Original paper

Human papilloma virus infection in basal cell carcinoma of the skin: a systematic review and meta-analysis study

Mazaher Ramezani[1], Masoud Sadeghi[2,3]

[1]Molecular Pathology Research Center, Emam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran
[2]Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran
[3]Students Research Committee, Kermanshah University of Medical Sciences, Kermanshah, Iran

Human papillomaviruses (HPVs) are a large and ubiquitous group of viruses that some of them have been suggested as a co-factor in the development of non-melanoma skin cancers. The aim of this meta-analysis study was to evaluate HPVs' prevalence in basal cell carcinoma (BCC) of the skin and the risk of them in the BCC patients compared with the healthy controls. Five databases were searched from January 1980 to February 2017. A random-effects meta-analysis was done with the event rate (ER) for the prevalence of HPVs and odds ratio (OR) for estimation of the incidence of HPVs. Out of 1087 studies, 45 studies were included in the review. The pooled analysis demonstrated that the incidence of γ-HPV was effective in the BCC patients compared with the healthy controls [OR = 1.97; 95% CI: 1.52-2.55; $p < 0.00001$], but not for α-HPV, β-HPV and epidermodysplasia verruciformis (EV)-HPV ($p > 0.05$). The pooled ER of incidence of β1-HPV in the BCC patients was 33.3% and for β2-HPV in BCC patients was 44.2%. In conclusion, this meta-analysis showed that probably the risk of γ-HPV was more on BCC patients and also the rate of γ-HPV was higher than α-, β- and EV-HPVs in the BCC patients.

Key words: human papilloma virus, basal cell carcinoma, prevalence, incidence.

Introduction

Human papillomaviruses (HPVs) are a large and ubiquitous group of viruses that can accompany benign, pre-malignant and malignant proliferations of the epithelium [1]. About 5% of all cancers in the world can be related to HPVs [2, 3]. More than 200 HPV types have been described and divided into five major genera: α-, β-, γ-, μ- and ν-papillomavirus [4]. HPVs can be divided into cutaneous types commonly found in common warts, mucosal types detected in genital condylomas and anogenital cancers and epidermodysplasia verruciformis (EV) types [5, 6]. EV is a rare genodermatosis associated with infections with specific HPVs belonging to the β genus of HPV [7]. Some of the cutaneous HPVs of the genus β have been suggested as a co-factor in the development of non-melanoma skin cancer (NMSC) [1, 8]. NMSCs are squamous cell carcinomas (SCC) and basal cell carcinomas (BCC) that BCC is the most common skin malignancy and represents approximately 75% of all skin cancers, mostly in the sun-exposed areas [9, 10]. HPV is increasingly considered as an important human carcinogen, but its role in the etiology and pathogenesis of BCC in immunocompetent individuals is unclear [11]. A sig-

nificant problem for investigations of an association between cutaneous HPV and non-melanoma skin cancer is that cutaneous HPV is part of the normal flora of human skin [12].

The aim of this meta-analysis study was to determine HPVs' prevalence in the BCC patients and the risk of them in the BCC patients compared with the health controls.

Material and methods

Search strategies

A comprehensive search was done with search terms included with "basal cell carcinoma OR BCC" and "HPV or human papillomavirus" in databases of PubMed/Medline, Web of Science, Science Direct, Scopus, and Cochrane Library from January 1980 to February 2017.

Study selection

Two authors revised selection of the studies. The first author (M.S) searched the studies and then the second author (M.R) screened them. Both authors assessed the studies based on criteria for selecting the studies included in this study. The studies included the following inclusion criteria: a) case-control, cohort or cross-sectional studies; b) human studies; c) reporting of the prevalence of HPVs in serum and/or tissue of the patients with BCC of the skin; d) reporting of the incidence of HPVs in serum or tissue of the BCC patients (BCC group or BCC patients) compared with serum or tissue of the controls (control group).

Data extraction

We extracted the name of author, the year of publication, country, the number of BCC patients, the number of patients in the control group (if), the number of HPV positivity in the BCC patients, the number of HPV positivity in the health controls (if), the type of HPV, the method of HPV detection and immune status of each study included in the review.

Statistical analysis

A random-effects meta-analysis was used by Comprehensive Meta-Analysis software version 2.0 (CMA 2.0) using the event rate (ER) and Review Manager 5.3 (RevMan 5.3, The Cochrane Collaboration, Oxford, United Kingdom) using odds ratio (OR) and 95% confidence intervals (CIs) for estimation of the incidence of HPV. Heterogeneity between estimates was assessed by the Q and I^2 statistic that for the Q statistic, heterogeneity was considered for $p < 0.1$. Two-sided p-value < 0.05 was considered to be statistically significant in this meta-analysis study.

Results

Selection of studies

Out of 1087 studies, 92 studies evaluated for eligibility (Fig. 1). Forty-seven studies were excluded because they were case-report, review studies, didn't report the prevalence of HPVs in BCC patients or report just one BCC patient. Therefore, 45 studies were included in the systematic review.

Characteristics of studies

Out of 45 studies reported during 1991 to 2017; two studies were reported in Australia [12, 13], one Romania [14], ten USA [15, 16, 17, 18, 19, 20, 21, 22, 23, 24], one Argentina [1], four Netherlands [25, 26, 27, 28], two Spain [8, 11], one Brazil [29], one China [30], one UK [31], one Croatia [2], four Iran [9, 32, 33, 34], one North Africa/France [35], one Germany/USA [36], two Greece [37, 38], one Sweden/Austria [39], two Germany [40, 41], five Italy [5, 42, 43, 44, 45], one Russia [46], one Germany/Poland [47], one Norway/Sweden [48] and two Sweden [49, 50] (Table I). Fifteen studies were case-control and 30 studies were cross-sectional studies. Twenty-four studies did polymerase chain reaction (PCR) [1, 2, 12, 14, 19, 20, 21, 25, 28, 29, 31, 32, 35, 36, 37, 39, 40, 41, 42, 43, 44, 46, 47, 49, 50], 2 *in situ* hybridization (ISH) [15, 18], 3 serology [16, 48, 24], 7 nested PCR [5, 8, 11, 26, 27, 34, 43], one loop-mediated isothermal amplification assay (LAMP)/PCR [30], 4 multiplex serology [17, 22, 38, 45], 2 immunohistochemistry (IHC) [9, 33], one

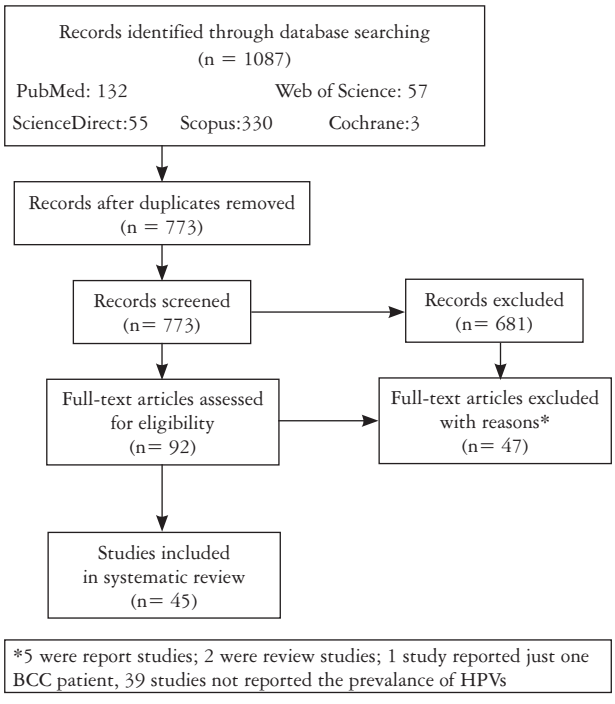


Fig. 1. The flowchart of study

Table I. The characteristics of studies included in meta-analysis (n = 45)

