Molecular Localization of Human Papillomaviru_18 (HPV_18) in Tissues from Thyroid Carcinoma in Mid-Euphrates

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Abstract

Background: THilnahyroid cancer is a cancer that starts in the thyroid gland and thought to be related to a number of environmental and genetic predisposing factors .Human Papil- loma Virus (HPV) the virus that causes cervical cancer ,is also linked to throat cancer and is one among their associated infective agents.
Objective: This study aimed at detecting DNA of HPV genotype-18 using in situ hybridization technique in thyroid tissues from benign thyroid hyperplasia and thyroid carcinoma, and elucidate the association between this HPV-18 and thyroid carcinogenesis.
Patients and Methods: Sixty (60) formalin-fixed, paraffin embedded thyroid tissue blocks were obtained ,among them (30) tissue biopsies from thyroid carcinoma with grade I and (20) benign thyroid neoplasm tissue blocks as well as (10) autopsies from apparently normal thyroid tissues were collected from the archives of Forensic Medicine Institute / Babil and used as thyroid healthy control group. Detection of HPV-18 was done by using highly sensitive version of in situ hybridization technique.
Results: Among malignant thyroid tumors 56.7% patients had HPV-18 while 35% HPV- 18 positivity was detected in benign thyroid tumor group. None of healthy thyroid tissues revealed ISH reactions. There was 32.7% female had HPV-18, and 24% male had HPV-18. No significant statistical associations were noticed between the presence of HPV-18 and the age of those patients.
Conclusion: Human Papilloma virus genotype-18 could share a role in pathogenesis of this group of patients with thyroid cancers.

Keywords: HPV_18, Thyroid Carcinoma, ISH

1. Introduction

Thyroid cancer is the most common cancer of the endocrine organs accounting for up to 2.5% of all malignancies [1] [2].

Incidence is, in fact, rising faster than all cancers, where females are more frequently affected than males. It is thought that this is in part the result of earlier detection; however, the increase in mortality as well as the increase in incidence of larger thyroidtumors suggests that there may be additional factors behind this increase [3].

The majority of thyroid cancers develop from follicular epithelial cells and according to their morphology and biology They are divided grossly into two groups; the first group, well differentiated thyroid cancers, which include the

usually slowly growing papillary thyroid carcinoma (PTC) and the follicular thyroid carcinoma (FTC). The PTC accounts for approximately up to 80% of thyroid tumours, whereas the FTC accounts for 5-15% of diagnosed thyroid malignancies [4]. These cancers are usually curable and in contrast to the second group which compromises the anaplastic thyroid cancers (ATC), which represent the poorly differentiated thyroid cancers and comprises only 1-2% of all diagnosed thyroid malignancies [5]. ATC is characterized by rapid and invasive growth resulting in fulminant disease course and poor outcome .In thyroid, approximately 5% of thyroid malignancies are diagnosed as medullary carcinoma, which in turn originates from the para follicular C cells [6].

From 2000 to 2009, incidence rates among men have decreased for five of the 17 most common cancers: prostate, lung-bronchus, colorectal, stomach, and larynx. In contrast, rates among men during the same time interval increased for six cancers: kidney, pancreas, liver, thyroid, melanoma of the skin, and myeloma. Among women, incidence rates have decreased from 2000 to 2009 for seven of the 18 most common cancers: lung, colorectal, urinary bladder, cervix uteri, oral cavity and pharynx (all tumors regardless of their potential association with HPV infection), ovary, and stomach. Incidence rates among women have increased from 2000 to 2009 for seven cancers: thyroid, melanoma, kidney, pancreas, leukemia, liver, and uterus [6].

Today, more than 200 types of HPVs have been reported, which are classified into low –oncogenic risk and high- oncogenic risk types according to their associations with malignant tumors [7].

High oncogenic risk HPV types may be integrate into the host cell chromosome, here they interrupt the integration of E2 gene that regulates the transcription & expression of HPV-E6 & E7 oncoproteins. The E6 and E7 genes represent transforming genes and their products are responsible for the alteration of growth patterns of the infected cells as well as acting, at least in part, by interfering with host cell control of transcription and the cell cycle [8].

