Transmission of carcinogenic human papillomavirus types from mother to child: a meta-analysis of published studies

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Currently, human papillomavirus (HPV) research focuses on HPV infection in adults and sexual transmission. Data on HPV infection in children are slowly becoming available. It is a matter of debate whether mother-to-child transmission of HPV is an important infection route and whether children born to HPV-positive mothers are at a higher risk of HPV infection compared with children born to HPV-negative mothers. The objective of this meta-analysis is to summarize the published literature on the extent to which genital HPV infection is vertically transmitted from mother to child. Medline, Web of Science, and CINAHL were searched for eligible reports published before January 2011. Differences in the risk of HPV infection between newborns from HPV-positive and HPV-negative mothers were pooled using a random-effects model. Twenty eligible studies, including 3128 women/children pairs, fulfilled the selection criteria. High heterogeneity could be found (I^2 = 96%). The overall estimated risk difference was 33% (95% confidence interval: 22–44%). On restricting to high-risk HPV-positive mothers only (n = 4; women = 231), the difference in risk was 45% (95% confidence interval: 33–56%). The heterogeneity was found to be low (I^2 = 15%). This meta-analysis indicates a significantly higher risk for children born to HPV-positive mothers to become HPV positive themselves. Plausible explanations include vertical transmission of HPV during pregnancy and/or birth or a higher infection rate during early nursing from mother to child. More research is required to gain an insight into the precise mode of transmission and the clinical effects of infection on the child. *European Journal of Cancer Prevention* **22:277–285 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Infection with the human papillomavirus (HPV) is well recognized as a necessary but insufficient cause of cervical cancer (IARC, 2007). Besides this, HPV also plays an important role in the etiology of other conditions. This includes head and neck tumors, skin diseases (warts, condyloma), genital benign and malignant tumors, and potentially even other conditions (Munoz *et al.*, 2006). Within the family of HPV viruses, two subclassifications can be distinguished on the basis of their oncogenic potential, that is, high-risk HPV (HR-HPV) and low-risk HPV types (LR-HPV). Different categorization protocols are used to distinguish HR-HPV and LR-HPV. Here, the categorization according to Schiffman *et al.* (2009) will be used, considering HVP16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV66, and HPV68 as oncogenic HPV types.

HPV is the most common, sexually transmitted virus in adults. Most young women become infected with HPV; their lifetime incidence is estimated to be as high as 80% (Einstein *et al.*, 2009). Most infections are asymptomatic and have the tendency to clear spontaneously (Sinal and Woods, 2005). Yearly, around 5 30 000 women are affected by cervical cancer, and the total burden of HPV-related cancers worldwide in women adds up to 6% of all cancer cases (Arbyn *et al.*, 2011).

HPV research has mainly been focused on disease prevention in adolescents and adults. However, HPV infection also affects children. Data on this topic are slowly becoming available. The presence of HPV in a wide range of pathologies indicates that HPV infection in minors is not essentially asymptomatic (Syrjänen 2010). Genital warts, oral papillomas, and recurrent respiratory papillomatosis are associated with mucosal HPV infections, whereas skin warts and lichen sclerosis are caused by cutaneous HPV types in children (Gutierrez-Pascual *et al.*, 2012). Most cutaneous HPV types (1, 2, 3, 4, 27, 57) can persist over a long time without causing any symptomatic disease. However, once skin warts are present, this might reflect decreased immunity and this implies a certain caution toward genital HPV lesions. The occurrence of common warts at the age of 11–16 years is significantly associated with a higher risk for development of cervical cancer (Montgomery *et al.*, 2002). Most recognized benign

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HPV lesions in minors are skin warts and laryngeal papillomas. Recurrent respiratory papillomatosis is a rare but serious HPV-related disease and can even be life-threatening because of total respiratory obstruction.