Study (year)	Country	Study type	BCC	Controls	Method of HPV detection	Immune status
Correa *et al*. 2017 [1]	Argentina	CS	96	–	PCR	IC/IS
Drvar *et al*. 2014 [2]	Croatia	CS	13	–	PCR	N/S
Zakrzewska *et al*. 2012 [5]	Italy	CS	100	–	Nested PCR	IC
Bernat-García *et al*. 2014 [8]	Spain	CS	26	–	Nested PCR	IC/IS
Mokhtari *et al*. 2009 [9]	Iran	CS	80	–	IHC	N/S
Escutia *et al*. 2011 [11]	Spain	CC	70	72	Nested PCR	IC
Forslund *et al.* 2003 [12]	Australia	CS	25	–	PCR	IC/IS
Trenfield *et al*. 1993 [13]	Australia	CS	11	–	Southern blot	IS
Rotaru *et al*. 2014 [14]	Romania	CC	20	40	PCR	IC
Elwood *et al.* 2014 [15]	USA	Cohort	13	–	ISH	N/S
Iannacone *et al*. 2013 [16]	USA	CC	224	300	Serology	N/S
Karagas *et al.* 2006 [17]	USA	CC	525	461	Multiplex Serology	N/S
Gibson *et al*. 2001 [18]	USA	CS	51	–	ISH	N/S
Pierceall *et al*. 1991 [19]	USA	CS	16	–	PCR	N/S
Karagas *et al.* 1997 [20]	USA	CS	25	–	PCR	N/S
Patel *et al.* 2008 [21]	USA	CS	98	–	PCR	IC
Karagas *et al*. 2010 [22]	USA	CC	898	805	Multiplex Serology	N/S
Rollison *et al*. 2008 [23]	USA	CS	15	–	Multiplex Serology/ PCR	N/S
Iannacone *et al*. 2012 [24]	USA	CS	204	297	Serology	N/S
Tieben *et al*. 1994 [25]	Netherlands	CS	4	–	PCR	IS
de Jong-Tieben *et al.* 1995 [26]	Netherlands	CC	8	23	Nested PCR	IC/IS
Berkhout *et al.* 2000 [27]	Netherlands	CS	14	–	Nested PCR	IS
Feltkamp *et al*. 2003 [28]	Netherlands	CC	432	333	PCR	N/S
Berberta *et al*. 2004 [29]	Brazil	CC	23	9	PCR	N/S
Yang *et al*. 2016 [30]	China	CS	50	–	LAMP/ PCR	N/S
Harwood *et al*. 2000 [31]	UK	CS	54	–	PCR	IC/IS
Nahidi *et al*. 2015 [32]	Iran	CC	42	42	PCR	N/S
Ramezani *et al.* 2016 [33]	Iran	CC	53	44	IHC	N/S
Shahmahmoudi *et al*. 2007 [34]	Iran	Cohort	99	–	Nested PCR	N/S
Luron *et al*. 2007 [35]	North Africa/ France	CC	27	9	PCR	IS
Iftner *et al*. 2003 [36]	Germany/USA	CC	18	106	PCR	IC
Zaravinos *et al*. 2010 [37]	Greece	CC	15	53	PCR	IC
Biliris *et al*. 2000 [38]	Greece	CS	72	–	Multiplex PCR	IC
Forslund *et al.* 2004 [39]	Sweden/Austria	CS	109	–	PCR	IC
Reuschenbach *et al*. 2011 [40]	Germany	Cohort	53	–	PCR	IC/IS
Stockfleth *et al*. 2004 [41]	Germany	CS	64	–	PCR	IS
Posteraro *et al*. 1996 [42]	Italy	CS	25	–	PCR	IC
Paolini *et al*. 2011 [43]	Italy	CC	37	37	Nested PCR	N/S
Borgogna *et al*. 2014 [44]	Italy	Cohort	31	–	PCR	IS

Table I. The characteristics of studies included in meta-analysis (n = 45)

Study (year)	Country	Study type	BCC	Controls	Method of HPV detection	Immune status
Paradisi *et al*. 2011 [45]	Italy	Cohort	49	–	Multiplex Serology	N/S
Shamanin *et al*. 1996 [46]	Russia	CS	16	–	PCR	IC/IS
Wieland *et al*. 2000 [47]	Germany/Poland	CS	69	–	PCR	IC
Andersson *et al*. 2012 [48]	Norway/Sweden	Cohort	1990	–	Serology	N/S
Faust *et al*. 2013 [49]	Sweden	CS	160	–	PCR	IC
Andersson *et al*. 2008 [50]	Sweden	CS	160	–	PCR	N/S

BCC – basal cell carcinoma; CC – case-control; CS – cross-sectional; IC – immunocompetent; IS – immunosuppressed; N/S – not specified; PCR – polymerase chain reaction; ISH – in situ hybridization; IHC –immunohistochemistry; LAMP – loop-mediated isothermal amplification assay
**Biopsy was used for interpretation (not swab) and in cases of absence of biopsy, serology was used for interpretation*

multiplex serology/PCR [23] and one southern blot [13] for detection of HPV. Also, immune status were immunocompetent/immunosuppressed (IC/IS) in 7 studies [1, 8, 12, 26, 31, 40, 46], IC in 11 studies [5, 11, 14, 21, 36, 37, 38, 39, 42, 47, 49], IS in 6 studies [13, 25, 27, 35, 41, 44] and 21 studies didn't report any status [2, 9, 15, 16, 17, 18, 19, 20, 22, 23, 24, 28, 29, 30, 32, 33, 34, 43, 45, 48, 50]. Out of 45 studies, seven studies checked HPVs on the serum [16, 17, 22, 38, 45, 48, 24] and the rest of studies on the BCC-involved and healthy tissues.

Meta-analysis

Figure 2 shows the incidence of number of HPVs in the BCC patients and controls. Some studies reported this incidence in the BCC patients and controls (case-control studies) and other studies only reported in BCC patients (cross-sectional and cohort studies).

α-HPV

Seven studies [1, 14, 16, 17, 24, 37, 43] reported the prevalence of α-HPV in the BCC patients and/or controls. Out of 1121 BCC patients, 338 (30.1%) were HPV positivity and out of 1188 controls, 358 (30.1%) were HPV positivity. The pooled analysis with dichotomous data demonstrated that the incidence of α-HPV was not effective in the BCC patients compared with the healthy controls [OR = 1.45; 95% CI: 0.90-2.33; p = 0.12] and [I^2 = 78%; p = 0.001] **(Fig. 3).**

β-HPV

Seven studies [1, 16, 17, 22, 24, 32, 43] reported the prevalence of β-HPV in the BCC patients and/or controls. Out of 2379 BCC patients, 951 (40%) were HPV positivity and out of 1942 controls, 863 (44.4%) were HPV positivity. The pooled analysis with dichotomous data demonstrated that the incidence of β-HPV was not effective in the BCC patients compared with controls [OR = 1.10; 95% CI: 0.83-1.45; p = 0.50] and [I^2 = 64%; p = 0.02] (Fig. 3).

