

REVIEW ARTICLE

An Overview of Research in the Field of Human Papilloma Virus (HPV) in Iran: a Systematic Review

Shahrzad Nematollahi^{1*}, Mitra Abdoli¹, Fereshteh Aliakbari¹, Arezoo Sheikh-Milani², Mahta Abbasi-Fashami³, Maryam Hosseini¹

1. Men's Health & Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

2. Department of Community health nursing, School of Nursing & Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

3. Student Research Committee, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Received: October 2019; Accepted: October 2019; Published online: December 2019

Abstract: **Introduction:** Human Papilloma Virus (HPV) has many different epidemiological, social and political aspects. The aim of this study was to determine the research priorities according to the necessary aspects of HPV in Iran. **Material and Methods:** The national and international databases were searched to obtain the published articles regarding HPV in Iran. All Epidemiologic studies were included in this review to assess research priorities. **Results:** Of 148 studies involving 14,661 participants, the most studies were conducted in Tehran (44.75%) province. Measuring prevalence of HPV (n=63, 42.5%), diagnosis of HPV by molecular techniques (n=52, 35.1%), Knowledge, Attitude and Practice studies (KAP) (n=13, 8.7%), vaccine efficacy (n=8, 5.4%), cost and cost effectiveness analysis (n=4, 2.7%), co-infection of HPV and sexually transmitted diseases (n=5, 3.3%) were the frequent aims of the included studies. Sixty percent (n=57) of the studies were conducted in clinical patients including patients with cervical cancer (n=30, 52.6%), patients with prostate cancer/Benign Prostate Hyperplasia (n=6, 10.5%), and patients with Esophageal carcinoma (n=5, 8.7%). **Conclusion:** According to our results, the high-risk groups such as female sex workers, injecting drug users and prisoners are in priority for research in the field of HPV. Despite ample epidemiologic studies on prevalence and association of HPV with specific cancers, evidence towards effectiveness and cost-benefits of HPV vaccination is required to prevent the infection and its complicated clinical consequences.

Keywords: Cervical cancer; HPV; Iran

Cite this article as: Nematollahi S, Abdoli M, Aliakbari F, Sheikh-Milani A, Abbasi-Fashami M, Hosseini M. An Overview of Research in the Field of Human Papilloma Virus (HPV) in Iran: a Systematic Review. Mens Health J. 2019; 3(1): e20.

1. Introduction

Human papilloma virus (HPV) is a Sexually Transmitted Infections (STIs) among young and sexually active people that spread through sexual contact (1). Previous studies have demonstrated that highly carcinogen genotypes of HPV are the major cause of cervical cancer. 118 types of HPVs have been detected according to their oncogenic and phylogenetic positions. About 40 HPV viral types observed in the genital tract which belonged to the Alpha papillomavirus genus (2). Also, genital HPV types have been subdivided into low-risk and high-risk types. High-risk types including subtype

16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59,66 and low-risk types are subtype 6 and 11. It is worth noting that HPV-16 is the most prevalent subtype throughout the world followed by HPV18, 45, 31 and 33 subtypes (3). Getting infected by high-risk HPV types is considered a higher risk for cervical cancer development than infection by low-risk HPV types. Implementation of screening programs have reduced the mortality and morbidity of HPV disease (4). HPV infection has different aspects from molecular, epidemiological, social and economic aspects. While we anticipate available scientific knowledge of these aspects, there is limited research information on many of these areas. On another perspective, conducting research requires specialist human, financial resources and time. Therefore, determining research priorities would help us to assign the resources in the required areas HPV and therefore, would contribute to a proper resource allocation. The aim of this study was to determine the epi-

*Corresponding Author: Shahrzad Nematollahi; Address: Men's Health & Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: shrzd.nematollahi@outlook.com



demologic research priorities according to the most important aspects of Human Papilloma-Virus Infection (HPV infection) in Iran.