Although there are approximately a dozen oncogenic HPV types, HPV 16 and 18 are the most common HPV types and are found in approximately 70% of cervical cancers. Human Papilloma virus 16 is found in approximately 90% of the non-cervical cancers that are often associated with HPV infection [9].

Experts have long suspected a link between HPV and oro-pharyngeal cancer (OPC) with an increasing body of evidence supporting this association. A case-control study of 100 patients with newly diagnosed oro-pharyngeal cancers (as compared to 200 matched controls) has found HPV-16 strain in 72% of these cancerous tumors [10]. Recent trends continue speculation that by 2020 year HPV will cause more cases of oro-pharyngeal cancers each year than cervical cancers [11].

Exposure to HPV is common through sexual contact, and most infections resolve over time. However, persistent infection with oncogenic HPV types is etiologically linked to cervical cancer [12], as well as cancers of the oropharynx [13], anus [14], vagina and vulva [15], and penis [16]. Virtually, all cervical cancers are due to HPV infection, along with 90% of anal cancers, more than 60% of certain subsets of oro-pharyngeal cancers, and 40% of vagina, vulva, and penile cancers [9].

Oral HPV16 & 18 DNA are common among female patients with HPV-OPC, but not among their spouses. Spouses of HPV-OPC female patients may

have an elevated risk or history of cervical cancer [17].

This research work, and up to our best knowledge, is the first in Iraq, that study the percentage of HPV18 genotype in a group of Iraqi patients with thyroid lesions.

2. Materials and methods

The study was designed as a retrospective one. It has recruited 60 selected formalin fixed, paraffin embedded thyroid tissue blocks were obtained ,among them (30) tissue biopsies with grade 1 invasive papillary thyroid carcinoma and (20) benign thyroid tissue blocks as well as (10) apparently normal thyroid tissue autopsies which were collected from the archives of Forensic Medicine Institute / Babylon and were used as thyroid healthy control groups. The diagnosis of these tissue blocks were based on their accompanied records. A consultant pathologist reexamined all these cases to further confirm the diagnosis following trimming process of these tissue blocks.

On the one hand, the detection of HPV18 by ISH kit (Zyto Vision GmbH. Fischkai, Bremerhaven. Germany) was performed on 4μm paraffin embedded tissue sections using digoxigenin-labeled oligo-nucleotidesprobe which targets HPV18 DNA. One section was mounted on ordinary glass slide and stained with hematoxyline and eosin, while another slide was mounted on charged slide to be used for ISH for detection of HPV18.

For the in situ hybridization procedure, the slides were placed in 60c hot-air oven over night then the tissue sections were de-paraffinized and then treated by graded alcohols according to the standard methods and the details of processes for performing ISH reaction with this probe were applied according the instructions of the manufacturing company(Zyto Vision GmbH. Fischkai, Bremerhaven. Germany). The main steps for ISH procedure are:

Incubation of slides for min at 70°C(e.g. on hot plate), then Incubation of slides for 5

min in xylene. After that incubation for 5 min in 100% ethanol (alternatively, dewaxing protocols routinely used in immunohistochemistry procedures, e.g. 2-5 min xylene, 2-5 min 100% ethanol, 2-5 min 96% ethanol, 1-5 min 70% ethanol, can be used. Air drying of sections. Then application (dropwise) Pepsin Solution(ES1) to the tissue/cell section and incubate for 20-30 min at 37°C in a humidity chamber. After that we immersed slides in distilled water and drain off the water, air dried sections, then we add the probe to the center of a cover slip and place cover slip upside down on target area). Denaturation of the slides at 75°C for 5 min, e.g. on hot plate, then are transferred the slides to a humidity chamber and hybridize for 60 min at 37°C for DNA-targeting probes or at 55°C for RNA- targeting probes) and the post-hybridization and detection process that included removing the cover slip by submerging in 1x wash buffer TBS, then washed for 5 min in 1x wash B\buffer TBS (prepared by using WB5) at 55°C (should not perform this step on slides hybridized with Zytofast RNA (+) control probe(PF6) as this will reduce signal intensity).