γ-HPV

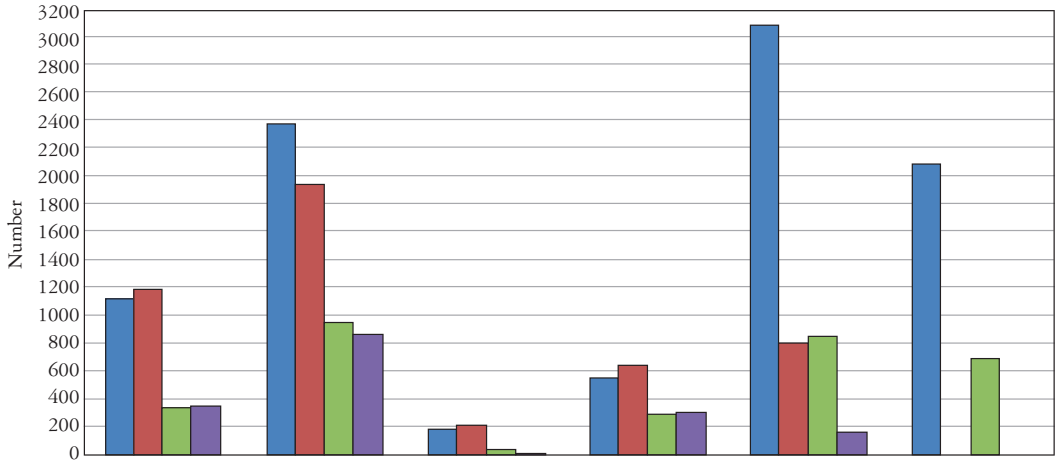
Four studies [1, 16, 24, 43] reported the prevalence of γ-HPV in BCC patients and/or controls. Out of 561 BCC patients, 291 (51.9%) were HPV positivity and out of 634 controls, 310 (48.9%) were HPV positivity. The pooled analysis with dichotomous data demonstrated that the incidence of γ-HPV was effective in the BCC patients compared with controls [OR = 1.97; 95% CI: 1.52-2.55; p < 0.00001] and [I^2 = 0%; p = 0.89] (Fig. 3).

Epidermodysplasia verruciformis-HPV (EV-HPV)

Six studies [11, 25, 26, 31, 35, 36] reported the prevalence of EV-HPV in the BCC patients and/or controls. Out of 181 BCC patients, 39 (21.5%) were HPV positivity and out of 210 controls, 16 (7.6%) were HPV positivity. The pooled analysis with dichotomous data demonstrated that the incidence of EV-HPV was not effective in the BCC patients compared with controls [OR = 2.04; 95% CI: 0.52, 7.98; p = 0.31] and [I^2 = 47%; p = 0.13] (Fig. 3).

α-HPV based on subgroups

Figure 4 shows the event rate of HPV 3, HPV 18, HPV 16, HPV 31, HPV 33, HPV 6 and HPV 11 in the BCC patients. Two [45, 49], six [15, 18, 19, 38, 34, 49], eleven [2, 15, 18, 19, 20, 28, 34, 38, 45, 49, 50], two [18, 49], three [18, 38, 49], four [18, 45, 49, 50], and three studies [18, 38, 49] reported the prevalence of HPV 3 (α2), HPV 18 (α7), HPV 16 (α9), HPV 31 (α9), HPV 33 (α9), HPV 6 (α10), and HPV 11 (α10) in the BCC patients, respectively. Table II shows the pooled ER of the articles for the incidence of α- HPVs in the BCC patients.



	α-HPV	β-HPV	EV-HPV	γ-HPV	β1-HPV	β2-HPV
Number of BCC patients	1121	2379	181	561	3086	2088
Number of controls	1188	1942	210	634	805	
Number of HPV+ in BCC	338	951	39	291	848	689
Number of HPV+ in control	358	863	16	310	155	