It was generally assumed that genital HPV infection and related diseases in children developed because of sexual abuse (Stevens-Simon *et al.*, 2000). This paradigm has changed over the past decade as children with no history of sexual abuse also develop HPV-related diseases. The route of transmission of genital HPV infection in infants still remains unclear, but autoinoculation, vertical, and horizontal transmission have been suggested (Syrjänen, 2010). Vertical transmission can be divided into three categories according to the time of HPV infection: periconceptual, prenatal, and perinatal transmission. HPV DNA has been detected in semen (Ostrow *et al.*, 1986; Green *et al.*, 1991; Olatunbosun *et al.*, 2001; Rintala *et al.*, 2004), endometrium, and ovaries (Lai *et al.*, 1992; O'Leary *et al.*, 1998; Fedrizzi *et al.*, 2009), indicating the possibility of periconceptual transmission. However, the significance of these findings is uncertain. Intrauterine or prenatal transmission is considered another possible route of infection because of the reported presence of HPV DNA in the amniotic fluid (Tseng *et al.*, 1992; Armbruster-Moraes *et al.*, 1994; Wang *et al.*, 1998), placenta (Gomez *et al.*, 2008; Rombaldi *et al.*, 2008; Sarkola *et al.*, 2008), and cord blood samples (Gutman *et al.*, 1992; Xu *et al.*, 1998; Worda *et al.*, 2005; Gajewska *et al.*, 2006; Srinivas *et al.*, 2006; Rombaldi *et al.*, 2008; Sarkola *et al.*, 2008). Perinatal transmission occurs after close contact of the fetus with the infected cervical and vaginal tractus of the mother during delivery (Syrjänen, 2010). It is a matter of debate whether mother-to-child transmission (MTCT) of HPV has to be considered an important infection route.

The same variability in the prevalence of genital HPV infection can be observed in pregnant women, ranging from 5 to 69% (Arena *et al.*, 2002). Several studies have reported an increased prevalence of genital HPV infections during pregnancy. This may be related to hormonal changes facilitating HPV replication and/or transient immunosuppression (Schneider *et al.*, 1987; Rando *et al.*, 1989; Pakarian *et al.*, 1994; Cason, 1996; Castellsague *et al.*, 2009; Rombaldi *et al.*, 2009). An important consequence is the decrease in trophoblast cells and the trophoblast–endometrial cell adhesion (Boulenouar *et al.*, 2010; Syrjänen, 2010).

This study aims to examine the possibility of MTCT of HPV by testing the association between the HPV status of mothers and their children. To achieve this goal, a meta-analysis of available literature was carried out.

Methods

Literature search

Relevant studies on MTCT and vertical transmission of HPV infection were identified through an extensive search of Medline, CINAHL, and ISI Web of Science. This search was based on the following keywords: 'mother to child transmission', 'MTCT', 'vertical transmission', 'newborn infection', 'maternal–fetal transmission' and 'perinatal infection/transmission' in combination with 'human papillomavirus,' and 'HPV'. Figure 1 summarizes the study selection process. Three authors (M.M., L.W.V.W., and D.V.B.) independently reviewed and critically evaluated all studies. The literature search was carried out until December 2010, without the limitation of publication starting date.

Selection criteria and extraction of data

The studies were limited to those written in English. The diagnostic methods for detecting HPV were limited to PCR, Southern blot DNA, and in-situ hybridization. All samples for HPV testing had to be collected from the cervix, vagina, placenta, or cervicovaginal lavages for the mother. Samples from the child could be taken from nasopharyngeal aspirate, cord blood, genital, or oral swabs. All eligible studies had to report the prevalence of HPV in the mother and the newborn, allowing extraction or computation of the absolute number of infected patients in both groups. The meta-analysis was restricted to the original reports. All study designs could be included except case–control studies. All eligible studies tested the child for HPV within the first week after birth and the mother during the pregnancy or immediately before birth. Detailed information on all included studies is presented in Table 1. This meta-analysis was carried out in agreement with the PRISMA guidelines (Moher *et al.*, 2009).

Statistical analysis

Two meta-analyses were carried out. The first included all studies that investigated the risk of MTCT of HPV overall, whereas the second focused on HR-HPV types.

The R Project for Statistical Computing was used for all data processing (R Development Core Team, 2010). The meta-analyses were carried out using the metafor package (Viechtbauer, 2010). Risk differences (RD) and their respective standard errors were calculated from the raw data provided. The overall absolute RD was estimated using a random-effects model by a restricted maximum likelihood approach (DerSimonian and Laird, 1986). Possible publication bias was evaluated by the asymmetry of the funnel plot (Egger *et al.*, 1997) using Begg's rank correlation (Begg and Mazumdar, 1994).

