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Cervical intraepithelial neoplasia or cancer after HPV vaccination: A review of the literature

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ABSTRACT

Introduction: This literature review focuses on examining whether there are studies documenting the emergence of cervical intraepithelial neoplasia (CIN) or cervical cancer among human papillomavirus (HPV)-vaccinated women who were initially HPV naïve, emphasizing the presence of genotyping upon diagnosis.

Methods: This study provides a literature search of available research in PubMed or EMBASE using specific criteria to identify original research on women developing CIN or cervical cancer following HPV-vaccination despite being initially HPV-naïve. The literature search culminates in the identification of four relevant studies: two randomized controlled trials, a retrospective cohort and a case-control study.

Results: A total of 1208 cases of HPV infections, CIN or cancer are presented, however only 104 cases are linked to potential vaccination failure. Vaccination failure is associated with various factors such as primary or secondary vaccination failure. However, a definite explanation for why it occurs for each individual cannot be stated with certainty.

Conclusion: This review supports the occurrence of CIN or cervical cancer after HPV vaccination. Among 1208 cervical HPV, CIN and cervical cancer cases, 104 suggest potential vaccination failure. However, uncertainties in defining HPV naivety across articles, make it tentative to solely attribute this to vaccination failure. This highlights a crucial knowledge gap, urging further studies. Despite vaccination, complete protection against CIN/cervical cancer is unassured; it may result from lack of naivety, vaccination failure or other oncogenic HPV types. Women should actively participate in cervical screenings for early detection, whether via gynecological exams or self-sampling tests.

Keywords: Human Papillomavirus; Cervical intraepithelial neoplasia; cervical cancer; HPV vaccination; vaccination failure; HPV naïve.

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INTRODUCTION

Human Papillomavirus (HPV) is a common sexually transmitted viral infection in men and women [2]. HPV encompasses a broad spectrum of genotypes, the majority of which are usually asymptomatic. These genotypes are considered non-malignant, as the immune system eliminates the infection effectively. However, some genotypes are carcinogenic and can manifest a persistent cervical infection in women over time [3]. The International Agency for Research on Cancer has identified 13 high-risk (HR) carcinogenic HPV genotypes [12]. Failure to eradicate the HPV infection may result in the emergence and progression of abnormal cervical cells known as cervical intraepithelial neoplasia (CIN), ultimately advancing into invasive cervical cancer at a later stage.

Primary prevention of cervical cancer (CC) can happen using prophylactic vaccines. The HPV vaccines consist of virus-like particles representing the respective HPV genotypes which initiate a strong humoral immune response [1]. Notably, Cervarix (bivalent, HPV 16 and 18) and Gardasil (quadrivalent, HPV 6, 11 and 16, 18) are no longer available commercially. Gardasil 9 represents the nonavalent HPV vaccine, effectively targeting seven high-risk oncogenic HPV types 16, 18, 31, 33, 45, 52 and 58, alongside low-risk strains 6 and 11 accounting for around 90% of genital wart occurrences. [4]. According to the European Medicines Agency, Gardasil 9 is anticipated to provide protection against approximately 90% of CC cases [9]. The vaccine efficacy for all three vaccines exceeds 90% which is satisfactorily high, but this only applies to the HPV-naïve population or the women who were not exposed to the vaccine-targeted genotypes before vaccination. Thus, the vaccines are probably ineffective if the infection is prevalent in the body [1].

Vaccination failure can occur for slightly different reasons. First, it is significant to understand that the occurrence of CIN or CC resulting from a current or previous infection does not indicate vaccination failure as the vaccines are prophylactic and not therapeutic [1]. Primary vaccination failure is characterized by the inability to generate an immunological response following vaccination due to a lack of seroconversion [17]. Factors such as genetics, age, and underlying medical conditions can influence the occurrence of these instances [16]. According to research, the immune response is particularly conditioned by the vaccination age, hence a two-dose vaccination schedule for 9–13-year-old girls is as effective as a three-dose vaccination plan for 16–26-year-old women [14]. Besides, the vaccine efficacy has been investigated in the FUTURE II trials, which reveal that the vaccines should exude 100% efficacy in HPV naïve women [15]. Furthermore, individuals react differently to the vaccine by mounting a stronger or weaker immune response. This variability can be linked to secondary vaccination failure, as some experience a gradual loss of immunity over time despite the initial immune response [17].