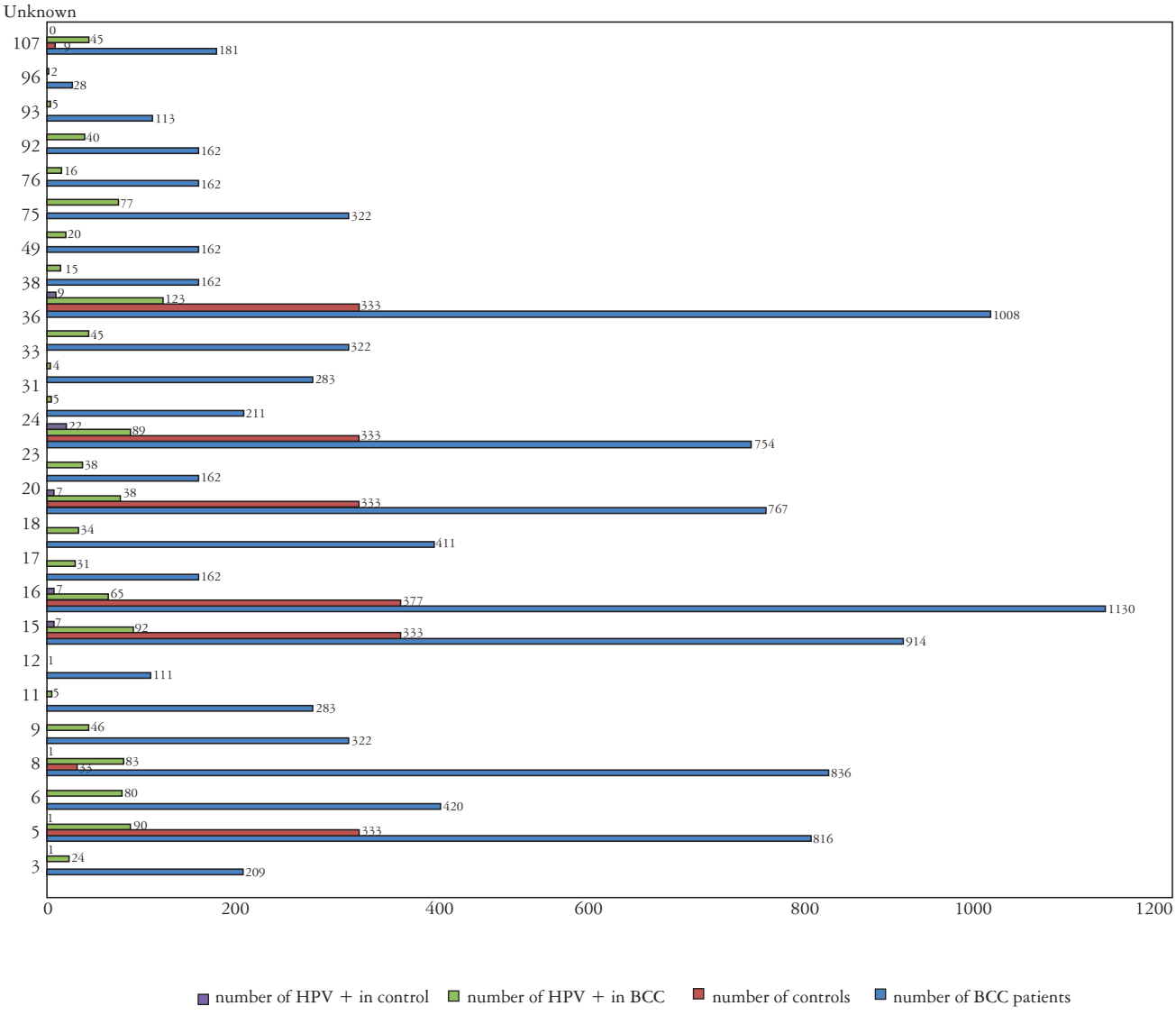


Fig. 2. The incidence of a number of HPVs in BCC patients and controls

Study of subgroup	BCC Events	BCC Total	Control Events	Control Total	Odds ratio Weight	Odds ratio M-H, Random, 95% CI
α-HPV						
Paolini *et al.* 2011	0	37	0	37		not estimable
Rotaru *et al.* 2014	125	525	134	461	9.7%	0.76 (0.57-1.01)
Iannacone *et al.* 2013	103	224	106	300	9.0%	1.56 (1.09-2.22)
Karagas *et al.* 2006	95	204	104	297	8.9%	1.62 (1.12-2.33)
Zaravinos *et al.* 201	5	15	8	53	2.5%	2.81 (0.76-10.43)
Iannacone *et al.* 2012	7	20	6	40	2.7%	3.05 (0.86-10.80)
Subtotal (95% CI)		**1025**		**1188**	**32.8%**	**1.45 (0.90-2.33)**
Total events	335		358			
Heterogeneity: Tau² = 0.19, χ² = 18.17, df = 4 (p = 0.001), I² = 78%						
Test for overall effect Z = 1.54 (p = 0.12)						
β-HPV						
Karagas *et al.* 2006	0	42	1	42	0.5%	0.33 (0.01-8.22)
Paolini *et al.* 2011	103	525	114	461	9.5%	0.74 (0.55-1.00)
Iannacone *et al.* 2012	396	898	369	805	10.5%	0.93 (0.77-1.13)
Nahidi *et al.* 2015	152	224	181	300	8.9%	1.39 (0.96-2.00)
Karagas *et al.* 2010	139	204	179	297	8.8%	1.41 (0.97-2.05)
Iannacone *et al.* 2013	26	37	19	37	4.0%	2.24 (0.86-5.82)
Subtotal (95% CI)		**1930**		**1942**	**42.2%**	**1.10 (0.83-1.45)**
Total events	816		863			
Heterogeneity: Tau² = 0.06, χ² = 13.76, df = 5 (p = 0.002), I2 = 64%						
Test for overall effect Z = 0.67 (p = 0.50)						
γ-HPV						
Iannacone *et al.* 2012	0	37	0	37		not estimable
Iannacone *et al.* 2013	151	224	155	300	8.9%	1.94 (1.35-2.77)
Paolini *et al.* 2011	140	204	155	297	8.8%	2.00 (1.38-2.91)
Subtotal (95% CI)		**465**		**634**	**17.7%**	**1.97 (1.52-2.55)**
Total events	291		310			
Heterogeneity: Tau² = 0.00, χ² = 0.02, df = 1 (p = 0.89), I² = 0%						
Test for overall effect Z = 5.12 (p < 0.00001)						
EV-HPV						
Iftner *et al.* 2003	4	27	2	9	1.4%	0.61 (0.09-4.06)
Luron *et al.* 2007	18	70	13	72	4.9%	1.57 (0.70-3.51)
Escutia *et al.* 2011	0	18	1	106	0.5%%	1.90 (0.07-48.46)
de Jong-Tieben *et al.*1995	4	8	0	23	0.6%	47 (2.14-1033.86)
Subtotal (95% CI)		**123**		**210**	**7.3%**	**2.04 (0.52-7.98)**
Total events	26		16			
Heterogeneity: Tau² = 0.89, χ² = 5.71, df = 3 (p = 0.13), I² = 47%						
Test for overall effect Z = 1.02 (p = 0.007)						
Total (95% CI)		**3543**		**3974**	**100%**	**1.38 (1.09-1.75)**
Total events	1468		1547			
Heterogeneity: Tau² = 0.13, χ² = 58.51, df = 16 (p < 0.000013), I² = 73%						
Test for overall effect Z = 2.68 (p = 0.007)						
Test for subgroup differences: χ² = 9.17, df = 3 (p = 0.03), I2 = 67.3%						

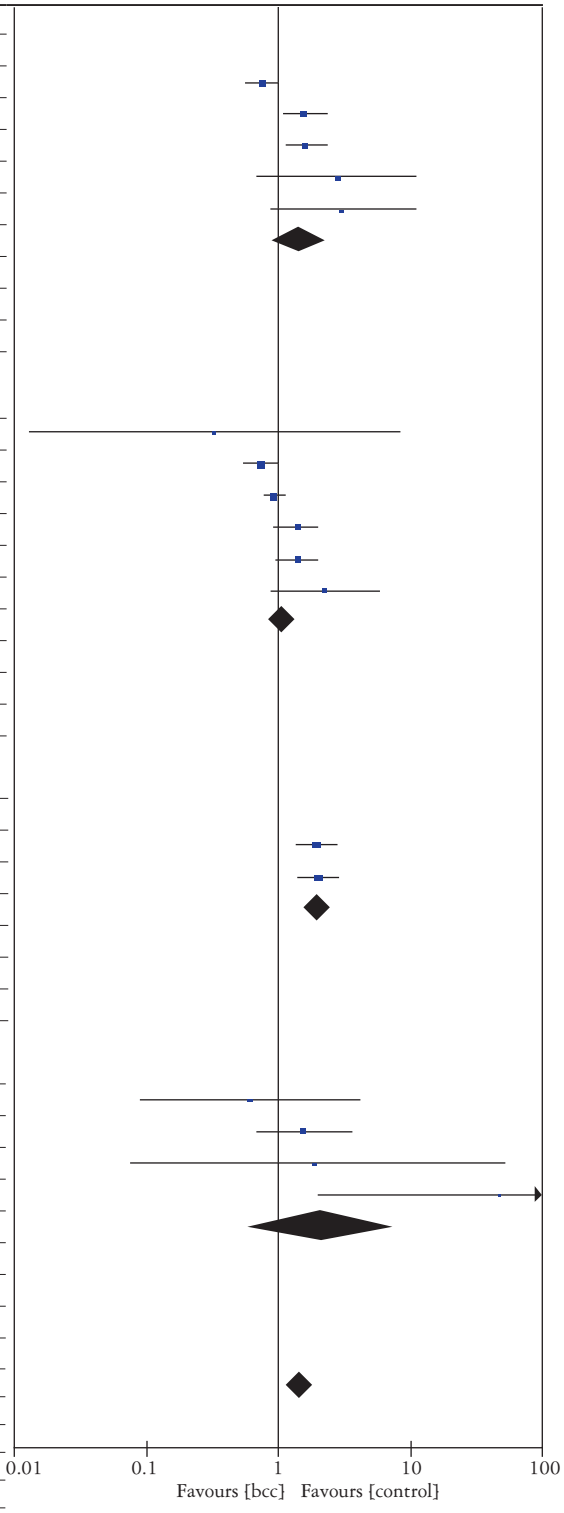
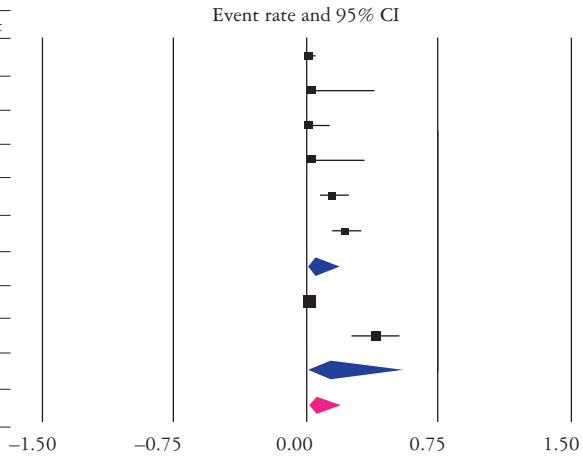


