Viral infections and risk of thyroid cancer: A systematic review and empirical bayesian meta-analysis

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Objective: The associations between viruses and the cancer have been conducted in several studies while there has been no systematic review and meta-analysis about the association between viral infections and thyroid cancer (TC). Therefore, we investigated the association between viral infection and TC risk.

Methods: Systematic search was done from 1994 to 2019 in Web of sciences (ISI), PubMed, and Scopus databases. Pooled logarithm of odds ratio (OR) and their corresponding 95 % confidence interval (CI) and pooled prevalence of viral infections were calculated to find the association between the viral infections and TC risk and overall prevalence of the viral infections in TC.

Results: Twenty-three of 852 original articles were selected and included in the study. According to the results of the random effect meta-analysis, the pooled prevalence of viral infections in the TC patients was 37 % (95 % CI: 31.6–42.4 %). In addition, there was a significant association between viral infections (log OR = 1.51, 95 % credible interval = 0.68–2.39) and TC risk. The highest associations were observed between TC risk and Simian Vacuolating Virus 40 (SV40) and B19 infections, respectively. The lowest non-significant association was found between TC risk and Poliovirus type 1 infection. The significantly heterogeneity was observed between included studies.

Abbreviation: TC, Thyroid Cancer; SI, Web of sciences; OR, odds ratio; CI, confidence interval; SV40, Simian Vacuolating Virus 40; B19 infection, Parvovirus B19 infection; DTC, The differentiated thyroid cancer; EGFR, epidermal growth factor receptor; VEGFR1, vascular endothelial growth factor receptor 1; EBV, Epstein-Barr virus; BL, Burkitt lymphoma; BKV, BK virus; HIV, Human immunodeficiency Virus; HCV, Hepatitis C Virus; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; HPV, human papillomavirus; PC, prostate cancer; NS, Newcastle-Octawa Scale; SD, The standard deviation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PTC, Papillary thyroid cancer; MTC, Medullary thyroid cancer; ATC, Anaplastic thyroid Cancer; FTC, Follicular thyroid cancer; ATC, Anaplastic thyroid carcinoma; FA, Follicular adenomas; CVPTC, Classic variant of papillary thyroid carcinoma; FVPTC, Follicular variant of papillary thyroid cancer; TCPTC, Tall cell papillary thyroid carcinoma; NS, Non-structural protein; TNF-α, Tumor necrosis factor-alpha; IL-6, Interleukin-6; RONS, reactive oxygen nitrogen species; IFN-γ, interferon gamma; T Ag, T antigen.

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1. Introduction

Mainly, thyroid tumors as the most common endocrine malignancy are dividing into three common histologic subtypes including differentiated, medullary, and anaplastic [1]. The differentiated thyroid cancer (DTC) itself is comprised of four sub-classes including papillary, follicular, Hürthle and poorly differentiated which the first and second subtypes have the highest prevalence with 80 % and 10 %, respectively [1–3]. There is a number of factors which could be engaged in the progression of these tumors including the changes in tumor micro-environments and the ionizing radiation [4]. The worldwide and local prevalence statistics of Thyroid Cancer (TC) prevalence in 2018 is including 567,233 newly diagnosed case, lead to 41,071 death reported [5,6]. Surveillance, The highest prevalence is observed in the patients aged 32–65 and significantly, the higher incidence in the female is observing [7,8]. Briefly, TC is a prevalent cancer that its incidence rate is grown during recent years [9].

Start and progress of TC are depended on different factors such as genetic factors, epigenetic factors and infectious agents. Major genetic alterations that influencing in the TC are entitled in the following: 1) Gene mutation in BRAF, RAS, etc. 2) Changing in gene amplification/ gene copy number in epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor 1 (VEGFR1), etc. 3) Gene translocation in RET-PTC and etc. and 4) Aberrant gene methylation as an epigenetic sign of TC. Until today, multiple signaling pathways involved in TC detected [10,11].

Among different infectious agents, viral infection is an important factor involved in the tumor pathogenesis. Since 1882 that tobacco mosaic virus discovered and subsequently discovering of yellow fever virus in 1901 until now, scientists are trying to understand any possible correlation between the viral infection and human diseases especially cancer [12]. Discovering the association between Epstein–Barr virus (EBV) and Burkitt lymphoma (BL) was one of the first approved succeed in this way [13]. Chronic viral infection are responsible for 20–25 % of all human cancers [14].

Nowadays the association between Epstein–Barr viruses (EBV) [8,15,16], Human parvovirus B19 (B19) [17,18], BK virus (BKV) [19], Human Herpes Simplex Virus (HSV) [20], and Hepatitis C Virus (HCV) [21–23] and TC investigated and confirmed by numerous studies. These viruses deploy their impacts on the initiation and progression of TC by one or many of above-mentioned molecular alterations. For instance, EBV intervenes in TC by affecting on the BRAF gene, metastases suppressor Mn23 gene, and NF-κB signaling pathway [24–26].

