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Association of Breast Cancer with Human Papillomavirus Types 16 and 18 in the North of Iran

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ABSTRACT

Background & Objective: In Iranian women, the age of breast cancer is 10-20 years earlier than women living in developed countries. Moreover, HPV infection has increased among Iranian women and it is more common compared to European women. The purpose of the present study is to investigate the role of HPV as a potential risk factor for breast cancer at younger ages.

Materials & Methods: This study is a case-control study that was performed on 46 specimens of breast cancer tissue and 46 samples of normal breast tissue with no malignancy. In coordination with the pathology laboratory of Poursina Hospital (Rasht, Iran), samples of breast cancer pathology templates that were available in the laboratory archives were selected after a preliminary examination of the accuracy of tissue diagnosis. After that, a tissue incision was prepared with H&E staining and the cancer diagnosis was again confirmed by a pathologist. Samples were cut with a microtome with disposable blades. Then the tissue sample was deparaffinized and its DNA was extracted. The data were analyzed by SPSS software version 21 (IBM SPSS, Armonk, NY, USA) using Chi-square, T-test, variance analysis and logistic regression.

Results: The results showed a significant difference between the two groups of women with breast cancer and without malignancy in the age of first pregnancy and gravidity. There was a significant difference in human papillomavirus type 16 infection between the two groups with breast cancer and without malignancy. The logistic regression model examined the effect of all variables and showed that infection with human papillomavirus type 16 increased the risk of breast cancer by 4.6 times, taking into account other variables.

Conclusion: The present study, independent of other studies, showed that human papillomavirus type 16 could be a risk factor for breast cancer. If the virus is found in an individual, it is recommended that the patient be monitored frequently and more detailed examinations for breast malignancies be performed.

Keywords: Breast Cancer, Human Papillomavirus, Risk Factor, Type16, Type18

Introduction

Breast cancer (BC) is the most common malignancy worldwide and the second leading cause of cancer death in women **(1, 2)**. In 2018, this cancer accounted for 2.08 million new cases (11.6% of all cancer cases in women) and it has 15% of all cancer deaths **(1)**. In Iran, breast cancer accounts for 16% of all female cancers which ranks first in Iranian women among various cancers **(3)**. A 17-year study showed that the age of BC in Iranian women is 10 years earlier than women living in developed countries **(4)**. A study by Ghods Elahy et al., found that the age of BC in Iranian women were 20 years less than in other countries **(5)**. There is an increasing trend of BC death in Iran. However, the death rate is still relatively low compared to other western developed countries **(6)**. Although the main cause of breast cancer is not fully known, it is believed that genetic background and hormonal effects play an important role in its development **(7-10)**. The role of viruses in some types of cancer has been identified **(11, 12)**. Human papillomavirus (HPV) is a common pathogen in oral, pharyngeal and genital cancers **(13-18)**. HPV is a DNA virus of the papovaviridae family **(19)**. The first researcher who reported HPV in BC-infected tissues was Di Lonardo **(20)**. Di Lonardo et al., showed HPV-16 DNA in 29.4% of 17 breast carcinoma samples analyzed by PCR **(20)**.

Then, many researchers studied the presence of this virus in breast tumors and reported the prevalence of HPV infection in the range of 1.6% to 86% **(10, 21-23)**. HPV is also found in breast milk, which is another sign of breast tissue infection **(24)**. In general, HPV types 16 and 18 are classified as high-risk factors for cancer and HPV types 6 and 11 are classified as low-risk factors. Epidemiological studies have shown that HPV-16 and HPV-18 are responsible for more than 70% of all cervical cancers **(25)**. The rate of HPV infection in triple-negative BC (TNBC) in different studies varies from 15% to 50% and HPV-16 is its most common subgroup. Also, the presence of this virus in adjacent and benign natural breast tissues was reported **(26-28)**. HPV infection is more common in developing countries (42.4%) than in developed countries (22.6%) **(29)**. The result of studies has shown that age of BC in Iran decreased during recent years and is 10 to 20 years less than in other countries **(4, 5)**. Moreover, HPV infection has increased among Iranian women and it is more common between them compared to European women **(30)**. Therefore, the purpose of the present study is to investigate the role of HPV as a potential risk factor for BC at younger ages. Considering the increasing trend of BC in Iranian women, investigating the possible link between HPV infection and this disease can be used in the health management planning of the country, setting targeted screening programs, early treatment of HPV infection and finally effective prevention and detection of BC.