Although the HPV vaccines have diminished cases of CC, the occurrences of CIN and CC persist in vaccinated women. This issue prompts an investigation to potential factors, including vaccination failure or oncogenic non-vaccine targeted genotypes. This review focuses on examining whether there are studies documenting the emergence of CIN or CC among pre-vaccinated women who were initially HPV naïve, with emphasis on whether genotyping was conducted upon diagnosis.

MATERIALS AND METHODS

The literature search for this literature review was conducted in February 2021 by applying the following search string in PubMed and EMBASE.

(((risk OR prevalence)) AND ((((cervi* cancer) OR (cervical intraepithelial neoplasia)) OR (cervi* dysplasia)) OR (CIN)) AND (((after HPV vaccination) OR (after human papilloma virus vaccination)) OR (after human papillomavirus vaccination)).

The main objective was to investigate vaccination failure, defined as the incidence of CIN or CC after completing the HPV vaccination program before sexual debut. The central focus revolved around extracting data related to cases of CIN or CC following HPV vaccination in women initially without prior HPV exposure. Simultaneously, pertinent information concerning the participants' age, study period, and the specific HPV vaccine utilized were collected. The chosen articles were published in English between 2009 and 2021, considering the childhood vaccination programs launched in Denmark, and most other countries, from the year

Table 1: Characteristics of the eligible studies

Country	Study period Follow-up (months)	Study design	Case vaccine	Control vaccine	Age of participants	No. of participants, *n*	Reference
Denmark + 17 more	2009-2015 72	Randomised double-blinded controlled trial	Gardasil 9	Gardasil	16-26	15.334	Huh et al. [10]
Costa Rica	2004/05-2009 48	Randomised controlled trial	Cervarix	Hepatitis A	18-25	7466	Beachler et al. [11]
Italy	2015-2017 Retrospective	Retrospective cohort	Cervarix or Gardasil	–	21-41	43	Bogani et al. [12]
Sweden	2006-2014 Case-control	Population based case-control	Cervarix or Gardasil	Cervarix or Gardasil	23*	305.320	Kann et al. [13]

**Median age*

2009. In terms of inclusion criteria, the emphasis was on selecting original research which addressed women who developed CIN or CC subsequent to vaccination, notwithstanding their initial HPV-naïve status. Moreover, the enrolled women were mandated to possess an HPV classification upon diagnosis. The sorted articles were subjected to exclusion criteria, hereby eliminating reviews, meta-analyses, duplications, and irrelevant publications based on title or abstract. The search yields a total of four publications that appear to be the most representative of what this review scrutinizes. The literature search strategy is illustrated in a PRISMA flowchart (figure 1), which outlines the different processes needed to find the relevant publications.

RESULTS

The four selected studies have undergone an evidence-based assessment and were judged to contain a great quality of evidence. The studies are presented as the following (table 1).

Huh et al. [10] conducted a randomized, double-blinded controlled trial to measure the efficacy, immunogenicity, and safety of the nonavalent vaccine in women aged 16-26. The study involved 14.215 generally healthy participants across 105 study sites in 18 countries. Inclusion criteria ensured no history of cervical abnormalities and no more than four lifetime sexual partners. The participants underwent a randomization process, resulting in a 1:1 allocation ratio, with 7099 participants assigned to the nonavalent vaccine (case group) and 7105 assigned to the quadrivalent vaccine (control group). Notably, most participants (97.6%) received the recommended three doses of the vaccine, while remaining blinded to their assigned vaccine. Regular cervical and serum samples are collected to detect high-risk HPV and assess vaccine immunogenicity, respectively, with a follow-up period of six years. The case group reported three cases of CIN related to vaccine-targeted HPV (table 2). In contrast, the control group presented 129 cases of CIN, where the vast majority are attributed to HPV genotypes included in the nonavalent vaccine (table 2). Unfortunately, information pertaining to the development of CIN concerning non-vaccine-targeted HPV types is unprovided. Beachler et al. [11] presented a randomized controlled trial from Costa Rica investigating the multisite effectiveness of the bivalent HPV vaccine against cervical, anal, and oral HPV infections over a four-year annual follow-up. Strictly, for the purpose of this review, only cervical HPV infection results were observed. The study involved 7466 women aged 18-25, randomly assigned to receive either the bivalent vaccine (HPV cohort) or the Hepatitis A vaccine (control cohort) over a three-dose regimen between 2004-2005. The full analytical cohort consisted of 4186 sexually active women (HPV cohort, n=2094 and control cohort, n=2092) who have undergone pelvic examinations and provided blood samples at vaccination enrollment and follow-up visits to detect HPV DNA infections and serologic HPV16/18. The pre-randomization characteristics were identical in both cohorts, as the participants were subsequently divided into three categories; 1) The 'naïve'-cohort (n=1919) included women without evidence of prior HPV infections at enrollment, considering they were HPV16/18 seronegative, HPV16/18 DNA negative, and have not received loop electro