The systematic reviews designing to detect the missing of evidence in a scientific field and determining the aspects that should be studied in the future because of the insufficient data. The systematic reviews can be included the meta-analysis or not [27]. We previously perform a systematic review to determine the impact of human papillomavirus (HPV) infection in prostate cancer (PC) and our findings clearly support the potential pathogenetic connection between HPV infection and increased risk of PC [28]. Considering the achievements of previous systematic review experience and as there is a lack of consensus between different points of view, this empirical Bayesian meta-analysis was done to assess the possible association between infection with viral agents and the risk of TC.

2. Methodology

2.1. Search strategies

A systematic search was conducted using ISI Web of Science, PubMed and Scopus to identify related and available articles (until August 2019). Searches were done by using the following keywords: “Thyroid Cancer”, “Thyroid Tumor/Tomour”, “Infection” and “Viral Infection”, alone or combined together with the Boolean operators “OR”, “AND” and “NOT” in the Title/Abstract/Keywords field. Unpublished studies were not included and duplicate ones were removed. The search was done by three reviewers independently and separately. Then the search results were compared to avoid missing any article. References of collected papers were also checked for relevant articles. We also searched other sources such as greylit.org, open-grey.eu, scholar.google.com and researchgate.net. In order to increase of specificity in the search results, the titles, abstracts and keywords field of all papers were scanned and irrelevant studies were excluded.

2.2. Inclusion and exclusion criteria

A protocol for the inclusion and exclusion of eligible peer-reviewed publications was defined that performed the following criteria. Inclusion criteria: (A) The studies published 1994–2019, (B) The studies reporting the presence of viral infections in TC patients, (C) All Studies included samples from Tissue and Serum. Exclusion criteria: (I) Studies with incomplete data or failed presented data clearly, (III) Animal models based researches, (IV) Researches that have bacterial infections /other infectious agents, (V) Studies with overlapping subjects, time, and place of sample collection, (VI) Case report articles, congress abstracts, meta-analysis or systematic reviews and studies reported in languages other than English.

2.3. Data extraction and quality assessment

Two authors separately extracted the data, including author’s name, year of publication, patient and control number, country, types of viruses, type of sample, type of detection methods and type of tumor. Individual data from each included study were used in this meta-analysis. Extracted data were compared and rechecked by the first and corresponding authors. The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). According to this scale, studies were classified as low (scores 0–3), moderate (scores 4–6) and high (scores 7–9) qualities [29]. NOS score for all of the included studies was more than 5 (range: 6–9).

2.4. Statistical methods

First, we used the Freeman-Tukey Double arcsine transformation of relative frequencies to calculate a pooled proportion as an effect size of viral infection prevalence in TC [30]. A random effect model derived the pooled prevalence of the viruses in the cancer patients, while the $I^2$ index is more than to 50 % and p-value of Cochran’s Q test less than 0.05, otherwise this pooled prevalence was derived by a fixed effect model. Next, pooled log odds ratio (OR) and corresponding 95 % credible interval as an effect size of the association of virus’s infection and TC risk using empirical Bayesian meta-analysis. The Bayesian meta-analysis is an alternative to the classical analysis for measuring accurate pooled effect size especially in situations with a small number of studies [31,32]. In Bayesian meta-analysis, any information about the
unknown parameters has been specified in the analysis as prior information. In addition, in meta-analysis, heterogeneity among the effect size measures is common because of variation in study characteristics [32,33]. To estimate the unknown variance of the prior distribution in a Bayesian model, Morris introduced a variance estimator it can use as the empirical Bayes estimator in some meta-analysis applications [33–35]. In this empirical Bayes meta-analysis, supposes that logarithm of the OR follows a normal distribution ($\theta$, $\tau^2$). The mean of the normal distribution, $\theta$, has a low informative normal distribution (mean = 0.525, SD = 100) and the variance of the normal distribution, $\tau^2$, has an inverse-gamma distribution (2.0001, 1.38). The hyper-parameters in the low informative normal distribution and the inverse-gamma distribution were estimated by classical meta-analysis based on the included studies. Cochran’s Q test was used to test heterogeneity, $\tau^2$ and $I^2$ indices was employed for calculating the total variation in the pooled estimations [36]. Forest plot displayed Log (OR) and 95 % credible interval for both the individual study and for the pooled effect size from this meta-analysis. In addition, heterogeneity plot displayed joint posterior density of the two parameters of the Bayesian meta-analysis model, Log (OR), and $\tau$ parameters. Publication bias was checked by Egger’s linear regression test and Begg’s test [37]. All statistical analyses were conducted by using “bayesmeta” and “metafor” R packages.