Methods

This is a case-control study performed on 92 paraffinized specimens, of which 46 were BC tissue and 46 were normal breast (NB) with no malignancy. Any specimen that was diagnosed by a pathologist with BC (ductal or lobular) was included in the study. The case and control subjects were matched for age with frequency matching. In coordination with the pathology laboratory of Poursina Hospital (Rasht, Iran), the samples of BC pathology templates that were available in the laboratory archives during the last ten years were selected after a preliminary examination of the tissue diagnosis. A tissue incision was prepared and cancer diagnosis was again confirmed with H&E staining by a pathologist. The demographic characteristics of the cases and controls at the beginning of the experiment, including their name, age, place of residence, family history, age of menarche, marital status, menopausal status and age of first delivery were recorded. Samples were minced using a microtome with disposable blades. The tissues were then deparaffinized and their DNA was extracted by DNA extraction kit (Zistak Company, Iran). One of the polymerase chain reaction (PCR) kits (Zistak Company, Iran) of HPV for two types of 16 and 18 was used for each sample, which had positive and negative controls. After these steps, the samples were placed in a PCR thermal cycler. The two strands of DNA were first separated at 94 °C for 30 seconds, then the device reached 56 °C, and HPV-specific primers were attached to the DNA genome in the annealing stage. The elongation step was performed by the Tag DNA Polymerase enzyme at 72 °C, which was repeated about 40 times for sufficient reproduction of the DNA strands. The extracted DNA was electrophoresed in 1.5% agarose supplemented with ethidium bromide. After 30 minutes, the formed strands were examined based on their movement from negative to positive pole using the transilluminator device and the positive and negative controls of the kit. Based on the result, the presence or absence of the virus in the sample was recorded.

Statistical analysiss

Finally, the statistical analysis was performed using SPSS software version 21 by the Chi-square test, Fisher's exact test and variance analysis. T-Test was used to compare the quantitative contextual variables, estimate the adjusted OR and matches the confounding variables of the logistic regression test. The differences were considered significant at values of $p<0.05$.

DNA extraction from the paraffinized block

To extract DNA from the paraffinized blocks, the blocks were first placed at -20 °C for 15 minutes to prevent fragmentation during incision. After that, 10 to 20 sections with a diameter of 10 µm were prepared using a microtome. During preparing the sections from the blocks, the sterilization conditions were carefully observed and the prepared sections were transferred to sterile appendages. After this step, DNA was extracted from the prepared sections. Samples were poured into 1.5 ml sterile microtubes. To remove paraffin, the samples were washed three times with pure xylene for 15 minutes and after the end of each step, they were centrifuged at 14000 rpm. To remove xylene, the samples were washed twice with absolute ethanol for 15 minutes and centrifuged under the same conditions. The tubes were placed at 37 °C for 15 minutes to completely remove the ethanol. After that, 180 µl of digestion buffer and then 20 µl of proteinase K enzyme were added to each tube and mixed thoroughly. The tubes were at 56 °C overnight (according to manufacturer's instructions). The rest of the extraction steps were followed according to the manufacturer's guidelines (Zistak Company, Iran) and with the aid of special chromatographic columns in the kit. The purity and efficiency of extracted DNA from the samples were measured using a spectrophotometer. The OD of the samples at 260 nm indicated the DNA concentration in the samples. The OD values at 260 and 280 nm were 0.232 and 0.102, respectively, and their ratio was lower than 2 which indicated that the DNA tissue was pure and had no protein contamination.