Fig. 3. The forest plot of odds ratios for the risk impact of α-HPV, β-HPV, γ-HPV and EV-HPV in BCC patients compared with controls

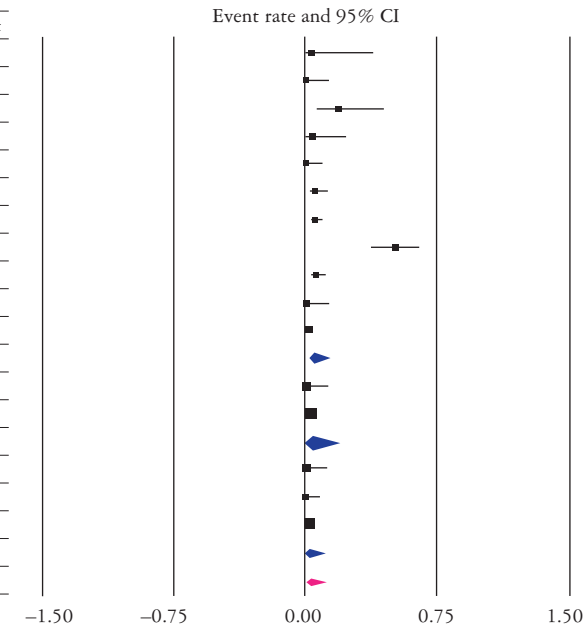
A

Study name	HPV type	Statistics for each study		
		Event rate	Lowert limit	Upper limit
Faust *et al.* 2013	18	0.013	0.003	0.049
Elwood *et al.* 2014	18	0.036	0.002	0.384
Gibson *et al.* 2001	18	0.010	0.001	0.136
Pierceall *et al.* 1991	18	0.029	0.002	0.336
Biliris *et al.* 2010	18	0.139	0.076	0.239
Shahmahmoudi *et al.* 2007	18	0.222	0.151	0.315
Total for subgroup		0.053	0.014	0.181
Faust *et al.* 2013	3	0.031	0.013	0.073
Paradisi *et al.* 2011	3	0.388	0.263	0.529
Total for subgroup		0.129	0.018	0.543
Overall		0.070	0.023	0.192



B

Study name	HPV type	Statistics for each study		
		Event rate	Lowert limit	Upper limit
Elwood *et al.* 2014	16	0.036	0.002	0.384
Gibson *et al.* 2001	16	0.010	0.001	0.136
Pierceall *et al.* 1991	16	0.188	0.062	0.447
Karagas *et al.* 1997	16	0.040	0.006	0.235
Biliris *et al.* 2010	16	0.007	0.000	0.100
Shahmahmoudi *et al.* 2007	16	0.061	0.027	0.128
Faust *et al.* 2013	16	0.056	0.030	0.105
Paradisi *et al.* 2011	16	0.510	0.373	0.646
Andersson *et al.* 2008	16	0.069	0.038	0.120
Ramezani *et al.* 2016	16	0.009	0.001	0.131
Feltkamm *et al.* 2003	16	0.023	0.012	0.042
Total for subgroup		0.055	0.022	0.135
Gibson *et al.* 2001	31	0.010	0.001	0.136
Faust *et al.* 2013	31	0.031	0.013	0.073
Total for subgroup		0.021	0.002	0.181
Gibson *et al.* 2001	33	0.010	0.001	0.136
Biliris *et al.* 2010	33	0.007	0.000	0.100
Faust *et al.* 2013	33	0.025	0.009	0.065
Total for subgroup		0.014	0.002	0.096
Overall		0.033	0.011	0.097



C

Study name	HPV type	Statistics for each study		
		Event rate	Lowert limit	Upper limit
Gibson *et al.* 2001	11	0.010	0.001	0.136
Faust *et al.* 2013	11	0.031	0.013	0.073
Biliris *et al.* 2010	11	0.007	0.000	0.100
Total for subgroup		0.017	0.003	0.082
Gibson *et al.* 2001	6	0.010	0.001	0.136
Faust *et al.* 2013	6	0.063	0.034	0.112
Paradisi *et al.* 2011	6	0.347	0.228	0.489
Andersson *et al.* 2008	6	0.331	0.263	0.408
Total for subgroup		0.155	0.055	0.367
Overall		0.057	0.006	0.0380

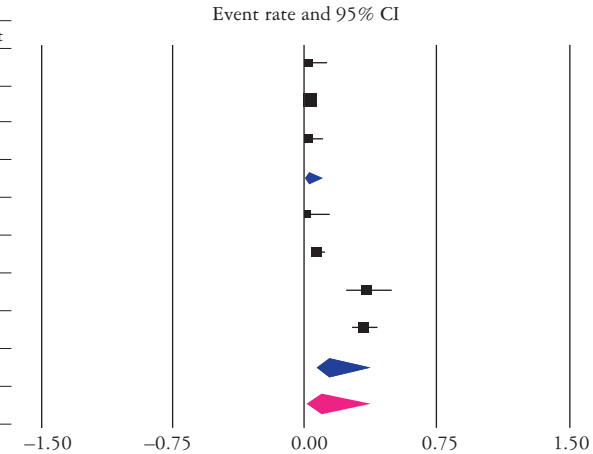


Fig. 4. The forest plot of event rate of (A) α2- and α7-HPVs, (B) α9-HPV and (C) α10-HPV in BCC patients

Table II. The pooled ER of the articles for the incidence of α-HPVs in BCC patients

HPV	Number of BCC patients	ER	95%CI
HPV 3	209	12.9	1.8-54.3
HPV 18	411	5.3	1.4-18.1
HPV 16	1130	5.5	2.2-13.5
HPV 31	211	2.1	0.02-18.1
HPV 33	283	1.4	0.02-9.6
HPV 6	420	15.5	5.5-36.7
HPV 11	283	1.7	0.03-8.2

