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Research article

A case-control study on cervical cancer screening outcome and HPV vaccination among young women in the Italian area of Udine

Francesca Valent*and Valentina Moretti

SOC Igiene e Sanità Pubblica, Dipartimento di Prevenzione, Azienda Sanitaria Universitaria Friuli Centrale, 33100 Udine, Italy

* **Correspondence:** Email: francesca.valent@asufc.sanita.fvg.it; Tel: +390432553210.

Abstract: The age for starting cervical cancer screening for women who were fully vaccinated against human papilloma virus (HPV) in adolescence could be increased from 25 to 30 years. In Italy, some regional governments have revised their screening programs accordingly, though others haven't. Local data on the effectiveness of the HPV vaccine may be helpful in encouraging updates in the screening protocols. We conducted a case-control study based on routine-collected anonymized administrative health data to evaluate the outcomes of first round cervical screening in women living in the Udine area of Italy, according to their vaccinal status. In the study, we included women born between 1993 and 1997, those that were living in the Udine area from 2008 to 2022, and those that participated in the regional cervical cancer screening program for at least one round from 2018 to 2022 (n = 2191). Of these women, 850 had been fully vaccinated before 15 years of age, 887 were vaccinated at age 15 or later, 39 were incompletely vaccinated, and 415 had never been vaccinated. 2140 women had a negative pap-test result and 51 had some type of non-normal result. The odds ratio for having a non-negative result was 0.23 for vaccinated vs non-vaccinated women (95% confidence interval 0.13−0.40). Only 0.2% of vaccinated women had CIN2+ lesions compared to 1.0% of CIN2 and 2.6% of CIN3 of non-vaccinated women (odds ratio of CIN2+ was 0.10, 95% confidence interval 0.04−0.26). The first invitation to the regional cervical cancer screening could be delayed in women who were vaccinated against HPV.

Keywords: human papilloma virus; cervical cancer; screening; vaccination; case-control study

Abbreviations: CIN1+: Cervical intraepithelial neoplasia grade I; CIN2: Cervical intraepithelial neoplasia grade II; CIN2+: Cervical intraepithelial neoplasia grade II or more; CIN3: Cervical intraepithelial neoplasia grade III

1. Introduction

Cervical cancer is the fifth most frequent cancer among women <50 in Italy [1]. According to the World Health Organization (WHO), although cervical cancer is a preventable and curable disease, if timely identified and treated, it is still one of the most common malignancies and causes of death among women at the global level [2]. The process of eliminating cervical cancer can only be accelerated through a strategy that integrates and coordinates various preventive and case management interventions at the population level [2].

This cancer is caused by an infection of the persistent Human Papilloma Virus (HPV), which is sexually transmitted. The risk factors include all conditions favoring infection, as well as scarce access to prevention (e.g., low socioeconomic level, number of partners, young age at the start of sexual activity, immunodeficiency, and familiarity) [1−3].

HPV infection is very common in the population and is the most common infection of the reproductive trait. Up to 80% of sexually active women are estimated to be infected in their lifetime with any HPV type, and more than 50% with an oncogenic type [4]. The low-risk types, such as HPV 6 and 11, can cause benign genital lesions with a low risk of malignant transformation, whereas the high-risk types, such as HPV 16, 18, 31, 33, 45, 52, and 58, can cause genital lesions with a high risk of malignant transformation, and are thus considered oncogenic. In fact, the high-risk types can be found in 99% of precancerous lesions. Type 16 is responsible for 50% of cancerous lesions, types 16 and 18 together account for up to 70% of cervical cancers, whereas HPV 31, 33, 45, 52, and 58 together account for 11% [2,5].

The prevalence of oncogenic types is greater among younger women, with a peak among those <25 years of age and a second smaller peak around or after menopause [4]. Despite the incidence being high, most infections spontaneously clear within one or two years. Only in a small number of cases does the infection persist, thus increasing the risk of neoplastic progression, depending on the type of HPV that was involved [5,6].

Persistent infections can cause intraepithelial lesions, which determine various clinical cases according to the HPV type. Such lesions can be detected through screening procedures. Low-grade squamous intraepithelial lesions (LSIL) often regress, whereas high-grade lesions (HSIL) are considered precancerous lesions and, if not treated, can progress into cervical cancer in either years or decades [5].