Results

The mean age was 48.96 years in normal breast controls without malignancy and 50.76 years in breast cancer patients. The results of the Chi-square test did

not show a significant relationship between age and cancer status. However, there was a significant difference in the age of first pregnancy and the number of pregnancies between the two groups (p=0.001 and p=0.017, respectively). The most important demographic variables were compared in Table 1. The results showed that invasive ductal carcinoma in BC patients and fibroadenoma in NB participants had the highest frequency among various pathological diagnoses in both groups (Table 2). According to the Chi-square test, a statistically significant relationship was observed in HPV-16 infection between the two groups with BC and without malignancy (Figure 1). The presence of HPV infection had also a significant difference between the two groups (P=0.01). However, the Chi-square test did not show a statistically significant relationship for HPV-18 between the two groups with BC and without malignancy (P=0.67). Using the logistic regression model, the odds of BC based on the studied variables and confounders were added into the regression model. By examining the effect of all variables on BC, it was found that only HPV-16 is an aggravating factor in BC and infection with HPV-16 increases the odds of BC by 4.6 times, taking into account other variables (Table 3).

Table 1. Frequency distribution of demographic characteristics of participating women in the study

variable	Without malignancy	With breast cancer	Significance level
Age (year) Mean (standard deviation)	48.6±96.94	50.11±76.9	*0.337
Menarche age (year) Mean (standard deviation)	12.1±04.53	12.0±26.92	Z=1.25 **P=0.211
Age of first pregnancy (year) Mean (standard deviation)	23.5±58.53	19.3±59.04	t=4.57 *P=0.0001
Menopause Frequency(percentage)			***P=0.500
Yes	16(34.8)	15(32.6)	
No	30(65.2)	31(67.4)	
Number of pregnancy Frequency(percentage)			***P=0.017
One	22(47.8)	10(21.7)	
Two	13(28.3)	14(30.4)	
Three and higher	11(23.9)	22(47.8)	
Family history of breast cancer Frequency(percentage)	46	46	***P=0.36
Yes	12(26.1)	16(34.8)	
No	34(73.9)	30(65.2)	

*T-test **Mann-Whitney ***Chi-Square

Table 2. Frequency distribution of various pathological diagnoses in two groups with breast cancer and without malignancy

pathological diagnoses	Without malignancy	With breast cancer	Sum (number %)
Invasive Ductal Carcinoma	-	41(89.1)	41(44.6)
Invasive Lobular Carcinoma	-	5(10.9)	5(5.4)
Abscess	4(8.7)	-	4(8.7)
Angiolipoma	3(6.6)	-	1(1.1)
Duct Adenosis	2(4.3)	-	1(1.1)

pathological diagnoses	Without malignancy	With breast cancer	Sum (number %)
Duct Ectasia	5(10.8)	-	3(3.3)
Epithelial Cyst	2(4.3)	-	1(1.1)
Epithelial Hyperplasia	2(4.3)	-	1(1.1)
Fibroadenoma	14(30.4)	-	12(13)
Fibrocystic	8(17.4)	-	7(7.6)
Fibrous Stroma	3(6.6)	-	1(1.1)
Granulomatous Mastitis	3(6.6)	-	1(1.1)

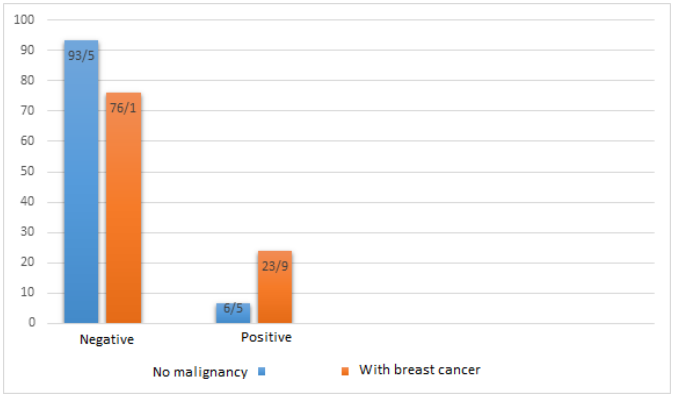

Figure 1. Frequency distribution of human papillomavirus type 16 infection in two groups with BC and without malignancy