Then application of AP-Streptovidin (AB9) drop wise (3-4 drops per slide) to the slides and incubate for 30 min at 37°C in a humidity chamber. Then they

were washed in wash buffer TBS (prepared by usingWB5) and then twice times for 1 min in distilled water and application of NBT/BCIP(SB4) drop wise (4 drops per slide) to the slides and incubated for 40 min at 37°C in humidity chamber .Then the color development is checked in intervals of approx, 5-10 min using microscope. Lastly, Slides were washed three times for min in distilled water. After that the sections are covered. Then the sections are embedded in an aqueous embedded medium, then by light microscope presents the final evaluation.

Chi –square test was used to detect the significance between variables of our study . All the statistical analysis was done by SPSS program(Version–17)&P value was considered significant when p <0.05.Table-1- shows the consistency between the type of tumor of thyroid cancer and control group with gender by applying Chi-square test ,the P-value was P>0.05 of the three groups with gender .There was no differences between the presence of tumor and the gender.

3. Results

The results of HPV18- ISH among study groups

It was found after application and analysis of (ISH) for detection of HPV-18 DNA in the tissues obtained from patients with Thyroid cancer as well as benign Thyroidneoplasia that seventeen (17) out of thirty (30) patients with carcinoma of thyroid showed positive In Situ Hybrization reaction where it constituted 56.7% of the total thyroid tumor cases of this study (table 1 and figure 1). None of control group presented positive signals for HPV18-ISH test. However , in comparison to the percentage of HPV18- DNA in healthy control group as well as in the group of benign Thyroidneoplasia, the differences between the percentages of HPV18- DNA in tissues of patients with Thyroid cancers and each of these above mentioned groups are statistically very highly significant (P value = < 0,0001).

Table (1): In Situ Hybridization for Detecting HPV18 – ISH in Tissues with Thyroid Tumors.

Studied groups		HPV18 -ISH		Total	Comparison of significant	
		Positive	Negative		P-value	Sig.
Thyroid Cancer	N	17	13	30	0.00	(P≤0.01)
	%	56.7	43.3	100		
Benign Thyroid neoplasia	N	7	13	20		
	%	35	65	100		
Healthy control	N	0	10	10		
	%	0	100	100		

Chi-square was done to test the scoring of HPV18-ISH signals of thyroid lesion (Table- 2& Figure 1), it was found that there was 47.1% thyroid lesions that had low scoring in malignant thyroid lesions group and 57.1% thyroid lesions had low scoring in benign thyroid lesions group. While there was 35.3% thyroid lesions have moderate scoring in malignant thyroid lesions group and 42.9% thyroid lesions have moderate scoring in benign thyroid lesions group. Finally, there were 17.6% thyroid lesions that have strong scoring in malignant thyroid lesions group and none in benign thyroid lesions group.