Table 2: The different studies and the distribution of HPV genotypes with relation to either an HPV infection or any grade of cervical intraepithelial neoplasia

		HPV infection		CIN1 cases (LG)		CIN2+ cases (HG)	
Refer-ence	HPV classification	Cases (n†/7099‡) *(n/N%)*	Control (n/7105) *(n/N%)*	Cases (n/7099) *(n/N%)*	Control (n/7105) *(n/N%)*	Cases (n/7099) *(n/N%)*	Control (n/7105) *(n/N%)*
Huh et al. [10]	HPV 16 or 18 HPV 31, 33, 45, 52 or 58* HPV 35, 39, 42, 51, 56, 59, 66, 68, 87 or 90**	25 (0.4%) 23 (0.3%) N/A	35 (0.5%) 657 (9.3%) N/A	– 1 (0.01%) N/A	2 (0.03%) 87 (1.2%) N/A	1 (0.01%) 1 (0.01%) N/A	– 32 (0.5%) N/A
Ref	HPV classification	Cases (n/970) *(n/N%)*	Control (n/949) *(n/N%)*	Cases (N/A)	Control (N/A)	Cases (N/A)	Control (N/A)
Beachler et al. [11]	HPV 16 or 18 HPV 31, 33, 45, 52 or 58* HPV 35, 39, 42, 51, 56, 59, 66, 68, 87 or 90**	8 (0.8%) N/A N/A	74 (7.8%) N/A N/A				
Ref	HPV classification	Cases *(N/A)*	Control *(N/A)*	Cases *(N/A)*	Control *(N/A)*	Cases *(n/43)* (n/N%)	Control *(N/A)*
Bogani et al. [12]	HPV 16 or 18 HPV 31, 33, 45, 52 or 58* HPV 35, 39, 42, 51, 56, 59, 66, 68, 87 or 90** None					2 (4.7%) 25 (58%) 12 (28%) 4 (9.3%)	
Ref	HPV classification	Cases (N/A)	Control (n/242) *(n/N%)*	Cases (n/125) *(n/N%)*	Control (N/A)	Cases (n/125) *(n/N%)*	Control (N/A)
Kann et al [13]	HPV 16 or 18 HPV 31, 33, 45, 52 or 58* HPV 35, 39, 42, 51, 56, 59, 55, 68, 87 or 90**		2 (0.8%) 19 (7.9%) 44 (18%)	3 (2.4%) 23 (18.4%) 76 (61%)		1 (0.8%) 29 (23.2%) 22 (17.6%)	

† n, defines the number of cases
‡ N, defines the total number of participants
**The HPV-genotypes are included in the nonavalent HPV vaccine*
***The given HPV-genotypes are not included in any vaccine*

surgical excision procedure (LEEP) during the vaccination phase; 2) 'Evidence of prior HPV exposure' (n=1655) refer to HPV16/18 seropositive women, but cervical HPV16/18 DNA negative; 3) 'Currently exposed' (n=488) are cervical HPV16/18 DNA positive. A further restricted 'naïve' cohort (n=1919) was presented; HPV cohort (n=970) and control cohort (n=949), including only participants from the 'naïve' category and were the focus of evaluation (table 2). Within the HPV cohort, eight cases of HPV16/18 infection were presented despite the participants' naivety status before vaccination (table 4). Additional information on

Table 3: provides an overview of the number of cases of HPV infections, dysplasia, or cancer and its corresponding HPV genotype.