3. Results

3.1. Characteristics of the included studies

Twenty-three studies were included in the final meta-analysis. The selected studies were included 1475 cases and 874 healthy subjects. Among all studies, 52.1 % (12/23) were conducted in Asian people as the most studied of all continents. Publication year of these studies was ranged from 1994 to 2019. The most common method of diagnosis was Polymerase chain reaction (PCR).

A total of 852 articles were retrieved by searching of the mentioned database. In a primary screening process, 95 of the publications were excluded due to duplication. Results of the secondary screening process were the exclusion of 702 publications based on the title and abstract evaluation, and 55 articles were retained for detailed full-text evaluation. Finally, 23 articles were included. Articles met our inclusion criteria and were considered in this meta-analysis (Fig. 1). The key characteristics of included studies are presented in Tables 1.

3.1.1. Prevalence of the viral infections in TC

Based on 23 included studies, 552 patients from 1475 TC patients had viral infections. According to the results of the random effect meta-analysis, the pooled prevalence of viral infections in the TC patients was 37 % (95 % C.I = 22 %–55 %). The heterogeneity of prevalence between studies was observed (Q test: p-value < 0.001; $I^2$ = 96.3 %; $\tau^2$ = 2.94). The highest and lowest prevalence of viral infections was observed in the TC patients related to B19 and HCV, respectively. Forest plot for the pooled prevalence was shown in Fig. 2.

3.2. Association between viral infections and TC risk

According to the results of empirical Bayesian meta-analysis based on 12 case-control studies, there was significant association between viral infections (log (OR) = 1.51, 95 % credible interval = 0.68–2.39) and TC risk. In other words, presence of viral infections significantly increased the risk of TC (Fig. 3). The highest associations were observed between TC risk and Simian Vacuolating Virus 40 (SV40) and B19 infections, respectively. The lowest non-significant association was found between TC risk and Poliovirus type 1 infection. The heterogeneity of
<table>
<thead>
<tr>
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<th>Normal control</th>
<th>Positive in tumor</th>
<th>Normal control</th>
<th>Type of virus</th>
<th>Method</th>
<th>Type of sample</th>
<th>Type of tumor</th>
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Papillary thyroid cancer (PTC), Medullary thyroid cancer (MTC), Anaplastic thyroid Cancer (ATC), Follicular thyroid cancer (FTC), Anaplastic thyroid carcinoma (ATC), Follicular adenomas (FAs), Classic variant of papillary thyroid carcinoma (CVPTC), Follicular variant of papillary thyroid cancer (FVPTC), Tall cell papillary thyroid carcinoma (TCPTC).
between studies was observed \( (Q \text{ test: } p\text{-value < 0.001; } I^2 = 73.82\% \text{; } \tau^2 = 1.08, 95\% \text{ Cr. I} = 0.47–1.94). \) (Fig. 4).

### 3.3. Publication bias and sensitivity analysis

Publication bias was evaluated by Egger’s and Begg’s tests. Publication bias was not statistically significant in the meta-analysis (Begg’s p-value = 0.39, Egger’s p-value = 0.14). Furthermore, the robustness of Bayesian analysis was confirmed by several sensitivity analyses. Sensitivity analyses with different choices of low-information prior distributions indicated robustness of these choices.

![Forest plot displaying the prevalence of viral infections in the TC patients.](image1)

![Forest plot displaying log (OR) and corresponding 95% credible interval as an effect size of the association between viral infections and TC risk.](image2)

### 4. Discussion

The discovery of new prognostic biomarkers is a significant unmet clinical need in the treatment of various cancers. This need is underlined by the increased TC rates worldwide [5]. In recent years, several factors involved in Biological carcinogens, such as viral infections [54]. Tumorigenesis and development of TC have been discovered and biological carcinogens, such as viral infections is one of the most important factor [8,14,17].