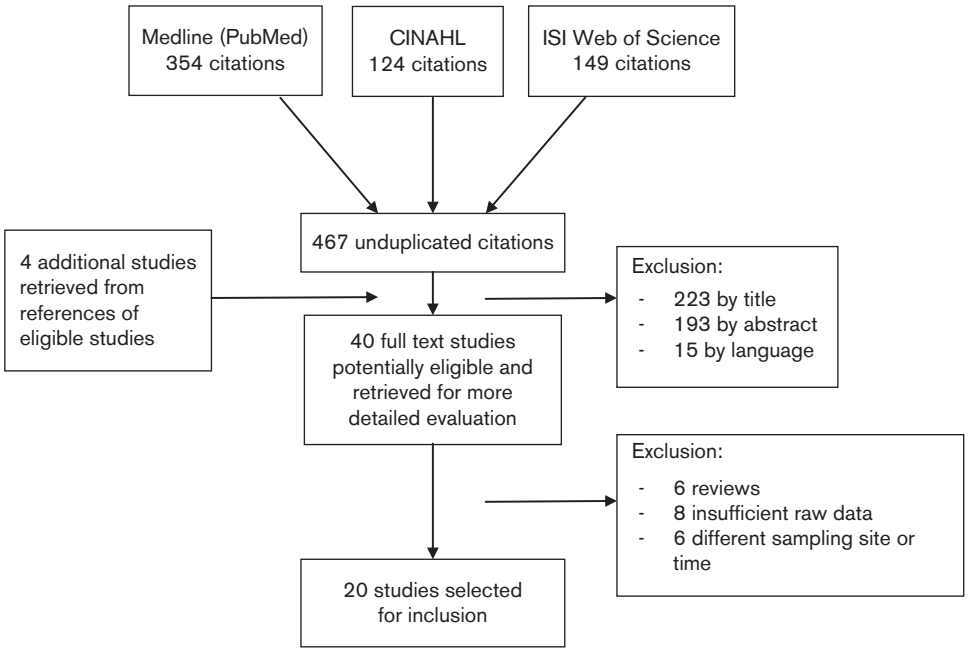
Interstudy heterogeneity was quantified by the I^2 index (Higgins and Thompson, 2002). The influence of individual studies on the overall effect was evaluated by estimating the combined RD after excluding one study at a time.

Results

Study identification and description

The initial search yielded 467 unduplicated studies. After reviewing these studies for language, titles, and abstracts,

Fig. 1



Flow-chart of article selection for inclusion in meta-analysis of mother-to-child transmission of human papillomavirus.

40 studies were considered of interest and were subjected to a detailed evaluation. Twenty eligible studies were identified, including a total of 3128 women/child pairs. Table 1 shows the characteristics of the studies included such as geographical location, study design, time of HPV testing in the mother, and the HPV assay.

Twenty studies reported HPV rates (Smith *et al.*, 1991, 1995, 2004, 2010; Pakarian *et al.*, 1994; Cason *et al.*, 1995; Mazzatenta *et al.*, 1996; Puranen *et al.*, 1997; Chatterjee *et al.*, 1998; Tseng *et al.*, 1998; Watts *et al.*, 1998; Xu *et al.*, 1998; Tenti *et al.*, 1999; Bandyopadhyay *et al.*, 2003; Gajewska *et al.*, 2005, 2006; Rombaldi *et al.*, 2008, 2009; Sarkola *et al.*, 2008; Castellsague *et al.*, 2009) in the mother and child and eight of them provided data on HR-HPV (Pakarian *et al.*, 1994; Cason *et al.*, 1995; Tseng *et al.*, 1998; Gajewska *et al.*, 2006). Six studies were carried out in resource-restricted countries (Chatterjee *et al.*, 1998; Tseng *et al.*, 1998; Xu *et al.*, 1998; Bandyopadhyay *et al.*, 2003; Rombaldi *et al.*, 2008, 2009) and 14 in developed countries (Smith *et al.*, 1991, 1995, 2004, 2010; Pakarian *et al.*, 1994; Cason *et al.*, 1995; Mazzatenta *et al.*, 1996; Puranen *et al.*, 1997; Watts *et al.*, 1998; Tenti *et al.*, 1999; Gajewska *et al.*, 2005, 2006; Sarkola *et al.*, 2008; Castellsague *et al.*, 2009).

One study included women with diabetes mellitus (Gajewska *et al.*, 2005) and another study included renal transplant patients (Gajewska *et al.*, 2006). These studies were equally incorporated into this meta-analysis, as no significant influence on the HPV prevalence of diabetes or immunosuppression was reported between the control and the affected cohort.

Initially, eight studies were selected for the meta-analysis focusing on HR-HPV. Three of these (Gajewska *et al.*, 2005; Rombaldi *et al.*, 2008, 2009) were excluded because of the lack of HPV-negative mothers. On the basis of the statistical findings, one other study (Puranen *et al.*, 1997) was excluded. Eventually, four studies (Pakarian *et al.*, 1994; Cason *et al.*, 1995; Tseng *et al.*, 1998; Gajewska *et al.*, 2006) were retained for meta-analytical pooling. The analysis included 231 mother/child pairs. Two studies were longitudinal and two were cross sectional. One study was carried out in Asia (Tseng *et al.*, 1998), and the other three in Europe. All studies used PCR as a diagnostic method and tested the mother in the third trimester of pregnancy.