2. Methods

2.1. Description of studies

The major national and international electronic databases were searched to obtain published re-search in the field of HPV in Iran with the following keywords: HPV, Human Papilloma Virus, and Iran. The international databases searched included, Medline (Jan 1950 to December 2019); Scopus (Jan 1973 to December 2019) and Ovid (Jan 1860 to December 2019). The national databases searched, included Scientific Information Database, MagIran and IranMedex up to December 2019. Inclusion criteria was defined as all studies investigating Human Papilloma Virus (HPV) without any language restriction. Exclusion criteria was defined as those investigating Non-Iranian population, or those whose first or corresponding author was affiliated to institutions/organizations outside Iran. We retrieved 180 studies including 133 references from international databases and 47 from the national databases (Fig. 1). Of these, 10 were excluded because of duplication, 14 were excluded because not related to the Iranian population. At the final phase, 8 studies were excluded including case-reports/series, editorials and letter to editors.

3. Results

We assessed 148 epidemiologic studies that conducted in Iran involved 14,661 participants. The first and last studies in the field of HPV, which included in this study, were published in 2002 and 2019, respectively. The trend of published studies within this period was increasing. The highest proportion of articles (22%) were published in 2011 and 2018. All of included studies were in English language.

3.1. Location

Regarding the location of study, 44.75% of the studies were conducted in Tehran province, which related to Tehran, Shahid Beheshti and Iran universities of Medical Sciences. Mazandaran and Isfahan universities of Medical Sciences had second and third ranks of published papers (12.9% and 9.5%, respectively).

None of the included studies was related to the catchment areas of universities in Arak, Ardebil, Bandar Abbas, Ghom, Ghazvin, Gonabad, Hamadan, Ilam, Kashan, Jahrom, Jiroft, Lorestan, Rafsanjan, Shahrekord, Sari, Sabzevar, Semnan, Shahroud, Zanjan, and Yazd. The lowest proportion of published papers belonged to universities located in border-line provinces such as North Khorasan, Khorasan Razavi,

Boushehr, West Azerbaijan, and Zabol.

3.2. Type of studies

During 2002 to 2019, cross-sectional studies consisted of 42.5% of conducted studies in Iran. Molecular studies and review/systematic review articles were the second and third highest proportion of published papers (35.1% and 13.5%, respectively).

3.3. Study subjects

Forty percent (n=39) of the included studies were conducted in general population while the rest (n=57, 60%) were conducted in clinical patients including patients with cervical cancer (n=30, 52.6%), patients with prostate cancer/Benign Prostate Hyperplasia (n=6, 10.5%), and patients with Esophageal carcinoma (n=5, 8.7%). Sporadic studies also were conducted on other clinical diseases such as patients warts Anal-genital warts (n=4, 7%), Infertile patients (n=2, 3.5%), Squamous cell carcinoma: eye conjunctive (n=1, 1.7%), Gastric carcinoma (n=1, 1.7%), Female Sex Workers (n=1, 1.7%), HIV positive cases (n=1, 1.7%), Lung cancer patients (n=1, 1.7%), Head & neck cancer (n=1, 1.7%), and illicit drug users (n=1, 1.7%).

3.4. Aim of the study

Various research objectives had been pursued by the authors in the field of HPV, which included Prevalence of HPV (n=63, 42.5%), Diagnosis of HPV by Molecular techniques (n=52, 35.1%), Knowledge, Attitude and Practice (KAP) studies (n=13, 8.7%), Vaccine efficacy (n=8, 5.4%), Cost and cost effectiveness analysis (n=4, 2.7%), Co-infection of HPV and STIs (n=5, 3.3%). On the other hand, we found no study on the effectiveness of education programs on prevention of HPV, issues related to survival and mortality of HPV-related cancers, measuring quality of life in HPV patients, studies on stigma and prejudice among HPV patients, and qualitative studies on experience, perception and behavior of HPV patients.