Table 3. Logistic regression test model

	B	S.E	Wald	df	Sig.	Exp(B)
HPV-16 positive	1.537	0.747	4.232	1	0.040	4.650
HPV-18 positive	0.771	0.999	0.595	1	0.440	2.162
Age more than 50 year	0.587	0.554	1.123	1	0.289	1.798
Menopause	0.777	0.670	1.343	1	0.246	2.175
Gravidity			2.305	1	0.316	
Gravidity 2 and less	0.847	0.599	1.999	1	0.157	2.334
Gravidity more than 3	0.786	0.693	1.286	1	0.257	2.194
Age at first pregnancy is less than 18 years	0.591	0.618	0.913	1	0.339	1.805
Family history of breast cancer	0.557	0.527	1.116	1	0.291	1.745
Constant	-1.663	0.541	9.430	1	0.002	0.190

S.E: standard error, Wald: is used to determine statistical significance for each of the independent variables.
df: degree freedom, Sig: significant
Exp (B): exponentiation of the B coefficient

Discussion

BC is one of the leading health problems and the most common cause of cancer death in women worldwide **(1)**. BC is a multifactorial and potentially fatal disease in which many genetic and environmental

factors play a role. However, these factors account for only a small percentage of patients and the need to address other risk factors for this disease is inevitable **(31)**. The studies conducted on this theory have shown that HPV, EBV and other viruses are present in BC tissue, but there were few studies that showed evidence for cause and effect. It should be noted that HPV and Mouse mammary tumor virus (MMTV) both have hormone-responsive components and can stimulate virus replication in the presence of corticosteroids and other hormones. This biochemical phenomenon was noteworthy because BC is also hormone-dependent **(32)**. On the other hand, studies had shown that BC increased with the migration of people from low-prevalence areas to high-prevalence area. The fact that HPV virus is also more prevalent in areas with a high prevalence of BC compared to low-prevalence areas strengthened this theory. Human papillomavirus DNA was also observed in BC tissue. However, this might be due to the transfer of the virus DNA from another organ **(21)**. Generally, the question remains whether viral agents such as HPV can cause BC. Also, since the prevalence of this virus in Iran is different from other parts of the world, it is necessary to study the relation of this virus with BC in Iran.

In the present study, there was no significant difference between people under the age of 52 and those over 52. However, the samples with cancer were more likely to be over the age of 52. Also, BC patients had an average age of about 52 years, and NB controls with no malignancy were examined in the same age range. The menarche age of patients with malignancy and participants with no malignancy was in the range of 12 years, and there was no statistical difference between them. Although the age of menarche was not different in the studied population, the age of the first pregnancy was lower among those with malignant pathology compared with benign pathology. It was observed that BC was developed at reproductive age in patients. But in general, among menopausal women, the frequency of malignant pathology was higher than benign pathology. On the other hand, patients with BC mostly had more than two children, but participants without malignancy mostly had one child.

Patients with malignant BC had 11 cases of HPV-16 genome in cancerous tissue which was significantly higher than the non-malignant group. This difference was not observed in the HPV-18. However, when we studied the frequency of these high-risk types of HPV in the tissues, it was observed that most samples with malignancy in their breast had relatively more DNA and genome of HPV. HPV was observed in 10.9% of participants without malignancy and 32.6% of patients with breast malignancy. In the study of Manzouri et al., in Isfahan, Iran, 18.2% of malignant samples and 13.7% of non-malignant samples had HPV DNA **(33)**. Islam et al., studied the role of the HPV in BC and found that HPV-16 was more common in American patients with BC, whereas HPV-18 and HPV-33 were more common in Chinese and Australian patients with BC **(34)**. De León et al., studied the prevalence of HPV in breast tumors in 51 BC patients using the PCR technique during 2009 in Mexico. They found that 15 patients were positive for HPV DNA, of which 10 patients were positive for HPV-16, three of them were positive for HPV-18 and two patients were positive for both **(35)**. The results of this study were almost in line with our study. However, in another study conducted in Mexico, completely different results were reported and no positive samples were observed in the control group and it was concluded that HPV does not play a significant role in breast cancer **(36)**.