Association between human papillomavirus status of mother and child

Women and children were considered HPV positive if they carried at least one HPV type. Only mucosal HPV infection was evaluated. The prevalence of HPV in the pregnant women included was 24.4%. The overall HPV prevalence of the included children was 7.6%.

Considering the concordance of the different HPV types, 196 of the 247 mother/child pairs (79.35%) reported at least one similar HPV type. Not all studies provided specific HPV-type data.

Table 1 Characteristics of the selected studies included in the meta-analysis mother-to-child transmission of human papillomavirus

References	Country	Study design	Number of cases enrolled	Number of cases used	Age range (years)	HPV prevalence mother (%)	HPV-positive mother	HPV-negative mother	HPV prevalence child (%)	HPV-positive child	HPV-negative child	HPV diagnosis	Diagnosis mother	MTCT HPV (mother/child pairs)	Concordance HPV types	Mode of delivery	Population
Puranen *et al.* (1997)	Finland	LS	105	105	18–40	40.95	43	62	38.1	40	65	PCR	Delivery	34	29	Not specified	Mixed population: treatment and no treatment for genital condilomas
Mazzatenta *et al.* (1996)	Italy	LS	104	47	–	12.76	6	41	8.51	4	43	PCR	Trimester 3	2	2	Vaginal delivery	Women in third trimester of pregnancy
Castellsague *et al.* (2009)	Spain	LS	143	117	–	45.3	53	64	5.98	7	110	PCR	Trimester 3	11	1	13% caesarian	Women at risk for HPV infection
Rombaldi *et al.* (2008)	Brazil	CS	71	49	14–41	24.49	12	37	20.41	10	39	PCR	Delivery	7	6	Not specified	Prior history of HPV infection or cervical abnormalities
Smith *et al.* (2004)	USA	LS	574	571	18–45	28.72	164	407	1.58	9	562	PCR	Trimester 3	6	1	13% caesarian	Routine obstetric care attendees
Smith *et al.* (2010)	USA	LS	582	333	18–45	29.73	99	234	1.5	5	328	PCR	Delivery	3	3	Not specified	Routine obstetric care attendees
Rombaldi *et al.* (2009)	Brazil	CS	63	63	14–41	77.78	49	14	15.87	10	53	PCR	First prenatal visit	12	9	Not specified	Women with prior history of HPV infection or cervical abnormalities
Watts *et al.* (1998)	USA	LS	235	145	–	37.24	54	91	0	0	145	PCR	Trimester 3	0	–	17% caesarian	Routine obstetric care attendees
Bandyopadhyay *et al.* (2003)	India	CS	149	135	20–39	28.15	38	97	10.37	14	121	PCR	Trimester 3	7	5	56% caesarian	Routine obstetric care attendees without any previous history
Sarkola *et al.* (2008)	Finland	LS	306	306	18–46	4.58	14	292	4.58	14	292	PCR	Delivery	10	9	Not specified	Routine obstetric care attendees
Tenti *et al.* (1999)	Italy	CS	711	711	16–43	5.2	37	674	1.55	11	700	PCR	Trimester 3	11	11	5% caesarian	Routine obstetric care attendees without any previous history
Tseng *et al.* (1998)	China	CS	301	98	17–45	69.39	68	30	27.55	27	71	PCR	Trimester 3	27	27	47% caesarian	Routine obstetric care attendees
Gajewska *et al.* (2005)	Poland	CS	45	45	18–38	26.67	12	33	17.78	8	37	PCR	Trimester 3	8	8	13% caesarian	Routine obstetric care attendees
Smith *et al.* (1995)	USA	LS	203	138	17–41	4.35	6	132	1.45	2	136	SBH	Delivery	1	1	Not specified	Routine obstetric care attendees
Xu *et al.* 1998	China	LS	30	30	22–36	53.33	16	14	46.67	14	16	PCR	Trimester 3	9	–	83% caesarian	Routine obstetric care attendees without any previous history
Pakarian *et al.* (1994)	UK	LS	32	32	17–37	65.63	21	11	37.5	12	20	PCR	Trimester 3	11	10	Not specified	Enriched population with prior history of HPV
Cason *et al.* (1995)	UK	LS	62	62	19–38	74.19	46	16	61.29	38	24	PCR	Trimester 3	34	–	Not specified	Enriched population with prior history of HPV
Smith *et al.* (1991)	USA	LS	71	71	17–41	4.23	3	68	2.82	2	69	SBH	Delivery	2	2	21% caesarian	Routine obstetric care attendees
Chatterjee *et al.* (1998)	India	LS	31	31	20–34	38.71	12	19	16.13	5	26	ISH	Delivery	5	5	30% caesarian	Routine obstetric care attendees
Gajewska *et al.* (2006)	Poland	CS	39	39	27–40	25.64	10	29	17.95	7	32	PCR	Trimester 3	7	7	Not specified	Routine obstetric care attendees with a number of renal transplant patients
				3128		24.39	763	2365	7.64	239	2889						