3.5. Recommendation for further studies

Based on the recommendations for more studies, 53% (n=33) authors of cross-sectional studies suggested more studies in the field of HPV. Further studies were also recommended in all the case-control studies (n=8, 100%), and experimental studies (n=2, 100%) (Table 1).

4. Discussion

According to our results, the most published studies were conducted in Tehran province consisting of Tehran, Shahid Beheshti and Iran Universities of Medical Sciences. The remaining studies were mainly belonged to other provinces

such as Mazandaran and Isfahan. Compare to the other parts of the country, population density of Tehran Province is substantially higher, which justifies the higher proportion of research works in Tehran Province. Consequently, the catchment area covered by the universities of medical sciences located in Tehran city is higher compared to other universities across the country.

We found that more than one-third of the research papers in the field of HPV had conducted in general population in Iran while more than half of these papers are in cross-sectional design. Epidemiologic studies on general population are mainly conducted to estimate the prevalence of HPV serotypes, in other words, estimates of natural exposure to types of HPV. Along with estimated prevalence of HPV exposure, cross-sectional studies might provide additional information such as age pattern of infection, geographic variation and high priority groups for HPV screening. This type of information, as a preliminary step, is useful toward planning for HPV vaccination and implementation of proper preventive programs for HPV infection and related clinical disorders(5).

On the other hand, limited studies have conducted on groups of patients, amongst them more than half of the studies conducted in cervical cancer patients. Certain genotypes of Human papillomaviruses (HPVs) are found to be involved in human malignancies. Infection by these specific types of HPV, particularly HPV16 and 18, is reported to be responsible in development of HPV-related cancers. The most HPV-related cancers are associated to infection by high-risk types including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 and 73(6, 7). After the initial infection, tumors progress in the epithelia. Persistent infection with expression of some viral genes, particularly E6 and E7 is needed for development of invasive cancer. However, most HPV infections have a benign outcome because nearly half of them clear within 6 months and up to 2 years the majority of cases clear from infection, but those that persist can progress to cancer(8). On public health perspective, the idea of biologic origin of cancers which led to the discovery of HPV as an important biologic cause of many malignancies is important. Due to the presence of an effective vaccine for HPV, the prevention of HPV-related cancer has become more promising (9, 10).

One of the most important HPV-related malignancies is cervical cancer. Cervical cancer is the third most common gynecologic cancer globally and the eleventh common cancer among Iranian women(11). Persistent infection with high risk human papilloma virus types in the development of cervical intraepithelial neoplasia and cervical cancer has been demonstrated for many years (12). However, epidemiological information is necessary to pave the way for better understanding the population-level mechanism and evaluating the risk of developing neoplasia in women who are found to

be infected with certain types of HPVs in each population.

We found that only one study has reported the prevalence of HPV in breast cancer patients while amongst the molecular studies, 15 (28%) were performed on breast tissues. Breast cancer is reported to be the most frequent malignancy in women globally. A number of risk factors have been associated with breast cancer, including age, obesity and familial history while their minor attribution to pathogenesis of breast cancer has highlighted the need to recognize other factors. The link between HPV and etiology of breast cancer dates back to 1992. The prevalence of HPV infection among women with breast cancer have been reported up to 86.2% (13). It was found that the pathogenicity of HPV on breast cancer depends on HPV genotypes. Therefore, HPV 16, HPV18 and HPV33, which consists of the high risk types are known for 70% of breast cancer cases worldwide (14).

Other studies in Iran have investigated the role of HPV in other morbidities such as STDs. Sexually transmitted infections (STIs) and Sexually Transmitted Diseases (STDs) are major public health concerns worldwide. Youth and high-risk populations have usually been considered to be at an elevated risk for getting STIs(15). This is of particular concern, as untreated STIs may result in infertility, ectopic pregnancy, preterm labor, fetal and neonatal death, cancer, and increased risk for HIV acquisition and transmission(16).