Very few studies, especially meta-analyses, have investigated the association between the viral infections and risk of TC. In a study, EBV infection was detected in 71.9 % of TC tissue as a risk factor for this cancer \( (\text{OR} = 1.631; 95\% \text{ CI} = 0.537–4.947). \) The results of this study demonstrated EBV infection may involve in the development of TC [8]. In the current meta-analysis, the pooled prevalence of viral infections in the TC patients was 37 % \( (95\% \text{ CI} = 22\%–55\% \text{; } \text{OR} = 1.51) \) and the risk of viral infection was \( \text{OR} = 1.51; 95\% \text{ CI} = 0.68–2.39 \) (Fig. 2,3). Also, we showed that the highest and lowest prevalence of viral infections was observed in the TC patients related to B19 and HCV, respectively (Fig. 2). Another important point of the current study was the highest associations were observed between TC risk and Simian Vacuolating Virus 40 (SV40) and B19 infections, respectively (Fig. 3). Etemadi et al. determined the presence of B19 and association between its proteins with increased inflammation in TC development. Their results indicated 86.11 % (31 / 36) of B19 DNA prevalence. They demonstrated a significant positive correlation between presences of parvovirus B19 and its protein and risk of thyroid tumor. Also, they showed the high level of Non-structural protein 1 (NS1), NF-κB, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and reactive oxygen nitrogen species (RONS) in all TC samples [17]. NS1 of B19 lead to expression of IL-6 and TNF-α through the NF-κB-binding site in the IL-6 promoter [55,56]. The role of IL-6 in the immunological microenvironment of TC and enhancement effect of B19 infection on IL-6 expression was shown by Al-Gharrawi research group [57]. In another investigation, 25 % of B19 infection and high level of interferon gamma (IFN-γ), IL-6, TNF-α has been shown [56].
Ozdarendeli et al. detected SV40 in 66% of papillary and 100% of anaplastic thyroid carcinomas, respectively [41]. SV40 is involved in tumor development in different ways and one of them is activates vascular endothelial growth factor expression through T antigen (T Ag) [58]. For determination of association between SV40 infection and TC development additional researches are required.

Another important viral oncogene is EBV. This virus has a role in tumor development through prevention of anoikis (a form of programmed cell death) [59]. Moghoofei et al. evaluated the association between EBV infection and TC. Their results showed the expression levels of inflammatory factors such as including IL-1, IL-6, TNF-α and INF-α/β were higher in the EBV-positive tumor tissues than the EBV-negative tissues. Also, they reported a positive correlation between EBV and its proteins with anoikis resistance. This research demonstrated that the presence of the EBV and its gene expression was associated with thyroid tumor development [8]. Among thyroid tumor types, papillary was most associated with viral infections [8,17,60]. This is probably because papillary type is the most common type of TC with approximately 80 percent of cases [61–63].

This meta-analysis is suffered some limitations. First, because of the insufficient original data, we could not perform a subgroup analysis based on the type of viral infections. Second, heterogeneity observed between included studies due to variations in demographic specifications among the studies, geographic factors, different viral infections, and differences in the inclusion criteria for the study populations. Despite significant results in the classical meta-analysis, the number of included studies was not considerably large, and thus the results should be interpreted with caution. In the Bayesian meta-analysis, the credible interval is slightly wider than that of classical meta-analysis and the results tend to be more consistent [32]. The viruses are involved in cancer development through the diverse biological pathways. Viral proteins have important role in this process, therefore the viral proteins and non-coding RNAs in precancerous and cancer tissues can be attractive targets for novel cancer therapies and as preventive. For example, Lamuvidine and Ganciclovir (antiviral drugs) target the viral replication machinery in HBV and Kaposi sarcoma virus [64].

Declaration of Competing Interest
The authors declare that they have no conflicts of interest with the contents of this article.

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We tender our apologies to those authors whose deserving research was not cited in this manuscript.

References
[8] M. Moghoofei, S. Mostafaei, A. Nesaei, A. Etemadi, J. Sadri Nahand, H. Mirzaei, Another important viral oncogene is EBV. This virus has a role in tumor development through prevention of anoikis (a form of programmed cell death) [59]. Moghoofei et al. evaluated the association between EBV infection and TC. Their results showed the expression levels of inflammatory factors such as including IL-1, IL-6, TNF-α and INF-α/β were higher in the EBV-positive tumor tissues than the EBV-negative tissues. Also, they reported a positive correlation between EBV and its proteins with anoikis resistance. This research demonstrated that the presence of the EBV and its gene expression was associated with thyroid tumor development [8]. Among thyroid tumor types, papillary was most associated with viral infections [8,17,60]. This is probably because papillary type is the most common type of TC with approximately 80 percent of cases [61–63].

This meta-analysis is suffered some limitations. First, because of the insufficient original data, we could not perform a subgroup analysis based on the type of viral infections. Second, heterogeneity observed between included studies due to variations in demographic specifications among the studies, geographic factors, different viral infections, and differences in the inclusion criteria for the study populations. Despite significant results in the classical meta-analysis, the number of included studies was not considerably large, and thus the results should be interpreted with caution. In the Bayesian meta-analysis, the credible interval is slightly wider than that of classical meta-analysis and the results tend to be more consistent [32]. The viruses are involved in cancer development through the diverse biological pathways. Viral proteins have important role in this process, therefore the viral proteins and non-coding RNAs in precancerous and cancer tissues can be attractive targets for novel cancer therapies and as preventive. For example, Lamuvidine and Ganciclovir (antiviral drugs) target the viral replication machinery in HBV and Kaposi sarcoma virus [64].

Ethics
This study does not need ethical approval and patient consent. All analyses were according to previous published studies.