CS, cross-sectional study; HPV, human papillomavirus; ISH, in-situ hybridization; LS, longitudinal study; MTCT, mother-to-child transmission; SBH, southern blot hybridization.

In eight studies, the RD was not significantly different from zero (Smith *et al.*, 1995, 2004, 2010; Mazzatenta *et al.*, 1996; Watts *et al.*, 1998; Xu *et al.*, 1998; Bandyopadhyay *et al.*, 2003; Castellsague *et al.*, 2009). All other studies showed a significantly higher risk for HPV infection in children from HPV-positive mothers. The RD in these studies ranged from 22% (Rombaldi *et al.*, 2009) to 70% (Sarkola *et al.*, 2008). No study reported a negative RD. Overall, children born to an HPV-positive mother have 33% [95% confidence interval (CI): 22–44%] more chance of becoming infected with HPV in comparison with HPV-negative mothers (Fig. 2). The three largest studies (Watts *et al.*, 1998; Smith *et al.*, 2004, 2010) did not report a RD significantly different from zero.

Analysis of the funnel plot did not show evidence of publication bias as no clear asymmetry could be detected (Fig. 3). Also, Begg's rank correlation test could not detect a significant asymmetry in the funnel plot ($\tau^2 = 0.053$, $P = 0.77$).

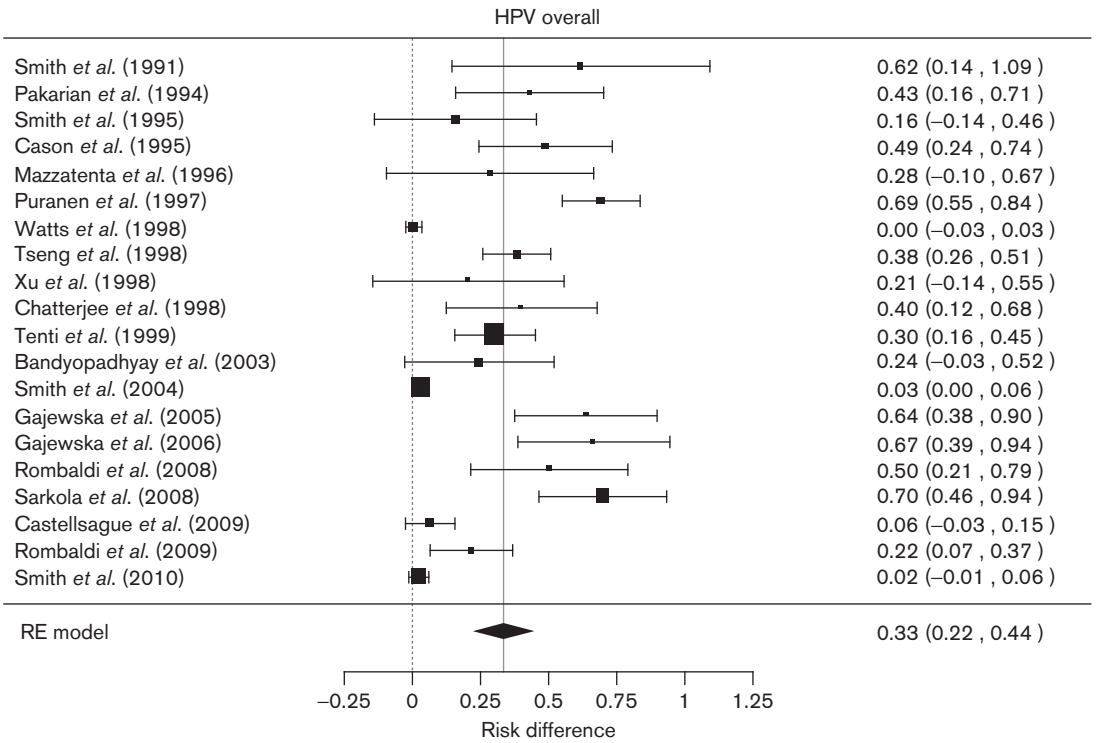
High interstudy heterogeneity could be found ($I^2 = 96\%$). Inclusion of study design, time of diagnosis for the mother, or a combination of both did not result in a significant improvement in the model. The influence of each individual study was tested by estimating the combined RD after excluding one study at a time. None of the studies was found to affect the result in a significant manner. All RD ranged from 30 to 35% in the evaluations.