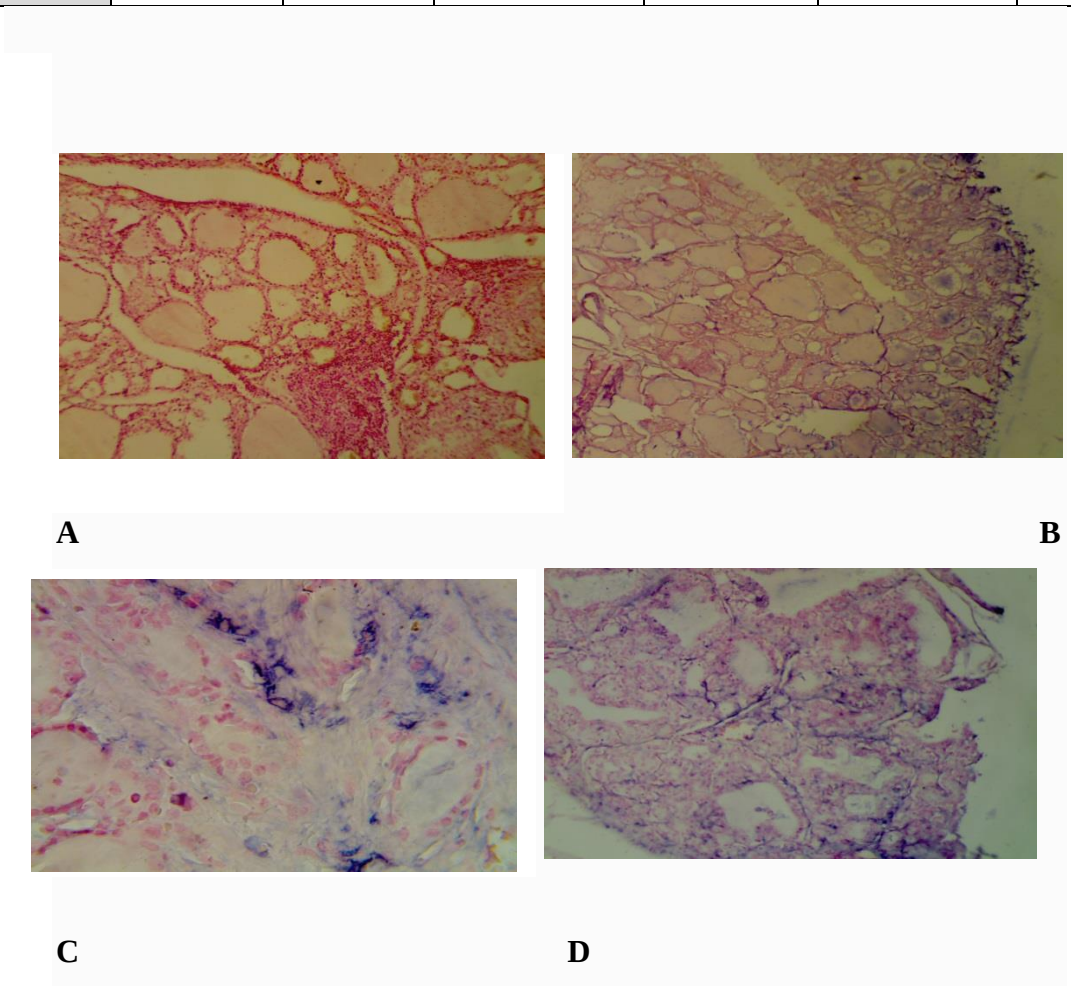
Table (2):Frequency Distribution of HPV 18 DNA-ISH Signal Scoring among the Malignant and Benign Thyroid Tumors.

HPV18Signal Scoring		Thyroid Tumors (n=30)		Benign Thyroid Tumors (n=20)		Normal Thyroid Tissues (n=10)		P
		N	%	N	%	N	%	
Negative		13/30	43.3	13/20	65	10	100.0	0.001
Positive		17/30	56.7	7/20	35	0	0.00	
Scoring	I	8/17	47.1	4/7	57.1	0	0	
	II	6/17	35.3	3/7	42.9	0	0	
	III	3/17	17.6	0	0.00	0	0	
Mean Rank		95.6		67.1		55.5		

Chi-square was done for evaluation of signals intensities of HPV18-ISH results according to type of thyroid lesions (malignant thyroid lesions, benign thyroid lesions groups) (Table- 3& Figure -1),there was 52.9% thyroid lesions that had weak intensity in malignant thyroid lesions group and 57.1% thyroid lesions had weak intensity in benign thyroid lesion group. While there was 29.5% thyroid lesions have moderate intensity in malignant thyroid lesion group and 28.6% thyroid lesions have moderate intensity in benign thyroid lesions group. The percentage of patients that had high intensity signals of HPV18-ISH in malignant thyroid lesions group was 17.6% whereas there was 14.3% patients that had high intensity signals of HPV16-ISH in benign thyroid lesions group.

Table (3): Frequency of Signal Intensity of Positive HPV18 DNA- ISH Reactions.