The prevention of cervical cancer includes three levels: primary prevention (i.e., the vaccination against HPV and behavioral education); secondary prevention (i.e., screening and early treatment of precancerous lesions); and tertiary prevention (i.e., diagnosis and treatment of cervical cancer) i8. In Italy, cervical cancer screening programs have been mandatory for the regions since 2001; however, in the Italian Region Friuli Venezia Giulia (FVG), a cervical cancer screening program has been in place since 1999, addressing 25-to-64-year-old women [7,8]. Currently, in the regional program of the FVG Region, the first step in the program is either a Pap-test, which is offered free of charge every 3 years to women from 25 to 29 years of age, or an HPV-DNA test, introduced only recently [9], which is offered free of charge every 5 years to women from 30 to 64 years of age. For cases where the Pap-

test and HPV-DNA test are positive after the cytology, women are invited for a colposcopy and possibly a biopsy for a histological diagnosis [3].

Since the end of 2007, a vaccination campaign against HPV has also been implemented [10], which is consistent with the WHO recommendations [11]: the priority target of the campaign was girls in their 12th year of life (in 2008, they corresponded to the 1997 birth cohort). Thus, since 2008, the vaccination has been offered actively and free of charge in the FVG region. In addition, the vaccination was also offered to adolescent girls in their 15th year of life (1993 birth cohort in 2008) in the FVG region [12]. The vaccination is available free of charge for women up to age 26 [13]. Various types of HPV vaccines were offered in the FVG region, according to subsequent approvals in the European Union: at the beginning, a 2-valent vaccine, approved in 2006 against HPV16 and HPV18; then, a 4-valent vaccine; and currently, a 9-valent vaccine, approved in the EU in 2015 against 7 more strains, in addition to the two strains that cause most HPV-related cancers.

The Italian FVG region released a Regional Prevention Plan, which includes the goals to be reached in 2021−2025. One of the objectives is to evaluate and possibly redefine cervical cancer screening protocols for women who were vaccinated in adolescence (<15 years) based on scientific evidence [14].

The objective of this study is to verify whether the outcomes of pap-tests and further colposcopies differ according to HPV vaccinal status among women that attended the regional cervical cancer screening program from 2018 to 2022, were born between 1993 and 1997, and lived in the 530000-inhabitant area of the Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), in the FVG Region.

2. Methods

This case-control study used the Regional Epidemiological Repository (RER) of the FVG region as the source of information. The RER, which has 100% population coverage, includes several health administrative databases, generated from different health application software and was normalized before being copied into the repository. In this study, we analyzed the following data: the list of potential healthcare beneficiaries, residencies, vaccinations, and cervical cancer screening data, which referred to the ASUFC population. The list of healthcare beneficiaries and residencies includes the date of birth, sex, the starting and final dates residencies, and the corresponding towns for all the healthcare beneficiaries of the region since 1978. The vaccination database contains the type, commercial name, dose, date, and place of administration for all vaccinations administered in FVG since 1995. The cervical cancer screening includes information on the invitation dates for the pap-tests and HPV DNA tests within the regional screening program, the participation dates in the proposed tests, and the outcomes of the conducted tests since 1998. All databases include millions of records. They are all anonymous because they do not contain any personal identifier; however, they can be deterministically linked (i.e., on the basis of an exact correspondence of a linkage key) at the individual level through a stochastic (i.e., casual), periodically modified key which, at a given time, is univocal for each person across all databases. For the researchers, there is no way to discover the identity of the subjects.

For this study, the following inclusion criteria were defined:

1. Women born between 1993 and 1997;
2. Residence in the ASUFC area from 2008 to 2022; and

3. Participation in the regional cervical cancer screening program for at least one round from 2018 to 2022.

The following exclusion criteria were adopted:

1. Women who did not participate in the regional screening program;
2. Women who participated in the regional screening program, with a non-negative cytological pap-test diagnosis (i.e., ASC-US with no subsequent HPV-test, pap-smear inadequate sample due to inflammation or due to technical issues) not followed by a colposcopic histological diagnosis;
3. Women with negative pap-test results after a hysterectomy; and
4. Women with a positive histological diagnosis from a colposcopy that preceded the screening starting age (i.e., 25 years).

For the purpose of this research, the cases included all women who fulfilled the inclusion criteria with a histological diagnosis of CIN1, CIN2, CIN3, or cancer through a colposcopy within the regional cervical cancer screening program.

The controls were women with a completely negative pap-test, those with a cytological diagnosis of ASC-US with a contemporaneous negative HPV-test, and those with a non-completely negative pap-test followed by a negative colposcopy.