β-HPV based on subgroups

Figure 5A shows the ER of β1-HPV, HPV 5, HPV 8, HPV 12, HPV 20, HPV 24, HPV 36 and HPV 93 in the BCC patients and Fig. 5B shows the ER of β2-HPV, HPV 9, HPV 15, HPV 17, HPV 23, HPV 38, HPV 75 and HPV 107 in the BCC patients. Also, Fig. 6 shows the ER of HPV 49, HPV 76, HPV 92, HPV 96 and HPV (unlisted) in the BCC patients. Three [21, 23, 45], four [21, 23, 45, 49], three [21, 23, 45], two [21, 23], and six studies [8, 9, 13, 29, 42, 46] reported the prevalence of HPV 49 (β3), HPV 76 (β3), HPV 92 (β4), HPV 96 (β5), and HPV (unlisted type) in the BCC patients. Four [5, 21, 22, 48], five [23, 28, 45, 49, 50], seven [2, 21, 23, 28, 45, 47, 50], two [2, 21], six [2, 21, 23, 28, 45, 50], five [21, 23, 28, 45, 50], four [21, 23, 45, 50] and three studies [21, 23, 45] reported the prevalence of β1-HPV, HPV 5 (β1), HPV 8 (β1), HPV 12 (β1), HPV 20 (β1), HPV 24 (β1), HPV 36 (β1), and HPV 93 (β1) in the BCC patients, respectively. In addition to, two [21, 48], four [21, 23, 45, 50], six [21, 23, 28, 45, 49, 50], three [21, 23, 45], three [21, 23, 45], eight [12, 21, 23, 28, 47, 45, 49, 50], three [21, 23, 45], two studies [2, 23] reported the prevalence of β2-HPV, HPV 9 (β2), HPV 15 (β2), HPV 17 (β2), HPV 23 (β2), HPV 38 (β2), HPV 75 (β2), and HPV 107 (β2) in the BCC patients, respectively. Table III shows the pooled ER of the articles for the incidence of β-HPVs in the BCC patients.

Table III. The pooled ER of the articles for the incidence of β-HPVs in BCC patients

HPV	Number of BCC patients	ER	95%CI
β1-HPV	848	33.3	19.9-50
HPV 5	816	13.6	7.2-24.1
HPV 8	836	12.5	7.1-29
HPV 12	111	1.6	0.02-10
HPV 20	767	12.5	6.8-21.8
HPV 24	754	13.4	7.2-23.5
HPV 36	322	15	7.3-28.3
HPV 93	162	23.8	10.8-44.8
β2-HPV	689	44.2	20.7-70.5
HPV 9	322	20.3	9.7-37.8
HPV 15	914	13.1	7-23
HPV 17	162	18.9	7.7-39.3
HPV 23	162	21.9	8.9-44.5
HPV 38	1008	14.9	8.8-24.1
HPV 75	162	15.1	5.4-35.5
HPV 107	107	7.2	1.3-31.9
HPV 49	162	17.9	9-32.7
HPV 76	322	23.4	15.4-33.8
HPV 92	162	3.5	0.04-23.5
HPV 96	113	6.9	1-35.7
HPV (unlisted type)	181	26.4	9.8-54.4

Discussion

The BCC is an immunogenic neoplasm [51] that its pathogenesis strongly associates with environmental and genetic factors [52]. We have conducted a comprehensive systematic review of studies addressing OR and ER of HPVs in the BCC of the skin in the world. There were 45 studies in this systematic review and meta-analysis that seven studies checked HPVs on serum [16, 17, 22, 38, 45, 48, 24] and 38 studies on the BCC-involved tissue. Our findings showed a significant risk of γ-HPV in the BCC patients compared with the healthy controls. Among α-HPVs reported (3, 6, 11, 16, 18, 31 and 33) in the BCC patients of skin, the highest of ER was HPV 6 (15.5%) and lowest was HPV 33 (1.4%). With regard to ER of β1-HPV in the BCC patients (33.3%) and among subgroups of β1-HPV reported (5, 8, 12, 20, 24, 36 and 93), HPV 93 (23.8%) and HPV 12 (1.6%) had the highest and lowest of ER of β1-HPV, respectively. With regard to ER of β2-HPV in the BCC patients (44.2%) and among subgroups of β2-HPV reported (9, 15, 17, 23, 38, 75 and 107), HPV 23 (21.9%) and HPV 107 (7.2%) had the highest and lowest of ER of β2-HPV, respectively.

Correa *et al.* [1] demonstrated that β-HPVs were the most frequently found in BCCs compared with α- and γ-HPVs. Andersson *et al*. [48] reported that out of β2-HPVs, HPV9 was significantly associated with BCC. Antibodies against any HPV 5, 8, 9, 15, 20, 24, 36 and 38 showed that 48.8% BCC patients

were positive while this was 53.2% among controls [50]. Escutia *et al*. [11] concluded β-types were frequently detected in skin samples from immunocompetent patients with BCC that there were differences in the prevalence of HPV in skin biopsies of BCC tumors and normal skin. Also, one study on HPV types (mostly β-HPV) [8] presented important differences in HPV prevalence between immunocompromised and immunocompetent patients. The higher prevalence of HPV types (mostly β-HPV) found in healthy perilesional skin proposed that HPV DNA was widely distributed in the general population and was found no correlation between the presence of HPV and skin cancer. Another study on β-HPVs [16] suggested that the combined serology and tumor DNA results showed that β-HPVs may have a role in BCC. Two studies [9, 45] did not find a significant relationship between BCC and HPV and also Nahidi *et al.*

A

Study name	HPV type	Statistics for each study		
		Event rate	Lowert limit	Upper limit
Patel *et al.* 2008	12	0.010	0.001	0.069
Drvar *et al.* 2014	12	0.036	0.002	0.384
Total for subgroup		0.016	0.002	0.100
Patel *et al.* 2008	20	0.071	0.034	0.142
Rollinson *et al.* 2008	20	0.133	0.034	0.405
Paradisi *et al.* 2011	20	0.388	0.263	0.529
Anderson *et al.* 2008	20	0.131	0.087	0.193
Drvar *et al.* 2014	20	0.036	0.002	0.384
Feltkamp *et al.* 2003	20	0.067	0.047	0.095
Total for subgroup		0.125	0.068	0.218
Patel *et al.* 2008	24	0.092	0.048	0.167
Rollinson *et al.* 2008	24	0.133	0.034	0.405
Paradisi *et al.* 2011	24	0.327	0.211	0.468
Anderson *et al.* 2008	24	0.088	0.053	0.142
Feltkamp *et al.* 2003	24	0.111	0.085	0.144
Total for subgroup		0.134	0.072	0.235
Patel *et al.* 2008	36	0.184	0.119	0.273
Rollinson *et al.* 2008	36	0.067	0.009	0.352
Paradisi *et al.* 2011	36	0.367	0.245	0.509
Anderson *et al.* 2008	36	0.050	0.025	0.097
Total for subgroup		0.150	0.073	0.283
Rollinson et al. 2008	5	0.133	0.034	0.405
Faust *et al.* 2013	5	0.306	0.240	0.382
Paradisi *et al.*. 2011	5	0.327	0.211	0.468
Anderson *et al.* 2008	5	0.125	0.082	0.186
Feltkamp *et al.* 2003	5	0.007	0.002	0.021
Total for subgroup		0.136	0.072	0.241
Patel *et al.* 2008	8	0.041	0.015	0.104
Rollinson *et al.* 2008	8	0.267	0.104	0.533
Paradisi *et al.* 2011	8	0.245	0.145	0.383
Anderson *et al.* 2008	8	0.225	0.167	0.296
Drvar *et al.* 2014	8	0.036	0.002	0.384
Wielund *et al.* 2000	8	0.188	0.113	0.298
Feltkamp *et al.* 2003	8	0.032	0.019	0.054
Total for subgroup		0.125	0.071	0.209
Patel *et al.* 2008	93	0.184	0.119	0.273
Rollinson *et al.* 2008	93	0.067	0.009	0.352
Paradisi *et al.* 2011	93	0.429	0.299	0.569
Total for subgroup		0.238	0.108	0.448
Patel *et al.* 2008	β1	0.408	0.316	0.508
Zakrzewska *et al.* 2012	β1	0.480	0.384	0.577
Anderson *et al.* 2008	β1	0.291	0.272	0.312
Karags *et al.* 2010	β1	0.200	0.176	0.228
Total for subgroup		0.333	0.199	0.500
Overall		0.149	0.096	0.224