Different studies seem to report quite contradictory results, even in almost the same geographical areas. In a meta-analysis study published in 2010, 24.49% of BC cases were related to HPV, of which 32.42% occurred in Asia and 12.91% were in Europe. The analysis of 10 case-control studies with 447 BC cases and 275 controls showed a significant increase in the risk of developing BC in HPV-positive cases **(30)**. Seyedi Alavi et al., evaluated the presence of HPV with low and high risk of malignancy in 50 cases of BC patients and its relation with clinical aspects. HPV infection was confirmed in 24 BC tissues (48%) by PCR and all 29 NB tissues were negative for HPV infection **(37)**. Wrede et al., studied 81 women with BC and found that they were all negative for HPV infection **(38)**. Khodabandehlou et al., studied the HPV virus and its possible relation with increased cancer progression in 72 BC patients and 31 NB controls. Human papillomavirus DNA was identified in 48.6% of patients whereas only 16.1% were identified as HPV-positive in the control group. In this study, HPV-18 was the most common genotype in patients **(39)** which is in contradiction with the results of the present study that HPV-16 was the most common genotype. This might be due to sample volume and possible geographical differences that could increase the prevalence of a particular type of virus genotype. In a study conducted by Sigaroodi et al., during 2012 in Iran, the prevalence of HPV in BC patients was 25.9% compared to 2.4% in NB controls **(40)**. In the present study, no significant relationship was found between HPV-18 infection and two groups of BC patients and NB controls, which was consistent with the study of Karimi et al., It was conducted to investigate the possible relation between HPV and BC in women in Sanandaj, Iran **(41)**.

The results of the present study showed that HPV-16 infection alone is an aggravating factor of breast cancer. HPV-16 infection increased the odds of breast cancer by 4.6 times, taking into account other variables. It was important to note that HPV infection alone did not cause malignancy in infected tissues. Also cofactors such as smoking, UV, pregnancy, folate deficiency and immunosuppression were involved in this process **(42)**. On the other hand, the prevalence of this virus in breast cancer suggests that HPV vaccination may be effective in limiting the disease in women **(34, 43)**.

In general, it is not possible to speak with absolute certainty about the relation of this virus with breast malignancy because in the present study, the sample size was small and the samples were not randomly selected. Hence, they didn't represent society. Except for age, other variables were not matched in the two groups. Besides, more extensive studies conducted in other countries have shown that quite contradictory results might be obtained in the same geographical area. However, the role of this virus as an etiological agent of breast cancer couldn't be ignored.

Conclusion

The present study, independent of other studies, showed that HPV-16 could be a risk factor for BC, and if the virus found in a person, it is recommended that the patient be monitored frequently for breast malignancy. Due to the increasing trend of BC in Iran, it is recommended that women be encouraged to undergo regular HPV screening with targeted planning to prevent the possibility of BC in addition to reducing sexually transmitted diseases. On the other hand, the heavy economic and psychological costs on the health system of the country can decrease. Finally, due to some contradictory results with other national and international studies, it is suggested that a study with a larger sample size be designed in multiple centers for more comprehensive and accurate investigation.

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Conflict of Interest

There are no conflicts of interest.

Ethical considerations

The present study was approved by the Ethical Committee of Guilan University of Medical Sciences in a meeting dated 2011-5-28 with the code of 1900136001. All information obtained from patients will be confidential.

Informed Consent

All information obtained from patients will be confidential.

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