2 (0.6)   | 0 (0)   | 2 (100.0)  |
| Histological diagnosis          |           |        | ----|
| Invasive ductal carcinoma       | 274 (78.3)| 14 (5.1)| 260 (94.9) |
| Ductal carcinoma in situ        | 26 (7.4)  | 0 (0)   | 26 (100.0) |
| Invasive lobular carcinoma/LIS  | 13 (3.7)  | 0 (0)   | 13 (100.0) |
| Mucinous carcinoma/malignant phyllodes tumor/Intraductal carcinoma | 13 (3.7) | 1 (7.7) | 12 (92.3) |
| Other                           | 24 (6.9)  | 0 (0)   | 24 (100.0) |
| T stage                         |           |        | ----|
| I                                | 126 (36.0)| 7 (5.6) | 119 (94.4) |
| II                               | 169 (48.3)| 6 (3.6) | 163 (96.4) |
| III                              | 30 (8.6)  | 1 (2.7) | 29 (97.3)  |
| IV                               | 7 (2.0)   | 0 (0)   | 7 (100.0)  |
| Unknown                         | 18 (5.1)  | 1 (5.6) | 17 (94.4)  |
| Tumor size                      |           |        | ----|
| < 2.5 cm                        | 161 (46.0)| 7 (4.3) | 154 (95.7) |
| > 2.5 cm                        | 178 (50.9)| 7 (3.9) | 171 (96.1) |
| Unknown                         | 11 (3.1)  | 1 (9.1) | 10 (90.9)  |
| Lymph node metastasis           |           |        | ----|
| No                               | 175 (50.0)| 7 (4.0) | 168 (96.0) |
| Yes                              | 167 (47.7)| 7 (4.2) | 160 (95.8) |
| N/A                             | 8 (2.3)   | 1 (12.5)| 7 (87.5)   |
| ER status                       |           |        | ----|
| Negative                        | 99 (28.3)| 1 (1.0) | 98 (99.0)  |
| Positive                        | 226 (64.6)| 13 (5.8)| 213 (94.2) |
| N/A                             | 25 (7.1) | 1 (4.0) | 24 (96.0)  |
| PR status                       |           |        | ----|
| Negative                        | 141 (40.3)| 5 (3.5) | 136 (95.5) |
| Positive                        | 183 (52.3)| 9 (4.9) | 174 (95.1) |
| N/A                             | 26 (7.4) | 1 (3.8) | 25 (96.2)  |
| P53 status                      |           |        | ----|
| Negative                        | 72 (20.6)| 1 (1.4) | 71 (98.6)  |
| Positive                        | 221 (63.1)| 12 (5.4)| 209 (94.6) |
| N/A                             | 57 (16.3)| 2 (3.5) | 55 (96.5)  |
| Ki-67 status                    |           |        | ----|
| Negative                        | 73 (20.9)| 3 (4.1) | 70 (95.9)  |
| Positive                        | 249 (71.1)| 11 (4.4)| 238 (95.6) |
| N/A                             | 28 (8.0) | 1 (3.6) | 27 (96.4)  |
| HER-2 status                    |           |        | ----|
| Negative                        | 169 (48.3)| 4 (2.4) | 165 (97.6) |
| Equivocal                       | 73 (20.9)| 4 (5.5) | 69 (94.5)  |
| Positive                        | 72 (20.6)| 6 (8.3) | 66 (91.7)  |
| Unknown                         | 36 (10.3)| 1 (2.8) | 35 (97.2)  |

Interestingly, the results from several studies found HPV frequency from fresh tissues extracted were lower than paraffin-embedded tissues, suggesting that the biopsy taken, sample preparation, designed primer sequences, detection method, processing protocol, etc may be affect the detection results (Li et al., 2011; Amarante et al., 2009; Joshi et al., 2012). However, it was conflicting results from the basic knowledge that HPV virion can be destroyed during sample fixation and processing and HPV detection rate from fresh tissues may have a higher than paraffin-embedded samples (Wang et al., 2012).

HPV 16 was the predominant genotype detected in both breast cancer and benign breast tumor group in this study as similar to the other studies (Kroupis et al., 2006; Khan et al., 2008; Hennig et al., 1999; Widschwendter et al., 2004). Almost of breast tissues were positive for high risk HPV types; HPV 16, 18, 33, 35, 52, 59, 66 which was not different from the several recent reported that found HPV 16, 18, 33 and 35 DNA sequences in breast cancer tissues, included some histological type of benign breast tumor (Khan et al., 2008; Heng et al., 2009; Li et al., 2011; Kroupis et al. 2006; de Villier et al., 2005; Wang et al.,...
However, it may be causative agents of only a relative to breast cancer or benign breast tumor development. To evaluate whether the HPV infection directly contributed to breast cancer and it is not the effectiveness and the relationship between HPV and breast cancer is still not clear and controversial. Furthermore, the highly controversial reported from numerous studies could not observe any significant difference in the hormone receptors status (estrogen and progesterone receptors) between HPV positive and HPV negative and the results were not variety as HPV types in cervical cancer or other genital lesions and some studies showed a higher HPV frequency was detected in breast cancer tissues rather than benign breast tumor or normal breast tissues (Yu et al., 1999; Tsai et al., 2005; Gumus et al., 2006). In contrast, the results from Hedau et al., (2011) and Lindel et al., (2007) which were unable to demonstrate the presence of HPV DNA in breast cancer tissues. Interestingly, the common HPV type that found in European women with breast cancer were HPV 11, 16, 18 and 33, whereas the other high risk or some low risk HPV type such as HPV 52, 59, 83 were found in Asian women, including Thai women rather than in European women (Mendizabel-Ruiz et al., 2009; Yu et al., 1999; Joshi et al., 2012; Wang et al., 2012; Gumus et al., 2006). It is suggested that variation sampling, genetic background, some demographic factors, population group, processing protocol, primers designed etc may be contribute to variation of HPV prevalence or HPV genotype in breast cancer tissues in different geographic and different populations (Hedau et al., 2012; Wang et al., 2012; Li et al., 2011; Amarante et al., 2009).

We also evaluated the relationship between HPV infection status, socio-demographic and clinico-pathological factors in this study. They showed no significant associated between HPV infection status, socio-demographic and clinico-pathological characteristic in both breast cancer and benign breast tumor groups. Similar to the report from Damin et al., (2007) that did not observe any significant difference in the hormone receptors status (estrogen and progesterone receptors) between HPV positive and HPV negative and the results were demonstrated by Hening et al., (1999) represented no significant difference in clinical and pathological factors between breast cancer and HPV infection status. However, a previous study which was reported by Kroupis et al., (2006) found the significantly association between high risk HPV detection and some histological factors such as tumor grade, estrogen receptors status. From the contrast results, suggesting that HPV infection may not interfere with the socio-demographic and clinico-pathological factors in some population group and the amount of sample size may affect these results.

In conclusion, the low frequency detection in our study, suggested that HPV infection did not play a carcinogenic role in breast cancer. Although, there are several studies could be detect HPV, especially high risk HPV type in breast cancer and it is not the effectiveness causes of cancer development as like as genital organs and the relationship between HPV and breast cancer is still not clear and controversial. Furthermore, the highly controversial reported from numerous studies could not evaluate whether the HPV infection directly contributed to breast cancer or benign breast tumor development. However, it may be causative agents of only a relative small proportion of all breast cancer or benign breast lesions and it is the interesting data for further investigation in virus associated cancer.

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