Reference	Total no. of participants *(N)*	Total no. of cases *(n) (n/N%)*	Cases due to HPV 16, 18 *(n) (n/N%)*	Cases due to HPV 31, 33, 45, 52 or 58 *(n) (n/N%)*	Cases due to HPV 35, 39, 42, 51, 56, 59, 55, 68, 87 or 90 *(n) (n/N%)*
Huh et al. [10]	14.204	864 (6.1%)	63 (0.4%)	801 (5.6%)	N/A
Beachler et al. [11]	1919	82 (4.3%)	82 (4.3%)	N/A	N/A
Bogani et al. [12]	43	43 (100%)	2 (4.7%)	25 (58.1%)	12 (28%)
Kann et al. [13]	367	219 (60%)	6 (1.6%)	71 (19.3%)	142 (38.7%)
Total, *n* (%)	16.533	1208 (7.3%)	153 (0.9%)	897 (5.4%)	154 (0.9%)

Table 4: Cases of infection or CIN with a vaccine targeted HPV genotype and its corresponding outcome.

Reference	Category	Vaccine	Total no. of cases *(n)*	Cases of vaccine targeted HPV-types *(n)*	Outcome
Huh et al.	Case	Gardasil 9	3	3	CIN1/2
			48	48	Persistent HPV infection
	Control	Gardasil	121	2	CIN1/3+†
			692	35	Persistent HPV infection
Beachler et al.	Case	Cervarix	8	8	HPV infection
	Control	Hepatitis A	74	N/A	
Bogani et al.	Case	Cervarix / Gardasil	43	2	CIN2+
	Control	N/A	N/A	N/A	N/A
Kann et al.	Case	Cervarix / Gardasil	154	4	CIN1/3
	Control		65	2	HPV infection
Total, *n* (%)			1208 (100%)	104 (8,6%)	

†Entails cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ or cervical cancer.

whether the HPV infection had persisted or progressed to CIN was absent.

Bogani et al. [12] conducted a retrospective cohort study in Italy to identify the genotypes of women who developed CIN2+ despite prior vaccination. Medical records were collected from four Italian centers between 2015-2017. Inclusion criteria encompassed a history of HPV vaccination with either the bivalent or quadrivalent vaccine, a diagnosis of CIN2+, and HPV classification of CIN upon diagnosis. The study included 43 cases of CIN2+ among women aged 21 to 41, with a median age of 28. Ten patients (23%) and 28 patients (65%) recorded previous vaccination with the bivalent or quadrivalent vaccine, respectively, whereas five patients (12%) had unavailable vaccine data. Thirty-one patients (72%) reported no previous history of HPV infection(s), whereas 12 patients (28%) reported a history of HPV infection(s) either before or after vaccination. Five patients had accessible data regarding the HPV genotypes, with four infected with HPV 16/18 and one with HPV 11.

A closer examination revealed that two patients (5%) had CIN2+ related to HPV16, and interestingly, both women recorded no history of HPV co-infections but received the vaccine after sexual debut (table 4). Further data on the remaining cases are displayed in tables 2 and 3.

Kann et al [13] displayed a population-based case-control study from Sweden using data from The Swedish National Vaccination Register at the Public Health Agency. This study focused on prevalent HPV types and their association with CIN development in HPV-vaccinated women. A total of 305.320 women received either the bivalent (0,5%) or quadrivalent vaccine (99,5%) between 2006-2014. Among them, 79.491 women (26%) attended cervical screening programs starting at age 23. The study included a limited cohort of women who received the first dose of vaccination before the age of 17 years or younger, increasing the likelihood that they were HPV naïve at the time of vaccination, considering the median age for female sexual debut in Nordic countries is 16.0 ± 1,1 SD. Exclusion criteria ensured no prior cervical abnormalities, histopathologies, or signs of previous HPV infections. The case group (n=125) was matched with a control group (n=242) at a ratio of 1:2 based on disease-free anamnesis, age of vaccination, type of HPV vaccine, and date of cervical sampling. HPV DNA was identified using cervical samples (table 2), with CIN as the outcome for the case group and HPV infection for the control group [13]. Table 4 provides data on cases that suggest possible vaccination failure. It displays cases of CIN or HPV infections attributed to vaccine-targeted HPV genotypes.