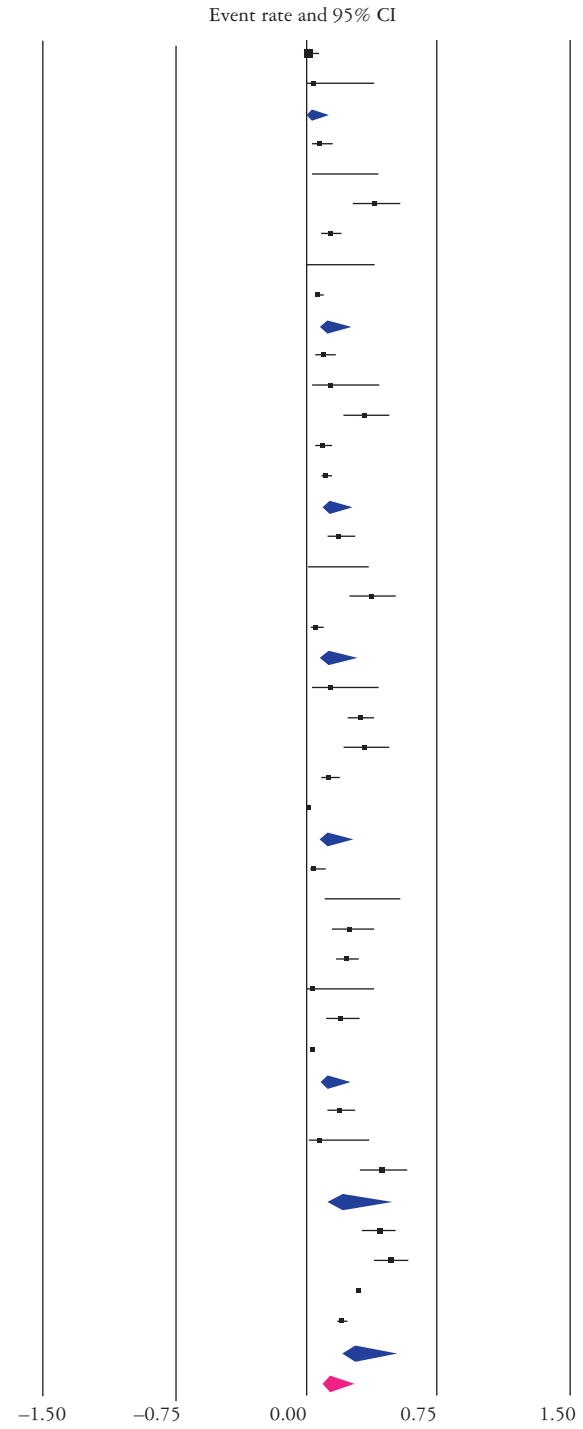


Fig. 5. The forest plot of event rate of (A) β1-HPV and (B) β2-HPV in BCC patients

B

Study name	HPV type	Statistics for each study		
		Event rate	Lowert limit	Upper limit
Rollinson *et al.* 2008	107	0.067	0.009	0.352
Drvar *et al.* 2014	107	0.036	0.011	0.391
Total for subgroup		0.072	0.013	0.319
Patel *et al.* 2008	15	0.143	0.086	0.227
Rollinson *et al.* 2008	15	0.133	0.034	0.405
Paradisi *et al.* 2011	15	0.388	0.263	0.529
Anderson *et al.* 2008	15	0.100	0.062	0.157
Faust *et al.* 2013	15	0.181	0.129	0.249
Feltkamp *et al.* 2003	15	0.028	0.016	0.048
Total for subgroup		0.131	0.070	0.230
Patel *et al.* 2008	17	0.163	0.102	0.250
Rollinson *et al.* 2008	17	0.133	0.034	0.405
Paradisi *et al.* 2011	17	0.265	0.161	0.405
Total for subgroup		0.189	0.077	0.393
Patel *et al.* 2008	23	0.184	0.119	0.273
Rollinson *et al.* 2008	23	0.194	0.127	0.284
Paradisi *et al.* 2011	23	0.067	0.009	0.352
Total for subgroup		0.219	0.089	0.445
Patel *et al.* 2008	38	0.102	0.056	0.179
Rollinson *et al.* 2008	38	0.200	0.066	0.470
Paradisi *et al.* 2011	38	0.245	0.211	0.468
Anderson *et al.* 2008	38	0.156	0.082	0.186
Faust *et al.* 2013	38	0.263	0.200	0.336
Feltkamp *et al.* 2003	38	0.023	0.012	0.042
Forslund *et al.* 2003	38	0.160	0.061	0.357
Wieland *et al.* 2000	38	0.246	0.159	0.361
Total for subgroup		0.149	0.088	0.241
Patel *et al.* 2008	75	0.010	0.001	0.069
Rollinson *et al.* 2008	75	0.200	0.066	0.470
Paradisi *et al.* 2011	75	0.327	0.211	0.468
Total for subgroup		0.151	0.054	0.355
Patel *et al.* 2008	9	0.184	0.119	0.273
Rollinson *et al.* 2008	9	0.133	0.034	0.405
Paradisi *et al.* 2011	9	0.265	0.161	0.405
Andersson *et al.* 2008	9	0.217	0.130	0.338
Total for subgroup		0.203	0.097	0.378
Patel *et al.* 2008	β2	0.571	0.472	0.665
Anderson *et al.* 2008	β2	0.326	0.306	0.347
Total for subgroup		0.442	0.207	0.705
Overall		0.181	0.120	0.264

