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Prevalence and type distribution of human papillomavirus among women older than 18 years in Egypt: a multicenter, observational study☆

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SUMMARY

Objectives: Persistent infection with high-risk (HR) human papillomavirus (HPV) is associated with premalignant lesions and cervical cancer, the third most common cancer amongst women globally and the second most frequent in Egypt. We studied the prevalence and type distribution of HPV and documented HPV infection awareness and health-related behaviours for HPV infection.

Methods: This was a multicenter, hospital-based observational study of women ≥18 years of age who attended for a gynaecological examination during October 2010–August 2011. Cervical samples were tested using Linear Array HPV genotyping. Two questionnaires on awareness and health-related behaviour were completed.

Results: Four hundred and forty-three women with a mean age of 39.3 ± 14.0 years were included in the analysis. HPV DNA was detected in 10.4% of women; a single HPV-type infection was found in 6.5% and multiple infections in 3.8%. The most prevalent HR types among HPV-positive women were HPV-16 (19.6%) and HPV-31 and HPV-51 (15.2% each); low-risk types included HPV-62 (17.4%) and HPV-84 (10.9%). The prevalence of HPV-18 was low (6.5%). The prevalence of any HR HPV-type was highest in women aged 45–54 years (9.2%).

Conclusions: The overall prevalence of HPV in Egypt was 10.4% and was highest (9.2%) amongst women aged 45–54 years. These data provide important reference information for public health authorities considering HPV prevention in Egypt.

1. Introduction

Persistent infection with high-risk human papillomavirus (HPV), a sexually transmitted disease,[1] is a necessary and established cause of cervical cancer.[2] This is the third most frequent cancer in women worldwide; in 2008, an estimated 530 000 new cases were recorded and 275 000 deaths were caused by this cancer.[3] The majority of cervical cancer-related deaths occur in developing countries,[1] such as Egypt where a population of 25.76 million women over 15 years of age are at risk of developing cervical cancer.[4] Indeed, it has been estimated that around 514 women are diagnosed with cervical cancer and 299 die from the disease in Egypt each year; thus cervical cancer ranks as the second most frequent cancer among Egyptian women.[4]

The epidemiological classification of cervical cancer-associated HPV types describes 15 as carcinogenic or high-risk (HR) (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82) and 12 as low-risk (LR) (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108).[5] Of these, HPV-16 and HPV-18 are the two most common HR HPV types. They are responsible for 61% and 10%, respectively, of cervical cancer cases worldwide, and 48% and 23%, respectively, of cervical cancer cases in Africa.[6]

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Two vaccines are currently licensed in many countries around the world, including Egypt, to protect against HR HPV types 16 and 18: Cervarix (bivalent; GlaxoSmithKline, Belgium) and Gardasil (quadrivalent; Merck and Co., Inc., Whitehouse Station, NJ, USA). Both vaccines have good safety and efficacy profiles[7–11] and are reported to provide cross-protection against non-vaccine HPV types.[12] Although both of these vaccines are already licensed in Egypt,[4] they are currently not included in the national immunization program.[13] In order to measure the impact of implementing a nationwide policy for HPV prevention, baseline epidemiological data are required. However, current epidemiological data for HPV in Egyptian women are limited, and only a few publications on HPV prevalence and attitudes towards and awareness of the infection are available.[14–16] To bridge this gap and provide baseline data, we evaluated the prevalence and type distribution of HPV, including HR and LR types, among Egyptian women attending routine gynaecological examinations in different age strata, and documented awareness of HPV infection and health-related behaviours for HPV infection.

2. Methods

2.1. Study design and population

This multicenter, observational study was carried out at two hospitals (Al Kasr Al Aini University Hospital, Cairo, and Ain Shams University Hospital, Cairo) and an outpatient clinic (Alexandria University Hospital, Alexandria) between October 2010 and August 2011. The study hospitals are tertiary university hospitals and treat patients within their catchment areas as well as patients from primary healthcare centres and secondary hospitals (including regional hospitals).

Women aged ≥18 years undergoing routine gynaecological examination and willing to provide a cervical sample were enrolled. Known diagnoses of immunosuppression, previous HPV vaccination, hysterectomy, pregnancy, or referral for an abnormal cervical sample were all reasons for exclusion. Two validated questionnaires were completed by all subjects enrolled: one on 'health-related behaviours' to solicit information about smoking, marriage history (e.g., age at first marriage), contraception, and reproductive history (parity), and the other to elicit information on HPV awareness, in order to assess the level and accuracy of understanding regarding the cause, transmission, and prevention of HPV infection. These 'knowledge–attitudes–practices' questionnaires were designed by a multidisciplinary team. The questionnaires were initially tested on 50 women in a short interview lasting for approximately 20 min and were subsequently provided to all enrolled women by the investigators.