Studied Groups	positive HPV18 signaling	Signal Intensity			Negative HPV18 signaling	Chi-square Tests
		Weak	Moderate	High		
Malignant Thyroid. Tumors (n=30)	17/30 (56.7%)	9/17 (52.9%)	5/17 (29.5%)	3/17 (17.6%)	13/30 (43.3%)	≤0.001 significant
Benign Thyroid Tumors (n=20)	7/20 (35%)	4/7 (57.1%)	2/7 (28.6%)	1/7 (14.3%)	13/20 (65%)	
Healthy Thyroid. Tissues (n=10)	0.00 (0.00%)	0.00 (0.00%)	0.00 (0.00%)	0.00 (0.00%)	10/10 (100%)	



Figure(1) :In Situ Hybridization(ISH) for HPV-18 Deduction Infiltrative Thyroid Cancers Using Biotinylated -Labeled HPV-18

4. Discussion

Head and neck cancers arise in the nasal cavity, sinuses, mouth, lips, salivary glands, throat, larynx and thyroid gland, are predominately squamous cell carcinomas. Globally, head and neck cancers are the sixth most common type of cancer, where more than 70% of cases occurring in developing countries. They are rare in the United States, accounting for 5% of all cancer cases. The majority of molecular events in the genesis of oral squamous cell carcinoma are unknown [18].

Although recent evidence has implicated viruses in the regulation of epithelial –to- mesenchymal transition and tumor progression, little is known regarding viral infections in thyroid malignancies [19].

In the current research, the rate of detection of positive results of HPV 18 DNA-ISH reactions in the group of malignant thyroid tumors was 53.3 % (16 of total 30) while in the benign thyroid tumors was 27.3%(6 of total 22).

To our best knowledge, this study is the first in Iraq that investigates the HPV18 genotype in a group of Iraq patients with malignant & benign thyroid lesions. Moreover, and on reviewing the available scientific research works in this entity, we found an extreme shortage of the articles in this respect. However, the present results are in disagreement with a work done by [18], who have examined and who did not able to find HPV-DNA on examination of their but were not able to find HPV-DNA in the examined thyroid lesions.

Regarding the copy number of viral infection in the examined thyroid lesions of this study, we found signal scoring is refers to the wide spread of the viral invasion in relation to the surface area of the examined tissues. However, the present study has found an in equal percentage of distribution of the 3 scores of HPV-ISH in the examined thyroid tissues.

Uterine cancer ranked fourth among women of each racial and ethnic group except API women, in whom thyroid cancer was the fourth most common cancer. Beyond the three commonly diagnosed cancers for men and four most commonly diagnosed cancers for women, cancers ranking have varied by race and ethnicity [11].

Despite great variability in the HPV detection rates worldwide, the majority of HPV types that have been detected were the high oncogenic risk group (HPV -16 & HPV-18) [19].

By analogy, it was found that the present findings of HPV18 in Iraqi patients with thyroid cancers have an equal proportions of consistency to those studies done in Iraq by [20] [21] [22] [23] [24] who found that the HPV 16 &18 as the most prevalent type in their studied group of patients with cervical, esophageal, oral, prostate and breast can- cers, respectively. However, other types of HPV, such as HPV18, 31 and 33 were found to have probable roles in such cancers. High-risk HPV encodes a series of proteins, some of which have oncogenic potential [25].

Although it is known and widely accepted for many years that integration of DNA of high-risk HPV types into cellular genome as the major contributing factor in cervical carcinogenesis [26], recently is also linked to a common head & neck cancers [27]. The transmission routes of HPV detected in thyroid cancers are still unclear. However, the researchers have indicated that infection with HPV is a risk factor for oro-pharyngeal carcinoma (OPC). HPV is most