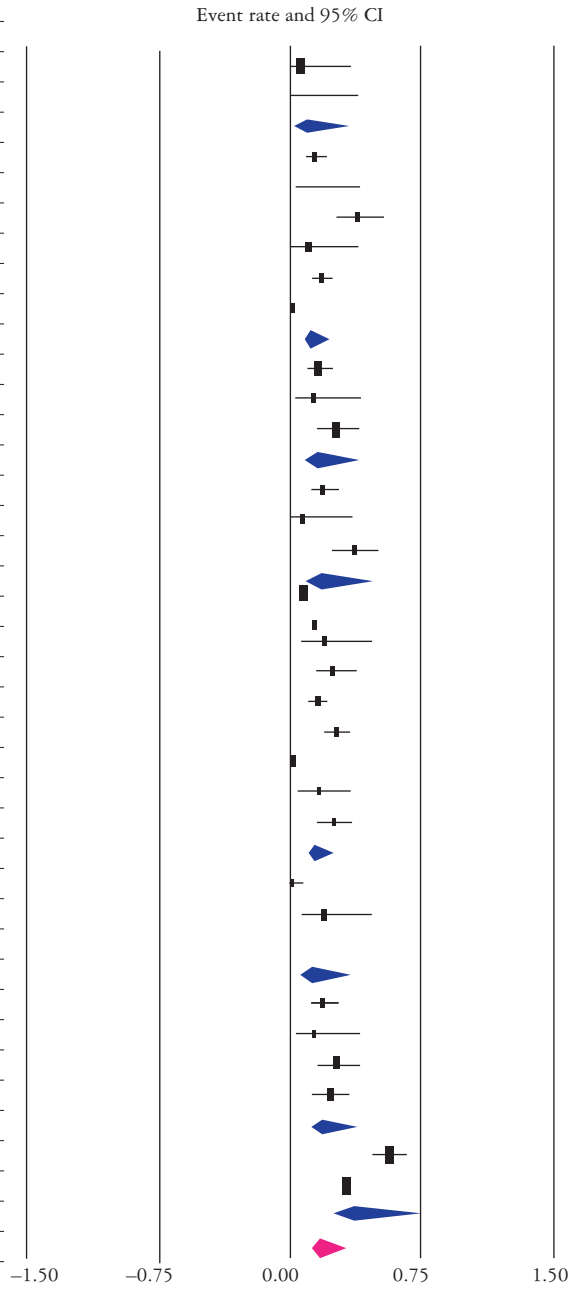


Fig. 5. *Cont.*

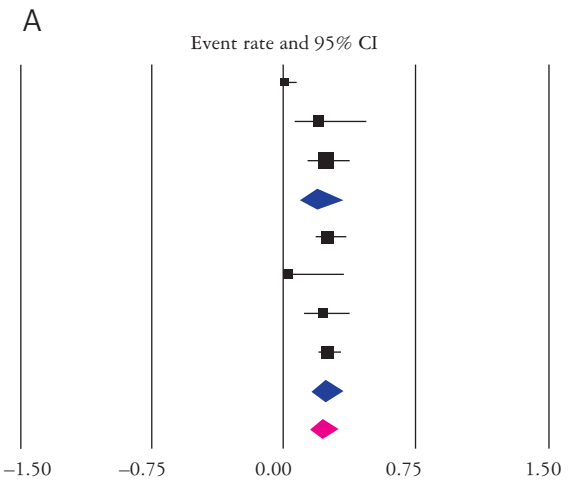
[32] that concluded that HPV was not likely to have a major role in the pathogenesis of BCC.

In one study [14], α-HPV in BCC was positive in 35% of the cases that the high-risk HPV genotypes observed in these patients were HPV 16, 35, 58 and 59. The findings of a research [5] demonstrated that β1-HPVs were the most common HPV types detected in the skin of BCC patients. Moreover, these types and mixed infections are significantly more frequent in tumor samples than in healthy perilesional skin and the results suggested that the types as well as co-infection with more than one viral type could be important in BCC.

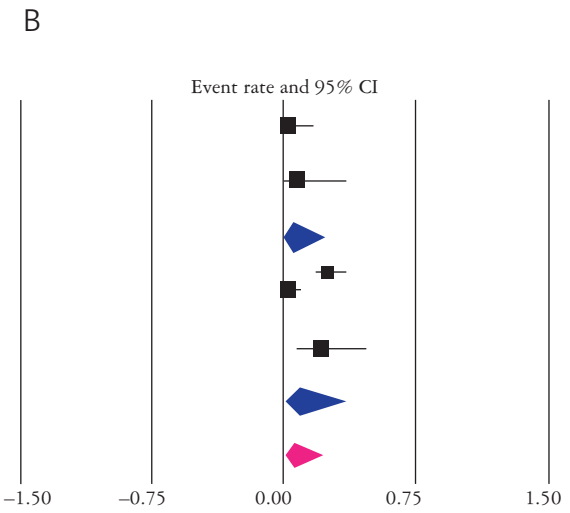
The findings suggested that EV-HPV types could be present in a higher percentage of skin cancers [25] and that EV-HPV-directed seroresponses were induced upon skin cancer formation, rather than upon infection [28].

Also, the findings of another study suggested that high-risk mucosal HPV types recently identified as significant risk factors for non-melanoma skin cancer [34] and also represents a risk factor for non-melanoma skin cancer in a non-immunosuppressed population [36]. Other results suggested that HPVs, particularly the oncogenic potential of certain types such as HPV 8, 18, and 5 could induce non-melanoma skin cancers [38].

Study name	HPV type	Statistics for each study		
		Event rate	Lowert limit	Upper limit
Patel *et al.* 2008	49	0.005	0.000	0.076
Rollinson *et al.* 2008	49	0.200	0.066	0.470
Paradisi *et al.* 2011	49	0.245	0.145	0.383
Total for subgroup		0.179	0.090	0.327
Patel *et al.* 2008	76	0.255	0.179	0.350
Rollinson *et al.* 2008	76	0.031	0.002	0.350
Paradisi *et al.* 2011	76	0.224	0.129	0.362
Faust *et al.* 2013	76	0.256	0.195	0.329
Total for subgroup		0.234	0.154	0.338
Overall		0.217	0.152	0.299



Study name	Subgroup within study	Statistics for each study		
		Event rate	Lowert limit	Upper limit
Patel *et al.* 2008	92	0.020	0.005	0.078
Rollinson *et al.* 2008	92	0.067	0.009	0.352
Total for subgroup		0.035	0.004	0.235
Patel *et al.* 2008	96	0.020	0.005	0.078
Rollinson *et al.* 2008	96	0.200	0.066	0.470
Total for subgroup		0.069	0.010	0.357
Overall		0.050	0.012	0.187



Study name	Statistics for each study		
	Event rate	Lowert limit	Upper limit
Berberta *et al.* 2004	0.609	0.402	0.782
Berant-Garcia *et al.* 2014	0.577	0.385	0.748
Posteraro *et al.*1996	0.019	0.001	0.244
Shamanin *et al.* 1996	0.438	0.225	0.676
Trenfield *et al.* 2008	0.091	0.013	0.439
Mokhtari *et al.* 2009	0.100	0.051	0.187
Total	0.264	0.098	0.544

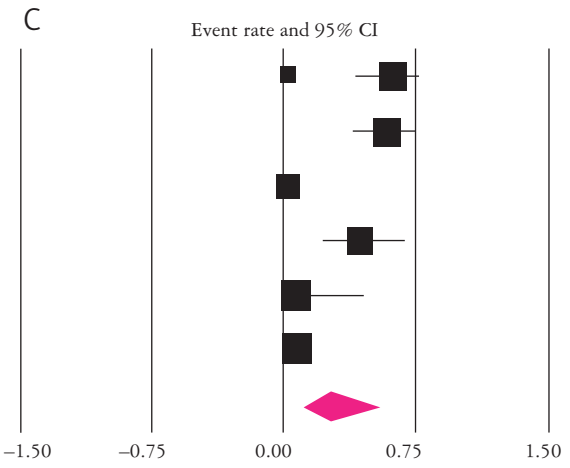


Fig. 6. The forest plot of event rate of (A) β3-HPV, (B) β4- and β5-HPVs and (C) HPV (unlisted) in BCC patients

Conclusions

Limitations such as the variation of HPVs, reporting HPVs in serum instead of tissue in some studies, and few studies reported; were caused that the relationship between HPV types and BCC have been not well done in the meta-analysis. Although there were a few case-control studies about the risk of HPVs in the BCC group compared with the healthy control, but this meta-analysis showed that probably the risk of γ-HPV was more in BCC patients. Also, the rate of γ-HPV was higher than α-, β- and EV-HPVs in the BCC patients.

The authors declare no conflict of interest.

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Address for correspondence

Masoud Sadeghi
Medical Biology Research Center
Kermanshah University of Medical Sciences
Kermanshah, Iran
e-mail: sadeghi_mbrc@yahoo.com