2.2. Sample collection and laboratory procedures

Cervical samples were collected by a gynaecologist/trained health practitioner using a cytobrush and placed in a liquid-based cytology medium (Thinprep, Hologic, Inc.). A 2-ml sample was subsequently stored at −20 °C and analyzed for the presence of HPV DNA using Linear Array HPV genotyping at Al Mokhtabar Laboratory, Cairo, Egypt. This technique, based on the L1 consensus primer PGMY09/11 for PCR amplification of HPV DNA and reverse-line blot hybridization, was used for the detection of 37 individual HPV genotypes.[17]

2.3. Statistical analyses

The primary objective was to describe the overall prevalence and types of HPV (including multiple infections) among women ≥18 years of age. Secondary objectives were to investigate HPV type prevalence amongst women in different age groups and to describe health-related behaviours. Based on an overall HPV prevalence of 15%[16] and allowing for 10% of non-evaluable samples, to give an overall estimate of HPV prevalence with 95% confidence and a precision level of 0.035, a total of 440 subjects were required, with at least 80 in each age-group (18–24, 25–34, 35–44, 45–54, and ≥55 years of age). The percentage of HPV-positive women in each category was tabulated with corresponding exact 95% confidence intervals (CI). A description of subject characteristics (i.e., educational level, age at first marriage, number of marital partners, parity, and smoking status) and HPV status is provided, including the 95% confidence intervals for the prevalence of these characteristics. All statistical analyses were undertaken using *SAS* version 9.2 statistical analysis software.

2.4. Ethical considerations

The study was approved by the National Ethics Committee of the Egyptian Ministry of Health and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. Informed consent was obtained from all eligible women before starting the study.

3. Results

3.1. Study population

Of the 1156 women aged ≥18 years who visited the practice, a total of 490 provided a cervical sample and were enrolled in the study. Cervical samples were not collected or tested in 47 cases, leaving 443 women in the final analysis, all of whom completed both questionnaires. The mean ± standard deviation (SD) age of women was 39.3 ± 14.0 years and the majority (78.6%) lived in urban areas. The baseline characteristics of women enrolled in the study are shown in Table 1.

Table 1
Baseline characteristics ($N = 443$[a])

Characteristics	Categories	n[b]	n'[c]	%	95% CI (LL–UL)
Education level	No formal education	88	7	8.0	3.3–15.7
	Primary	140	17	12.1	7.2–18.7
	Secondary	143	15	10.5	6.0–16.7
	Post-secondary/ university	72	7	9.7	4.0–19.0
Parity	0	87	10	11.5	5.7–20.1
	1–2	153	14	9.2	5.1–14.9
	3–5	183	18	9.8	5.9–15.1
	≥6	20	4	20.0	5.7–43.7
Age at first marriage, years	≤16	20	0	0.0	0.0–16.8
	17–19	173	21	12.1	7.7–18.0
	20–22	155	17	11.0	6.5–17.0
	≥23	95	8	8.4	3.7–15.9
Number of marital partners	1	419	41	9.8	7.1–13.0
	2–5	24	5	20.8	7.1–42.2
Smoking status	No	422	42	10.0	7.3–13.2
	Yes	21	4	19.0	5.4–41.9

95% CI, exact 95% confidence interval; LL, lower limit; UL, upper limit.
[a] Number of subjects whose cervical samples were tested.
[b] Number of subjects whose cervical samples were tested and who answered the health-related behavior questionnaire.
[c] Number of HPV-positive subjects in the given category.

3.2. Overall HPV prevalence and type distribution

HPV DNA was detected in 10.4% (46/443) of women, of whom 6.5% were infected with a single HPV type and 3.8% with multiple HPV types. The overall prevalence of any HR HPV type was 6.5% (predominantly HPV-16 (2.0%), HPV-31 (1.6%), and HPV-51 (1.6%)) compared with 5.0% for any LR HPV type (predominantly HPV-62 (1.8%), HPV-84 (1.1%), and HPV-6 (0.7%)) (Table 2).

3.3. HPV prevalence and type distribution among HPV-positive women

The prevalence of any HR HPV type was 63.0% (95% CI 47.5–76.8; 29/46) and the prevalence of any LR HPV type was 47.8% (95% CI 32.9–63.1; 22/46).

The most prevalent HR HPV types were HPV-16 (19.6%), HPV-31 and HPV-51 (15.2%, each), and HPV-52 (13.0%). LR HPV types HPV-62 (17.4%), HPV-84 (10.9%), and HPV-6 (6.5%) were prevalent among women positive for HPV. The prevalence of HPV-18 was low (6.5%).

3.4. HPV prevalence and type distribution by age

The overall prevalence of HPV infection was highest (13.2%, 12/91) in women aged 18–24 years. The prevalence of any HR HPV type was highest (9.2%, 8/87) in the 45–54 years age group, while the prevalence of any LR HPV type was highest (9.2%, 8/87) in women aged 35–44 years (Figure 1).

The type distribution of HPV by age is summarized in Table 3. The highest number of HR HPV type 16 infections was observed in women aged ≥55 years, followed by those in the 18–24 years age group.