Our results showed that the proportion of studies that conducted on drug addicts, female sex workers, or patients with HIV was low. These groups are hidden, hard-to-reach in Iran. Therefore, more studies should be done in these groups(17). Treatment effectiveness in patients depends to complete adherence in patients who getting HPV vaccination. HPV vaccination is essential to prevention of HPV and decrease in the risk of its transmission. Despite presence of an effective vaccine, limited studies on the effectiveness and cost-benefits of HPV vaccines are conducted in Iran. Only 8 studies (5.4% of all studies) are conducted with the aim to provide enough evidence for HPV vaccination. Given that the quadrivalent Gardasil vaccine is not yet apart of the Iranian national immunization program, cost-effectiveness analysis are highly warranted for new vaccines to determine whether its impact will be great enough to economically benefit the country (18). Better management and treatment of HPV depends heavily on having an overview of knowledge and attitude toward HPV infection in general population. Several studies have indicated that despite the high prevalence of HPV, even among informed people, there is lack of knowledge or false perceptions towards HPV(19). There is evidence that acceptance of HPV vaccination is increased when parents or young women are well informed about its risks and benefits (20). So, knowledge and attitude toward HPV infection and HPV vaccines will greatly influence the success of an immunization program against cervical cancer (20). Our study showed that



nearly 10% of all studies aimed to measure Knowledge, Attitude, and Practice (KAP) regarding HPV prevention. Also, systematic review and meta-analysis have performed in this field. Systematic review and a meta-analysis that conducted on KAP studies in the field of HPV showed that knowledge and attitude of Iranian individual towards prevention of HPV is not satisfactory(21).

More studies in people who living with HPV is necessary to identify factors that could affect prevention of HPV among Iranian patients. Studies that related to HPV patients suggested that more research must perform in this people. These findings emphasize on preventive studies.

Qualitative investigations related with experience, perception and behavior of HPV patients had a low proportion of conducted studies in the field of HPV in Iran. Some aspects of life among people with HPV are better surveyed using qualitative investigations. On the other hand, we propose that qualitative research is useful for evaluation some dimensions of life among people who are living with HPV. Reviews/Systematic reviews and meta-analysis were studies with relatively high proportion. In the category of observational studies, there has been no prospective cohort study on HPV outcomes and complications. Additionally, clinical and field trails, especially in forms of educational interventions, are recommended for evaluation of new treatment or therapeutic options for HPV prevention and control. Epidemiologists and biostatisticians were as the important members of investigation teams for evaluation methodological aspects of these studies.

The recommendations that studies have mentioned for further research include: cost-effectiveness programs for HPV vaccination, increasing knowledge of the general population regarding importance of HPV, the importance of HPV screening for cervical percutaneous lesions, sexual health education specifically for adolescents, the need to diagnose HPV in young females, and the need to screen for HPV in males to prevent prostate cancers. Our results indicated that High risk behavior/ High risk group and co-infection of HPV are the investigation priorities in Iran.

5. Conclusion

According to our results, the high-risk groups such as female sex workers, injecting drug users and prisoners are in priority for research in the field of HPV. Despite ample epidemiologic studies on prevalence and association of HPV with specific cancers, evidence towards effectiveness and cost-benefits of HPV vaccination is required to prevent the infection and its complicated clinical consequences.

6. Appendix

6.1. Acknowledgements

This review was a part of a project entitled: "Delineation of men's health status in Iran during 2009-2019" which is sponsored and supervised by the Men's Health and Reproductive Health Research Centre (MHRHRC). The authors wish to forward their gratitude for the MHRHRC for their sincere collaboration and support.

6.2. Author contribution

SN created the idea and contributed to data extraction and manuscript drafting; MA created the idea, literature review, and manuscript drafting; FA contributed in data extraction, data management and manuscript drafting; ASM and MAF and MH contributed in literature review and manuscript drafting.