commonly passed from person to person during sexual activity, including oral intercourse. However, the risk of developing HPV-positive OPC is low for spouses (1).HPV is most commonly passed from person to person during sexual activity, including oral inter- course. Michael Douglas [28] recently related HPV16-associated throat cancer to oral sex as a possible cause of their studied throat cancers. High viral load of HPV has been associated with the microscopical diagnosis of a concurrent lesions as well as an indication to progress to precancer and cancer [29]. Studies concerning HPV association with cancer, especially cervical cancers, have revealed that an increase in HPV load is significantly associated with cervical carcinoma. [30] [31]. However, it has been well documented that the episomal viral DNA frequently integrates into the host genome as HPV-infected lesions progress to cervical cancer [32]. High proliferation of the infected host tissues has been considered to be crucial for the persistence of HPV that infects a basal layer cell of the cervical stratified squamous epithelium, the HPV DNA only replicated during cell divisions of the host before the differentiation of the infected cells. This allow the copies of viral DNA preserves in a large number in premature cells. In a similar way, infection of mammary epithelial cells ,that partly loses control in proliferation the HPV DNA copies may be preserved in nearly every clone of its first host that may further interact with other carcinogenic factors and involve in the later carcinogenic steps of breast cancer [33]. In an infected cell, vegetative viral replication end- ing with the release of the virus from cell, where this is definitely against its transformation into a malignant one [34]. Only E6 and E7 genes remain in the host genome during HPV DNA integration and therefore, their presence in tumor tissues may better represent the real HPV participation in carcinogenesis [32]. Although in the present study, a respective percentage of HPV-18 infection was found in tissues obtained from thyroid cancers as well as a highest percentage of HPV-18 ISH – reactions with low signal scoring, for this reason, ISH signals of HPV DNA ought to be of low intensity while the high intensity could reflect and indicate for viral replication inside the cells and is as such have rush an additional conflict for HPV participation in thyroid cancer and more researches could be forwarded to explore their actual role in that carcinogenesis .The fact that we have not found the Human Papilloma viral DNA in healthy thyroid specimens could support, to certain extent, the hypothesis that the virus might play a role in the etiology of thyroid cancer in only a sub set of population of patients. On the other hand, it is logical to believe that the presence of high-risk types of HPV alone is not sufficient to implement full process of tumorigenesis and that further changes should be accumulated over time in a step-wise manner to cause the disease. It could be concluded from the present results that Human Papilloma virus genotype-18 could share a role in pathogenesis of this group of patients with thyroid cancers.

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الخلاصة

خلفية علمية: سرطان الغدة الدرقية هو السرطان الذي يبدأ في الغدة الدرقية و التي يعتقد أنها مرتبطة بتهيئة عدد من العوامل البيئية و الوراثية تربط Human Papilloma Virus (HPV) المسبب لسرطان عنق الرحم ، وأيضا يعتبر المسبب لسرطان الحنجرة والذي يعد واحد من العوامل المعدية ذات الصلة.

الهدف : تهدف هذه الدراسة للكشف عن الحمض النووي ل Human Papilloma Virus-18 باستخدام تقنية situ hybridization technique في أنسجة الغدة الدرقية المأخوذة من تضخم الغدة الدرقية الحميد و سرطان الغدة الدرقية ، و توضيح العلاقة بين هذا الورم الناجم عن HPV-18 وسرطان الغدة الدرقية.

المرضى و طرق العمل : ستين (60) عينة من formalin-fixed paraffin ، وتم الحصول على أنسجة الغدة الدرقية كالتالي، من بينهم (30) خزعة نسيجية من سرطان الغدة الدرقية من الصنف الأول و (20) عينة من الأنسجة الحميدة Thyroidneoplasm وكذلك (10) من تشريح أنسجة الغدة الدرقية العادية التي تم جمعها من أرشيف معهد الطب العدلي/ بابل باستخدام عينات الغدة الدرقية لأصحاء. وقد تم الكشف عن فيروس Human Papilloma Virus-18 باستخدام نسخة حساسة للغاية من situ hybridization technique.

النتائج : من بين أورام الغدة الدرقية الخبيثة نسبة ا 56.7 ٪ من المرضى مصابين بالفيروس HPV – 18 في حين تم الكشف عن 35 ٪ من مجموعة ورم الغدة الدرقية الحميدة مصابين بالفيروسHPV – 18 . لم تظهر أي من عينات مجموعة السيطرة ISH reactions. كان 32.7 ٪ إناث مصابات بفيروسHPV – 18 ، في حين كان 24 ٪ من الذكور مصابين بفيروس HPV – 18. ولم تظهر أي دلالة إحصائية بين وجود الفيروس وعمر هؤلاء المرضى .

الاستنتاجات : HPV – 18 أن له دورا بالمشاركة في التسبب في الإصابة لدى مجموعة المرضى الذين يعانون من سرطان الغدة الدرقية.

الكلمات المفتاحية: HPV – 18سرطان الغدة الدرقية, التهجين الموضعي,