2.1. Statistical analysis

For this research, we did not sample cases and controls from the source population. Instead, since the RER covered 100% of the population and this was in fact a population-based case-control study, we used all the women who fulfilled the inclusion criteria, since their data were already available for analysis in the administrative data warehouse. Expecting a source population of approximately 2000 women, assuming a control: case ratio of 40:1, and assuming approximately 95% of the controls (women with negative pap-test) were among vaccinated women, we estimated that our population size allowed us to estimate an odds ratio (OR) of 0.3 at a 95% confidence level with a power >80% (calculation done according to Kelsey method using Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, www.OpenEpi.com).

The associations between at least one histological positive diagnosis (CIN1, CIN2, CIN3, or cancer) and the HPV vaccinal status (either classified dichotomously as unvaccinated or at least one dose and classified on more levels as unvaccinated, incompletely vaccinated, fully vaccinated after age 15, or fully vaccinated before age 15) were assessed through chi-square tests and logistic regression analyses. P-values <0.05 were considered statistically significant. The precision of the OR was indicated by the 95% confidence interval (95%CI). The receiver operating characteristic (ROC) curve was calculated as a measure of the performance of the model to classify the observations.

Among the vaccinated women, the association between the screening outcome and the type of vaccine (bi-valent vs tetra-valent) was assessed.

As a sensitivity analysis, alternative regression models were built that excluded cases who participated in two screening rounds and had a positive outcome on the second round.

All the analyses were conducted using the SAS Enterprise Guide v 7.15 (SAS Institute Inc., Cary, NC, USA).

2.2. Ethical statement

The study was approved by the Ethics Committee of the Friuli Venezia Giulia Region (CEUR) on January 9, 2024 (Parere CEUR-2024-Os-1 seduta 09.01.2024 – odg 4.1).

All the data used in the analyses were anonymous and the subjects could not be identified by the researchers. Since the identity of the subjects was unknown, no informed consent could be administered.

3. Results

From 2018 to 2022, 2423 resident women born between 1993 and 1997 participated in the regional cervical cancer screening in the ASUFC. Nine women were excluded from further analyses because they underwent colposcopies before the screening age, 2 were excluded because they underwent screening after a hysterectomy, and 221 were excluded because they had a non-completely negative pap-smear that was not followed by a colposcopy. Thus, our study base consisted of 2191 women. Of them, 51 had a positive histological diagnosis after a colposcopy and were then analyzed as cases. The remaining 2140 women were included in the analyses as controls (Figure 1).