DISCUSSION

Overall, the results exhibit that HPV infection or CIN caused by vaccine-targeted HPV can occur after vaccination - however, it is rare. In cumulative, this review elucidates a total of 1208 cases of CIN or HPV infection following vaccination, with only 104 cases attributed to potential vaccination failure (table 4).

Primary vaccination failure

Beachler et al. [11] detected eight cases of HPV16/18 infections (table 4) in participants who were considered HPV naïve before vaccination. In these cases, it is plausible that the HPV infection could have been transmitted by their partners, representing a potentially transient infection or a persistent infection that might resolve or progress into CIN over time. Notably, the infection rate was only 0.8%, suggesting that primary vaccination failure can be a contributing factor. Another less likely possibility can be related to participants having an immunodeficiency, rendering their immune system unable to generate an effective response to the vaccination, leading to no discernible effect. Kann et al. [13] reported six cases of vaccination failure for both the case and control group. The participants were all HPV naïve before vaccination, why lack of naivety is less likely the cause. It can potentially be a case of primary vaccination failure. It is plausible that the number of doses had an influence. However, it is not immediately applicable, given 88% and 91.3% of all participants in the case and control group, respectively, had completed a three-dose immunization program. On the other hand, it could also be a matter of secondary vaccine failure. The time between vaccination and cervical cytology/HPV sampling is 7.00 ± 1.51 years and 6.89 ± 1.44 years for the case and control group respectively. Consequently, the chosen participants with cases of vaccination failure may have waned their immunity.

Secondary vaccination failure

Bogani et al. [12] reported two cases of CIN2+ caused by HPV16/18 after vaccination (table 4). The two women did not record any previous HPV co-infections but received the vaccine after their sexual debut. Consequently, it is conceivable that the vaccination was ineffective due to a lack of naivety. However, assuming they were HPV 16/18 seronegative and cervical HPV16/18 negative at the time of vaccination, then it could be a case of secondary vaccine failure as the participants' immunity may have waned with time.

Huh et al. [10] documented 51 cases of vaccination failure in the case group (table 4), which appeared to be attributed to secondary vaccination failure. According to the immunogenicity profile, 99.6-100% of the trial subjects had completely seroconverted seven months after vaccination. However, at the endpoint (month 60), the serology was ascertained at 77.5-100%, suggesting some participants experience a lack of sustained protection despite the initial immune response, why cases of persistent HPV infections and CIN were seen. The control group reported 37 cases of vaccination failure (table 4). Arguably, in a scenario where the immunogenicity profile is assumed to be identical to the case group, this also constitutes a case of secondary vaccination failure.

Continue screening despite HPV status

The findings indicate that despite vaccination, HPV infections, CIN, and CC still occur. Correspondingly, it is crucial for women, regardless of their HPV status, to actively engage in cervical screening programs. It is important to acknowledge the limitations of HPV vaccines, considering they do not provide absolute protection, as previously discussed. Cervical screenings must continue, albeit in a modified form. Numerous women in Denmark and globally are diagnosed with CIN or CC due to vaccination failure or the presence of oncogenic non-vaccine-targeted HPV genotypes. These cases require special attention, involving comprehensive data collection from national pathology registries to ascertain the underlying reasons for CIN or CC development despite vaccination. Additionally, it is crucial to type-define the HPV genotype in cases, where CIN or CC manifests after vaccination. This information helps differentiate between vaccination failure caused by vaccine-targeted HPV or the presence of an oncogenic non-vaccine-targeted HPV. Tables 2 and 3 present 154 (0.9%) cases of mild to severe dysplasia caused by non-vaccine-targeted oncogenic HPV genotypes.