6.3. Funding/Support

This study was a part of an ongoing project, with no independent financial support.

6.4. Conflict of interest

None.

References

1. Palmer T, Wallace L, Pollock KG, Cuschieri K, Robertson C, Kavanagh K, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. *bmj*. 2019;365.
2. Eftekhaar NS, Niya MHK, Izadi F, Teaghinezhad-S S, Keyvani H. Human papillomavirus (HPV) genotype distribution in patients with recurrent respiratory papillomatosis (RRP) in Iran. *Asian Pacific Journal of Cancer Prevention: APJCP*. 2017;18(7):1973.
3. Bergman H, Buckley BS, Villanueva G, Petkovic J, Garrity C, Lutje V, et al. Comparison of different human papillomavirus (HPV) vaccine types and dose schedules for prevention of HPV-related disease in females and males. *Cochrane database of systematic reviews*. 2019(11).
4. Sultana F, Winch K, Saville M, Brotherton JM. Is the positive predictive value of high-grade cytology in predicting high-grade cervical disease falling due to HPV vaccination? *International journal of cancer*. 2019;144(12):2964-71.
5. Aghakhani A, Mamishi S, Sabeti S, Bidari-Zerehpooosh F, Banifazl M, Bavand A, et al. Gender and age-specific seroprevalence of human papillomavirus 16 and 18 in general population in Tehran, Iran. *Med Microbiol Immunol*. 2017;206:105-10. DOI 10.1007/s00430-016-0487-5.

6. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens-Part B: biological agents. . *Lancet Oncol*. 2009;10:321-2.
7. Doorbar J, Quint W, Banks L, et al. The biology and life-cycle of human papillomaviruses. . *Vaccine*. 2012;30:55-70.
8. Rodriguez AC, Schiffman M, Herrero R, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. *J Natl Cancer Inst*. 2010;102:315-24.
9. Bae JM, Kim EH. Human papillomavirus infection and risk of breast cancer: a meta-analysis of case-control studies. *Infect Agent Cancer*. 2016;11(14).
10. Karimi M, Khodabandehloo M, Nikkhoo B, Ghaderi E. No Significant Association between Human Papillomavirus and Breast Cancer, Sanandaj, Iran. *Asian Pac J Cancer Prev*. 2016;17(10):4741-5.
11. Jalilvand S, Shoja Z, Hamkar R. Human Papillomavirus Burden in Different Cancers in Iran: a Systematic Assessment. *Asian Pac J Cancer Prev*. 2014;15(17):7029-35.
12. Jamdar F, Farzaneh F, Navidpour F, Younesi S, Balvayeh B, Hosseini M, et al. Prevalence of human papillomavirus infection among Iranian women using COBAS HPV DNA testing. *Infectious Agents and Cancer* 2018;13(6).
13. Mou X, Chen L, Liu F, Shen Y, Wang H, Li Y, et al. Low prevalence of human papillomavirus (HPV) in Chinese patients with breast cancer. *J Int Med Res* 2011;39:1636-44.
14. Haghshenas MR, Mousavi T, Moosazadeh M, Afshari M. Human papillomavirus and breast cancer in Iran: a meta- analysis. *Iran J Basic Med Sci* 2016;19:231-7.
15. Newman L, Rowley J, Vander-Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. . *PLoS ONE*. 2015;10(12):e0143304.
16. Gottlieb SL, Low N, Newman LM, Bolan G, Kamb M, Broutet N. Toward global prevention of sexually transmitted infections (STIs): the need for STI vaccines. . *Vaccine*. 2014;32(14):1527–35.
17. Shahesmaeili A, Karamouzian M, Shokoohi M, Kamali K, Fahimfar N, Nadjji A, et al. Symptom-Based Versus Laboratory-Based Diagnosis of Five Sexually Transmitted Infections in Female Sex Workers in Iran. *AIDS and Behavior*. 2018:doi.org/10.1007/s10461-018-2130-5.
18. Yaghoubi M, Nojomi M, Vaezi A, Erfani V, Mahmoudi S, Ezoji K, et al. Cost-Effectiveness Analysis of the Introduction of HPV Vaccination of 9-Year-Old-GirlsinIran. *Value In Health Regional Issues* 2018;15:112-9.
19. Pourkazemi A, Fakour F, Ghorbani S. Knowledge and attitudes of medical students toward human papilloma virus in Rasht. . *J Guilan Univ of Med Sci*. 2016;25:1–10.
20. Klug SJ, Hukelmann M, Blettner M. Knowledge about infection with human papillomavirus: a systematic review. . *Prev Med* 2008;46:87–98.
21. Taebi M, Riazi H, Keshavarz Z, Afrakhteh M. Knowledge and Attitude Toward Human Papillomavirus and HPV Vaccination in Iranian Population: A Systematic Review. *Asian Pac J Cancer Prev*. 2019;20(7):1945-9. doi: 10.31557/APJCP.2019.20.7.1945.