Taking only HR-HPV infections into consideration, the RD was 35% (95% CI: 4–66%) if five studies (262 mother/child pairs) were included (Pakarian *et al.*, 1994; Cason *et al.*, 1995; Puranen *et al.*, 1997; Tseng *et al.*, 1998; Gajewska *et al.*, 2006). Begg's rank correlation test did not detect a significant bias asymmetry in the funnel plot ($\tau^2 = 0.0526$, $P = 0.77$). This was mainly attributed to one study (Puranen *et al.*, 1997), which caused substantial interstudy heterogeneity ($I^2 = 89\%$). The exclusion of this reduced the heterogeneity ($I^2 = 14.9$, $P = 0.48$). Hence, the occurrence of publication bias could not be assessed for HR-HPV because of the low number of studies included. In this final analysis, 232 mother/child pairs were included. The resulting RD was 45 (95% CI: 33–56%) (Fig. 4). Influence analysis indicated that none of the studies had a major impact on the estimated overall RD; the RD ranged from 0.40 to 0.52 after excluding one study at a time (Fig. 5).

Discussion

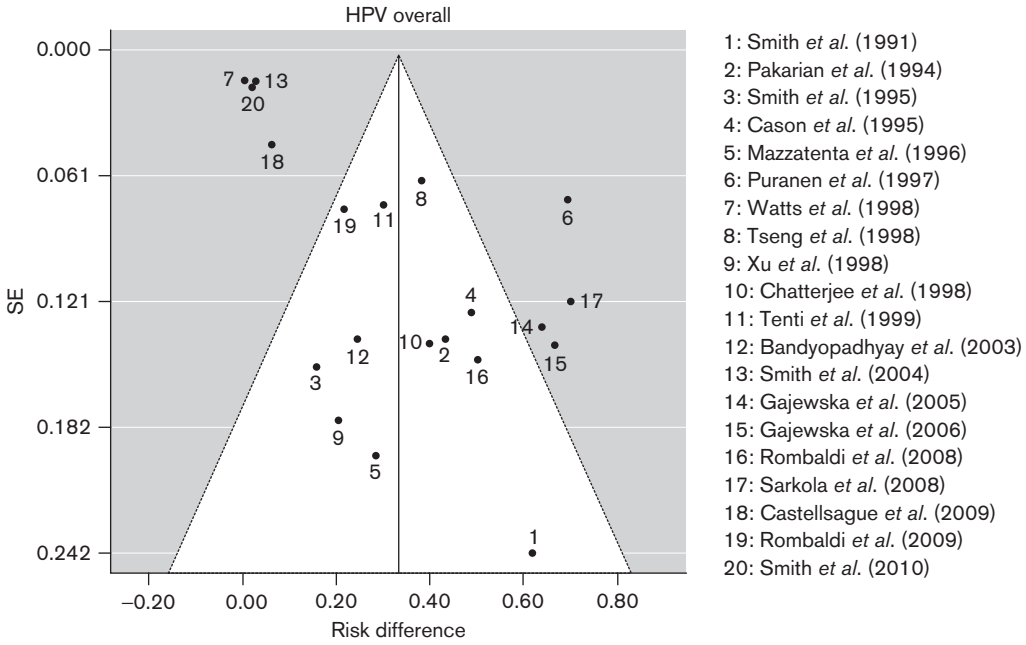
To our knowledge, this was the first meta-analysis addressing the risk of HPV infection in newborn babies according to the HPV status of their mother. We were

Fig. 2



Forest plot of human papillomavirus (HPV) overall estimated risk differences.

Fig. 3



Funnel plot [human papillomavirus (HPV) overall] to assess publication bias.

able to systematically review the existing literature and extract results indicating that children of HPV-positive mothers had 33% more chance of becoming infected than children of HPV-negative mothers. This difference in risk even increased up to 45% when only considering HR-HPV infection.