Self-testing

A gynecological examination is opposed by some women, which becomes an obstacle to cervical screening programs. According to the Danish Healthcare Authority, cervical screenings are not attended by 25% of the invited women. These women account for roughly half of all CC cases [18]. Danish studies have investigated the association between non-attendance in cervical screen-

ings among natives and non-natives. Among natives, it appears to be due to poor health-preventive demeanor, while socio-cultural factors impede non-natives, why a suited interference responsive to the needs of non-native women is needed [5-6]. Nonetheless, regardless of whether the reason is due to practical or personal matters, a self-test is currently available as an alternative to a cervical screening performed by a gynecologist [7-8, 20]. However, if the test is made commercially available without going through a healthcare authority, the national overview of how many women are screened and the benefit of having a cervical screening program will be lost.

Strengths and limitations

The assessment presented has strengths and limitations. It is based on a limited number of four research studies. However, these study designs collectively hold high credibility in the evidence hierarchy, thus indicating great quality of evidence for the presented results. Notably, the randomized controlled trials have utilized substantial data to establish causation. The exceptional validity of these trials is ensured by their rigorous randomization process, which minimizes patient or viewer bias by making the exposure to the vaccine the only distinguishing factor between the treatment groups. Of all the studies, Warner K. Huh et al. [10] stands out as it was conducted across 18 different countries, resulting in a diverse participant population with various ethnic backgrounds, thereby enhancing the research's credibility.

The retrospective cohort study [12] has the strength of including cases of CIN caused by non-vaccine targeted HPV types. However, its credibility is low due to the absence of a control group why it is prone to selection bias. Additionally, there is insufficient certainty regarding the patients' HPV naivety before vaccination, and other crucial information about their vaccination status is absent, introducing confounding factors and missing covariates. On the other hand, the population-based case-control study includes a corresponding control group and examines the prevalence of CIN linked to non-vaccine-targeted HPV genotypes, which enhances its credibility.

However, the main limitation pertains to the collective scope of these studies, which, despite upholding credibility, does not furnish an ideal foundation for a conclusive standpoint. Notably, not all studies conduct HPV testing before vaccination; instead, many rely on indicators to presume HPV-naivety. Ideally, all participants should undergo HPV testing before vaccination to ensure their HPV naïve status comprehensively. This limitation significantly impedes the ability to reach a definitive conclusion, revealing a pertinent knowledge gap within this subject area.

Moreover, information regarding important outcomes in most studies is missing, which further limits the ability to draw reliable and accurate conclusions concerning this issue. For example, Huh et al. [10] and Beachler et al. [11] do not provide data on the development of persistent infection, CIN, or CC caused by non-vaccine-targeted HPV genotypes. Specifically, Daniel et al. fail to present any data on the progression of the reported cases to persistent infections or any cervical abnormalities related to non-vaccine-targeted HPV genotypes. Moreover, this review displays no cases of CC, further restricting the understanding of vaccination failure concerning cancer development. Nonetheless, it is ethically questionable to use invasive cervical cancer as an endpoint in randomized controlled trials. As a result, the studies used in this review testing HPV vaccination effectiveness, mainly look at cancer surrogate endpoints. Nevertheless, the time interval between HPV infection and cancer development is typically more than ten years, during which the infection may be cleared. For that reason, CIN of any grade does not necessarily indicate the development of cancer.

CONCLUSION

Overall, this review supports the occurrence of CIN or CC after HPV vaccination. It presents a comprehensive analysis encompassing 1208 cases of cervical HPV infections, CIN, or CC, within which 104 suggest potential vaccination failure. However, uncertainties arise due to discrepancies in defining HPV naivety across articles. Notably, HPV naivety is not uniformly confirmed as not all studies conduct pre-vaccination HPV testing. This underscores a significant knowledge gap, highlighting the necessity for further studies to address this research objective. Nonetheless, it is of utmost importance to educate

women that, despite vaccination, complete protection against the development of CIN or CC cannot be guaranteed, as it may arise due to either vaccination failure or infections with non-vaccine-targeted HPV genotypes. Consequently, it remains critical for women to actively engage in cervical screening programs, whether through conventional gynecological examinations or self-sampling tests.

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