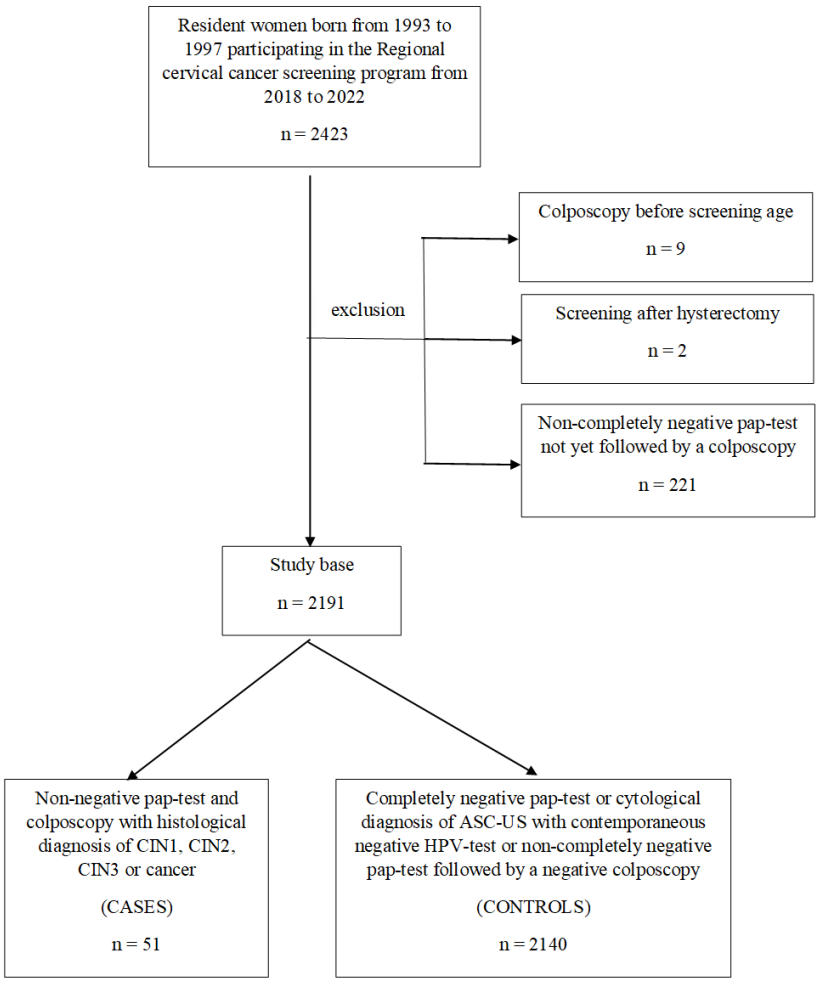

Figure 1. Study flow-chart.

Of the 51 cases, 29 had a histological diagnosis of CIN1, 8 of CIN2, and 14 of CIN3. No cancers were detected in this group of young women that attended the regional screening program.

Of all the 2191 women included in the analyses, 81.0% were administered ≥1 dose of the anti-HPV vaccine before the screening age: 850 were vaccinated with a complete cycle before age 15, 887 received a complete vaccination cycle at age ≥15, 39 did not complete the cycle, and 415 women were not vaccinated before the screening age.

Table 1 describes the vaccinal status according to the screening outcome. Almost half of the cases had never been vaccinated (25 out of 51, 49.0%), whereas, among the controls, only 18.2% were not vaccinated (390 out of 2140). Such a remarkable difference was statistically significant (p-value of chi-square test <0.0001¸ crude OR = 0.23, 95%CI: 0.13−0.40). Among the cases, the proportion of unvaccinated women increased with an increased severity of diagnosis: 34.5% in CIN1 women (10 out of 29), 50.0% in CIN2 women (4 out of 8), and 78.6% in CIN3 women (11 out of 14). Table 2 emphasizes the proportion of different screening outcomes among the vaccinated and unvaccinated women: the proportion of CIN2 and CIN3 was much more common in the unvaccinated women than among those who received ≥1 dose (crude OR of CIN2+ in vaccinated women as compared with unvaccinated women: 0.10, 95%CI: 0.04−0.26).

Table 1. Characteristics of the study sample and HPV vaccination status in women living in the ASUFC area (Udine, Italy), born from 1993 to 1997 and participating in the regional cervical cancer screening program from 2018 to 2022, by screening outcome.

HPV vaccination status	Negative outcome (CONTROL)	Any positive outcome (CASE)	Total
Age at vaccination (years at 1st dose) – mean ± standard deviation; median	14.2 ± 2.2; 14	16.3 ± 4.6; 15	14.2 ± 2.3; 14
Age at screening (years) – mean ± standard deviation; median	25.3 ± 0.9; 25	25.2 ± 1.12; 25	25.2 ± 0.8; 25
Follow-up time (days) – mean ± standard deviation; median	792 ± 484; 646	888 ± 565; 795	814 ± 491; 673
Residency at time of screening			
Udine (main city of the study area)	403 (97.6%)	10 (2.4%)	413 (100%)
Other towns	1347 (97.0%)	41 (3.0%)	1388 (100%)
Vaccination status			
Vaccinated ≥1 dose	1750 (98.5%)	26 (1.5%)	1776 (100.0%)
Complete cycle at age <15 years	836 (98.4%)	14 (1.6%)	850 (100.0%)
Complete cycle at age ≥15 years	875 (98.7%)	12 (1.3%)	887 (100.0%)
Incomplete cycle	39 (100.0%)	0 (0%)	39 (100.0%)
Not vaccinated	390 (94.0%)	25 (6.0%)	415 (100.0%)
Total	2140 (97.7%)	51 (2.3%)	2191 (100.0%)

*Note: p-value of chi-square test for vaccinated ≥1 dose vs not vaccinated <0.0001; crude Odds Ratio: 0.23, 95%Confidence Interval: 0.13−0.40.

Table 2. Cervical cancer screening outcome in women living in the ASUFC area (Udine, Italy), born from 1993 to 1997 and participating in the regional cervical cancer screening program from 2018 to 2022, by HPV vaccination status.