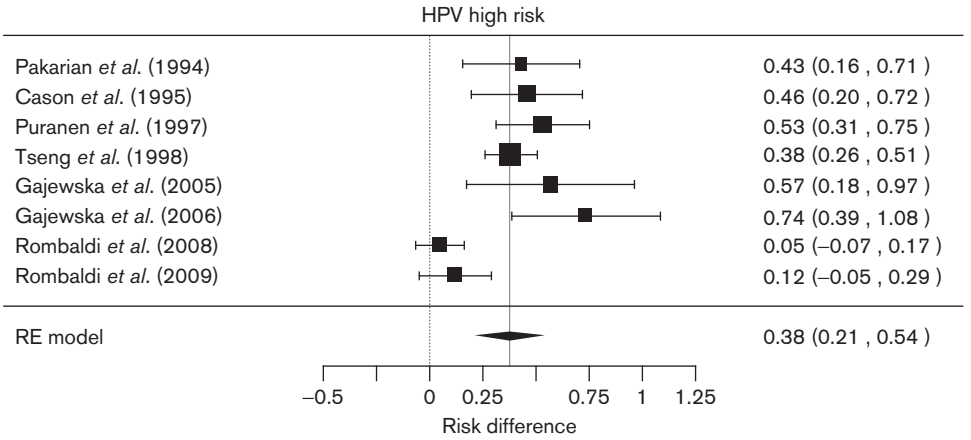
The prevalence of HPV in the women included in our study was 24%. Data on this prevalence are highly discordant in the existing literature as stated in the introduction. This diversity could be because of a variety of factors such as the diagnostic techniques, the characteristics of samples, and the inclusion criteria. The overall HPV prevalence of the children included was 8%. Most of these HPV infections are likely to clear as the child grows older (Kaye *et al.*, 1994; Pakarian *et al.*, 1994; Cason *et al.*, 1995), but more research is required in this field. Syrjänen (2010) reported persistent oral and genital mucosa infections in less than 10 and 2%, respectively.

Substantial interstudy heterogeneity was found when including all HPV types in this meta-analysis. Consequently, the pooled results should be interpreted with necessary caution. A number of variables may have contributed toward this heterogeneity. In all studies, a large variation in the sampling sites and the time of diagnosis of HPV could be observed. Also, technical differences (e.g. collection of specimen, subjectivity, sensitivity and specificity of the HPV assays used) may have been responsible for the observed variation in RDs. The same observations were made at the time of HPV testing for the mother and the interaction of both variables.

Sexually transmissible infections such as HIV, hepatitis B and C virus, herpesviruses, *Treponema pallidum*, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae* have been proven to be transmissible from mother to child during the prenatal and perinatal period (Younes *et al.*, 2009). Rice *et al.* (1999) even reported that they were not aware of any sexually transmitted viruses that are not vertically transmitted. The presence of HPV has been found in amniotic fluid (Tseng *et al.*, 1992; Armbruster-Moraes *et al.*, 1994; Wang *et al.*, 1998); thus, vertical transmission may be plausible. The most recent study in this field again confirms the HPV genotype-specific concordance between oral HPV in newborns and maternal amniotic fluid and cord blood. With these findings, Koskimaa *et al.* (2012) strengthen the possibility of vertical transmission of HPV from the mother to the child.

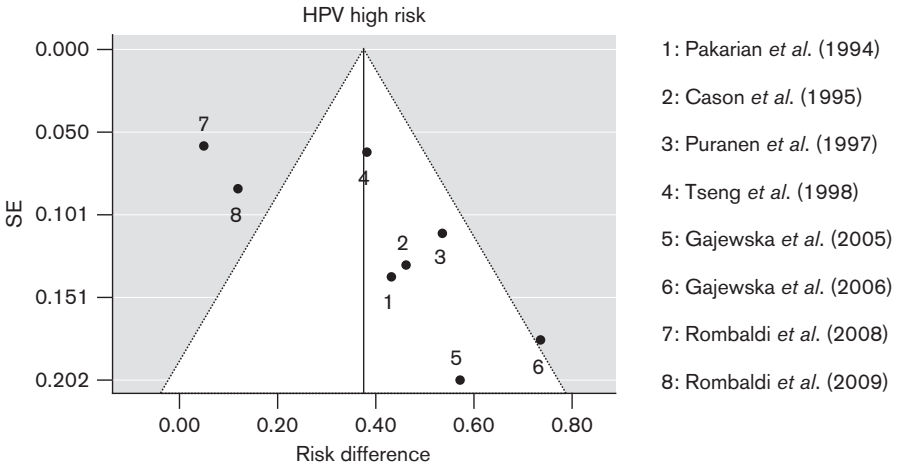
When vertical transmission of HPV occurs, the infection is acquired before the child's immune system is mature. This may cause HPV-specific immunological tolerance (Cason, 1996). However, immune responses have not been tested in the studies included. It is therefore not known whether the early infection will result in the generation of virus-specific antibodies and cell-mediated immunity or specific immune tolerance (Rice *et al.*, 1999). In later life, the persistence of HPV and/or the inability to clear subsequent HPV reinfections may result in the

Fig. 4



Forest plot of high-risk human papillomavirus (HPV) estimated risk differences.