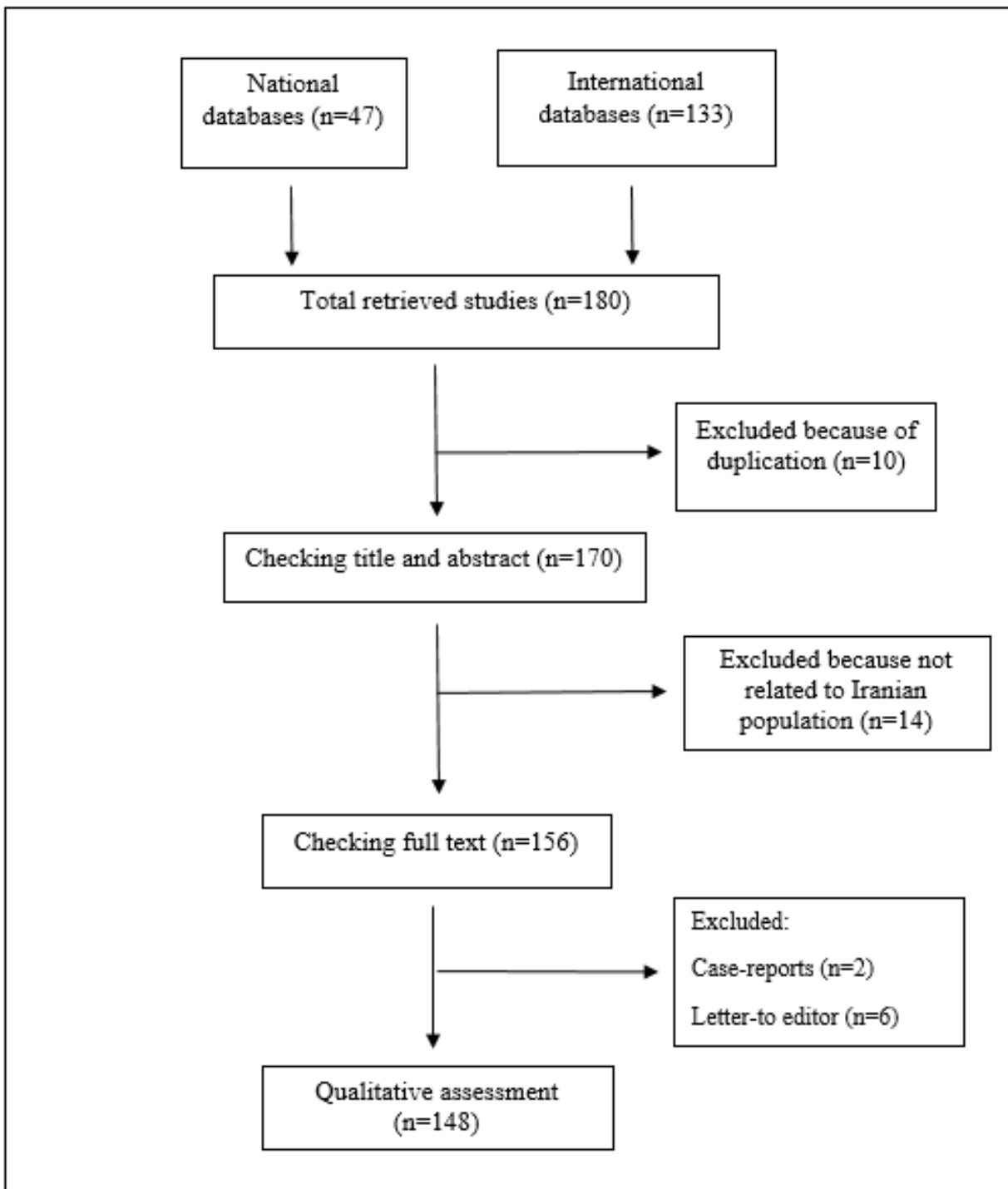


Figure 1: Flowchart of the included studies to determine research priorities in the field of HPV.

Table 1: Distribution of studies according to study type, study population, aim and recommendation for further studies in Iran.

Variable	Freq.	Percent	Recommendation for further studies		
			No N (%)	Yes N (%)	
Type of study	Cross-sectional	63	42.5	30 (47)	33 (53)
	Case-control	8	5.4	0(0)	8 (100)
	Case-series	3	2.0	3 (100)	0(0)
	Prospective cohort	0	0.0	-	-
	Retrospective cohort	0	0.0	-	-
	Laboratory studies	52	35.1	22 (42)	30(58)
	Clinical trial	2	1.3	0 (0)	2(100)
Review/Systematic review	20	13.5	18 (90)	2 (10)	
Study population	General population	39	40.0	0 (0)	39 (100)
	Clinical Patients	57*	60.0	20 (35)	37 (65)
	Cervical cancer	30	52.6	10	20
	Prostate cancer/BPH [‡]	6	10.5	3	3
	Esophageal carcinoma	5	8.7		
	Anal-genital warts	4	7.0		
	Patients with Oral Tumors	2	3.5	2 (100)	0 (0)
	Infertile patients	2	3.5		