	Cervical cancer screening outcome			
HPV vaccination	Negative	CIN1	CIN2	CIN3
	N (row %)	N (row %)	N (row %)	N (row %)
Not vaccinated	390 (94.0%)	10 (2.4%)	4 (1.0%)	11 (2.6%)
Vaccinated ≥1 dose	1759 (98.5%)	19 (1.1%)	4 (0.2%)	3 (0.2%)

*Note: crude Odds Ratio of CIN2+ vs negative or CIN1 in vaccinated ≥1 dose vs not vaccinated: 0.10, 95% Confidence Interval: 0.04−0.26.

A multiple logistic regression analysis, which included vaccination status (any dose vs none) and birth year (continuous) as independent variables, confirmed a significant 77% reduction in the risk of a positive histologic diagnosis (CIN1, CIN2, or CIN3) in women with at ≥1 dose of HPV vaccination before the screening age as compared with unvaccinated women (OR = 0.23, 95%CI: 0.13−0.41) and a non-significant 14% decrease in the risk of a positive histologic diagnosis for each increasing year of birth (OR = 0.86; 95%CI: 0.70−1.06). The area under the ROC curve was 0.68.

The model that assessed the effect of the four levels of vaccination statuses showed a statistically significant and reduced risk of a positive histological diagnosis for women fully vaccinated before age 15 compared to unvaccinated women (OR = 0.26; 95%CI: 0.13−0.51) and for women fully vaccinated at age ≥15 years compared to unvaccinated women (OR = 0.21; 95%CI: 0.11−0.43); however, the risk reduction did not reach statistical significance for women vaccinated with an incomplete cycle (OR<0.01; 95%CI: 0-infinity). The area under the ROC curve was 0.67.

The model that only included vaccinated women showed no significant difference in the effect of the 4-valent vaccine (used in 439 women) and the 2-valent vaccine (used in 1337 women): the OR of the positive histological diagnosis in women using the 4-valent vaccine was 0.91 (95%CI: 0.36−2.29) as compared with those using the 2-valent vaccine.

Of all the women included in the study, 302 controls and 6 cases underwent two screening rounds. In the sensitivity analyses, which excluded the 6 women with a positive histological diagnosis at the second round, the risk reduction among women vaccinated with ≥1 dose did not change substantially: OR = 0.23 (95%CI: 0.13−0.42). The effect of the birth cohort on the risk of a positive histological diagnosis became less evident: OR for each increasing year of birth was 0.95 (95%CI: 0.77−1.19).

4. Discussion and conclusions

This analysis of administrative data showed that in this Italian area, the HPV vaccine, either 2-valent or 4-valent, administered before screening age, was effective in reducing the risk of a positive outcome at the cervical cancer screening in the age group 25−29 years. Vaccinated women had a 77% risk reduction of any positive outcome; however, the beneficial effect of vaccination was even greater when specifically looking at the most serious lesions (i.e., CIN2 and CIN3), which only affected 0.4% of vaccinated women overall compared to 3.6% of unvaccinated women. The fact of being vaccinated before or after age 15 did not seem to substantially affect the outcome of the screening.

It is possible that we could not find a difference in the vaccine effectiveness according to age at vaccination because of the relatively small size of the study (in fact, we observed only 51 cases of non-negative tests, including low-grade lesions). Although this was a population-based study, in which all the women who fulfilled the inclusion criteria were included with no sampling, women who did not participate in the regional cervical screening program did not fulfill the inclusion criteria and thus were not included in the study, limiting our study size. In the years of interest (2018−2022) the adherence to the invitation to a pap-test within the regional program ranged from 58% to 72%, with variability due to organizational issues during the Covid pandemic emergency.

An alternative possible explanation for not finding a difference in the vaccine effectiveness according to age at vaccination may be that the age cut-off that we used (15 years, chosen according to the vaccine indications regarding the number of doses required to complete the cycle) was not appropriate to detect a difference. In fact, a large Swedish study by Lei et al. [15] showed a difference in the effectiveness against cervical cancer using 17 years as the cut-off age.

Nonetheless, our finding supports the current Italian and regional FVG vaccination policy, which includes a free offer of the HPV vaccine to all women up to age 26, not only to adolescents, and recommends the vaccine to all women of any age if were never vaccinated before with a co-payment [9,13].