Fig. 5



Funnel plot of high-risk human papillomavirus (HPV) to assess publication bias.

development of (pre)malignant cervical lesions or other lesions (Cason *et al.*, 1995). This may be accelerated by sexually transmitted cofactor(s) that activate quiescent HPV infections and increase the viral load (Rice *et al.*, 1999). Depending on these possibilities, the risk of genital cancers may be present at a much earlier age than believed previously. The prognosis of children infected during the prenatal and the perinatal period is unknown (Cason *et al.*, 1995). Serological evaluations can be carried out to clarify the prognosis and determine the implications of childhood infections in respect of several carcinoma and the optimal timing for prophylactic vaccines (Ullman and Emery, 1996; Rice *et al.*, 1999).

Horizontal transmission of HPV has also been considered as an important contributor toward infection in newborns, for example, during nursing or breast feeding. Highly contradictory results have been obtained in terms of breast milk. Breast milk has been described as a potential reservoir of viruses (e.g. HIV; Van de Perre *et al.*, 1991; Cason, 1996), but no unambiguous results can be retrieved from the existing literature on HPV. In general, breast feeding can be considered as a potential mode of horizontal transmission (Cazzaniga *et al.*, 2009); however, recent findings have shown a rather low likelihood for transmission through breast milk (Mammas *et al.*, 2011; Yoshida *et al.*, 2011).

Vertical and early horizontal transmission are not easy to differentiate. To establish a clear distinction between these two routes of transmission, accurate and repeated HPV detection and genotyping are necessary. The absence of an association in children born by cesarean section may be an argument supporting transmission by

passage contact with the infected lower genital tractus. Multiple samplings from the parents, siblings, and care givers must be considered in further research (Castellsague *et al.*, 2009).

Considering the positive HPV status of the child, the question remains as to whether this represents only a passive contamination with maternal cells or whether we can classify this positive status as a true HPV infection. The latter can be diagnosed by the detection of virus-induced epithelial changes or the presence of intracellular HPV DNA/RNA in epithelial cells of the child. Repeated detection of HPV DNA at the same site at different time points indicates a true infection and not a passive contamination of the mucosal surfaces (Syrjanen and Puranen, 2000). Controversy exists in the literature on the clearance or the persistence of HPV in follow-up periods. Clearance of HPV infection in the child after birth can occur through antibodies that have migrated from the mother to the fetus and induce a silent neutralization, or, in case of a passive contamination, the maternal infected cells may tend to disappear during the first months of life (Rombaldi *et al.*, 2009). This indicates that the clearance of HPV does not necessarily mean that the HPV-positive status was a reflection of passive contamination with HPV from the mother.

A major difficulty in the analysis of these kinds of data is the fact that a complete separation in the dataset is expected, that is all children of HPV-negative mothers are expected to be HPV-negative themselves. To overcome this problem, we used absolute RD. Therefore, the large differences between the number of HPV-positive and HPV-negative mothers can lead to violations of the assumptions of the model used. The CIs around the individual estimates of the RD should be interpreted with care, especially for the studies of Watts *et al.* (1998) and Smith *et al.* (2004, 2010). Because of the very low fraction of HPV-positive children, there exists a high risk of underestimating the variance in the RD. However, the use of a random-effects model ensures that the variance in the final combined RD estimate is not influenced by the heterogeneity observed in the data.

A major limitation of this meta-analysis was the small sample size of most of the studies included. Also, the history of cervical lesions was not always reported in the studies included. It is therefore unclear whether this variable may cause a difference in the transmission of HPV to the child. Only a few studies included HPV-type-specific data. Several studies have reported cases of HPV-positive children born to HPV-negative mothers, which can be attributed to false-negative tests in the mother, false-positive tests in the child, postnatal horizontal transmission, or sample contamination.

Clinical implementations for reproductive health and protection against HPV may involve the vaccination of pregnant women preferably before or eventually during their pregnancy. This may reduce the viral load of HPV and increase the HPV immunological antibodies for both the mother and the child through transplacental transmission. In light of lifelong HPV protection, the vaccination of infants should be considered. However, further research is necessary to gain more insight into the consequences of HPV infection in children and the duration of protection of prophylactic vaccines if administered to infants.

More research is required to gain insights into the mode of transmission from mother to child and the natural history of HPV infection in children.

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Conflicts of interest

There are no conflicts of interest.

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