	Squamous cell carcinoma: eye conjunctive	1	1.7	0 (0)	1(100)
	Gastric carcinoma	1	1.7	0(0)	1(100)
	Breast cancer	1	1.7	1(100)	0(0)
	Female Sex Workers (FSW)	1	1.7	1(100)	0(0)
	HIV ⁺ patients	1	1.7	1(100)	0(0)
	Lung cancer	1	1.7	0(0)	1(100)
	Head & neck cancer	1	1.7	0(0)	1(100)
Illicit Drug users	1	1.7	1 (100)	0(0)	
Aim of the study	Prevalence of HPV	63	42.5	60 (95.2)	3 (4.8)
	Diagnosis of HPV by Molecular techniques	52	35.1	30 (57.7)	22 (42.3)
	KAP ^Ω study	13	8.7	3 (23)	10 (67)
	Vaccine efficacy	8	5.4	2 (25)	6 (75)
	Cost and cost effectiveness analysis	4	2.7	0 (0)	4 (100)
	Co-infection of HPV and STIs	5	3.3	1 (20)	4 (80)
	High risk behavior/ High risk group	3	2	0 (0)	3 (100)
	Effectiveness of education programs	0	-	-	-
	Survival and mortality	0	-	-	-
	Quality of life	0	-	-	-
	Prevention	0	-	-	-
	Stigma and prejudice	0	-	-	-
	Experience, perception and behavior of patients	0	-	-	-

*excluding molecular studies, [‡] Benign Prostate Hyperplasia, ^Ω Knowledge, Attitude, and Practice study.