In our analysis, there was no significant difference between women vaccinated with the 2-valent vaccine and those vaccinated with the 4-valent vaccine, which is consistent with the fact that types 16 and 18 account for the vast majority of precancerous lesions. However, an even higher protection should be provided by the 9-valent vaccine, which is currently administered, since it protects against many more HPV types. In fact, our study showed that the HPV vaccine was very effective in reducing the risk of finding a CIN1+ lesion at the first rounds of the cervical cancer screening program; however, some lesions, especially CIN1, were still observed in vaccinated women. It is possible that those lesions were accounted for by the HPV types which were not included in the two vaccines used in the cohorts of interest; in fact, the 9-valent vaccine has been marketed in Italy since 2017. This hypothesis could not be proven since we had no information on which HPV genotypes were found within the cervical lesions. The lack of data on the HPV genotypes was a limitation of this study.

Additional limitations should be taken into consideration when interpreting our results. First, we did not have any individual information about the age when sexual activity started. This could represent an uncontrolled confounding factor in our analysis.

Then, in our study base, only a few women had not completed the vaccinal cycle, making it impossible to estimate the effect of a single vaccine dose. In April 2022, after evaluating the emerging evidence, the WHO Strategic Advisory Group of Experts on Immunization recommended updating the dose schedules for HPV vaccination using either a one or two-dose schedule for the primary target of girls aged 9−14, one or two-dose schedule for young women aged 15−20, and two doses with a 6-month interval for women older than 21 [16]. Unfortunately, due to the excessively small number of exposed women, we could not assess whether the effectiveness of a single dose in real life was analogous to that of the complete cycle in our context.

In 2015, a consensus conference by Gruppo Italiano Screening del Cervicocarcinoma (GISCi) [17] proposed that the age for starting cervical cancer screening in girls vaccinated in their 12th year of life could be increased from 25 to 30 years of age. Subsequently, Italian regions, such as Veneto in 2021 [18], Emilia-Romagna [19], Abruzzo [20], and the Autonomous Province of Trento [21] in 2022, started

offering cervical screening at age 30 in women who had been vaccinated against HPV, where they received two doses before 15 years of age.

In FVG, including ASUFC, cervical cancer screening is still being offered to all women from 25 years of age. Screening is needed, even for vaccinated women, because the vaccines provide protection from the most common HPV carcinogenic strains, but not from all. Nonetheless, our study showed that the risk of developing CIN2+ lesions in women vaccinated with a complete cycle before 25 years of age is extremely low when compared with non-vaccinated women. This study, based on local context-specific data, confirmed the indications provided by the consensus conference [22] for redefining cervical cancer screening protocols for women who were vaccinated in adolescence (<15 years), which is one objective of the Regional Prevention Plan of FVG. Consistent with the new screening protocols adopted by other Italian regions and in agreement with our Regional Prevention Plan objectives, the FVG should consider a revision of its cervical screening protocol. It would be important to re-assess again the effectiveness of HPV vaccination in the second and third screening rounds and to evaluate whether a further delay in screening start age could be considered as the first cohorts of vaccinated girls turn 35 years of age.

Our study also shows that, in this local context, there is little difference in the vaccine effectiveness among women vaccinated with a full cycle <15 and ≥15 years of age. The idea that the vaccine cycle should ideally be completed <15 years is that the best protection is achieved in girls vaccinated before being exposed to the virus (i.e., before starting sexual activity). The fact that 3-dose cycles completed >15 years of age were still very effective in preventing CIN2+ lesions in 25-year-old women might indicate a delayed first exposure to the virus in this context. Thus, efforts to catch up on HPV vaccination among older girls (and boys) are not in vain. Investing in effective strategies to improve communication toward adolescents in high-school or those that are college age and their parents may be useful, especially if they take the students' media preferences into account [23]. Various interventions proved effective in increasing knowledge on HPV vaccinations, the intention to vaccinate, and uptake, although not all succeeded in closing the intention-behavior gap [24]. Better education and information of healthcare professionals themselves is also needed to improve their promotional strategies and, in turn, HPV uptake in adolescents [25].

In our area, HPV vaccination was effective in significantly decreasing the likelihood of finding higher-grade lesions in the first round of cervical cancer screening. Our vaccination services should perseverate in offering free vaccination to all adolescents, including boys and girls >15 years of age, and invest in sound communication strategies to provide better information to the population and to other healthcare professionals. Policymakers in the FVG may consider revising the age of the first cervical screening invitation for women who were fully vaccinated in adolescence.

Author contributions

Francesca Valent: study design, data curation, data interpretation, statistical analyses, critical review and writing; Valentina Moretti: study design, data curation, data interpretation. All authors have read and approved the final version of the manuscript for publication.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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