Table 2
HPV prevalence and type distribution (N = 443[a])

HPV prevalence/types	n[b]	%[c]	95% CI (LL–UL)
HPV-negative	397	89.6	86.4–92.3
HPV-positive	46	10.4	7.7–13.6
Single infection	29	6.5	4.4–9.3
Multiple infections	17	3.8	2.3–6.1
Any high-risk HPV	29	6.5	4.4–9.3
HPV-16	9	2	0.9–3.8
HPV-31	7	1.6	0.6–3.2
HPV-51	7	1.6	0.6–3.2
HPV-52	6	1.4	0.5–2.9
HPV-59	5	1.1	0.4–2.6
HPV-18	3	0.7	0.1–2
HPV-58	3	0.7	0.1–2
HPV-66	2	0.5	0.1–1.6
HPV-56	1	0.2	0–1.3
HPV-73	1	0.2	0–1.3
Any low-risk HPV	22	5	3.1–7.4
HPV-62	8	1.8	0.8–3.5
HPV-84	5	1.1	0.4–2.6
HPV-6	3	0.7	0.1–2
HPV-40	2	0.5	0.1–1.6
HPV-CP6108	2	0.5	0.1–1.6
HPV-26	1	0.2	0–1.3
HPV-53	1	0.2	0–1.3
HPV-61	1	0.2	0–1.3
HPV-67	1	0.2	0–1.3
HPV-70	1	0.2	0–1.3
HPV-81	1	0.2	0–1.3
HPV-83	1	0.2	0–1.3

HPV, human papillomavirus; 95% CI, exact 95% confidence interval; LL, lower limit; UL, upper limit.
[a] Number of subjects whose cervical samples were tested.
[b] Number of subjects in a given category.
[c] b/number of subjects with available results × 100.

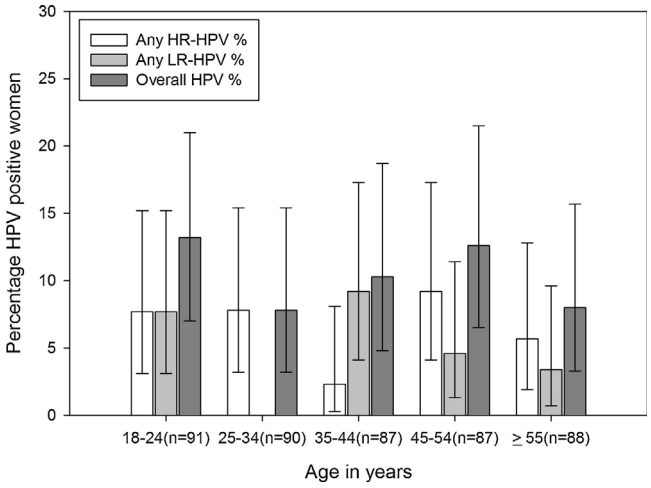

Figure 1. HPV type distribution among women with a single or multiple HPV type infection by age (N = 443; number of subjects whose cervical samples were tested).

3.5. HPV co-infection

Overall, 37.0% (17/46) of HPV-positive women were co-infected with more than one HPV type. Four out of nine HPV-16-positive women (44.4%) were co-infected with other HR HPV types and one out of three HPV-18-positive women (33.3%) was co-infected with other HR HPV types.

3.6. HPV prevalence by risk factors

Data derived from the completed questionnaires indicated that most women (90.1%) were married; 32.3% had received secondary education and 16.3% had undertaken post-secondary/university level education (Table 1).

The assessment of health-related behaviours (age at first marriage, number of marital partners, parity, education, and smoking status) did not show major differences between HR and LR HPV infections (Table 1).

3.7. HPV awareness questionnaire

The awareness questionnaire indicated that 33.2% of women had previously received information about HPV and almost 99% expressed an interest in vaccination (Table 4).

4. Discussion

This is the most recent study to estimate the prevalence and type distribution of HPV in Egyptian women aged at least 18 years. In our study, conducted at three large hospitals, 10.4% of women attending routine gynaecological examinations were found to be HPV-positive, which is comparable to the overall prevalence reported previously in Egypt (10.3%[4] and 15%[16]), Northern Africa (10.9%),[18] and globally (11.4%).[4]

In this study, HPV-16, 31, and 51 were the most prevalent HR HPV types, and HPV-62, 84, and 6 were the most prevalent LR HPV types, which is consistent with the global circulating HPV types.[6,18] In contrast to the worldwide estimates that HPV-16 and 18 are responsible for nearly 70% of cervical cancer cases,[6] our study showed a relatively low (0.7%) prevalence of HPV-18 in Egyptian women.

Our study found that the prevalence of HR HPV types was highest in women aged 45–54 years, which is consistent with the global trend of higher disease burden in older women.[18] We also noted a higher prevalence of HR-HPV type 16 in women

Table 3
Distribution of HPV types among subjects with single or multiple HPV infections by age ($N = 443$[a])

HPV types	18–24 years (n[b] = 91)			25–34 years (n = 90)			35–44 years (n = 87)			45–54 years (n = 87)			≥55 years (n = 88)		
	n'[c]	%[d]	95% CI (LL–UL)	n'	%	95% CI (LL–UL)	n'	%	95% CI (LL–UL)	n'	%	95% CI (LL–UL)	n'	%	95% CI (LL–UL)
Any high-risk HPV	7	7.7	3.1–15.2	7	7.8	3.2–15.4	2	2.3	0.3–8.1	8	9.2	4.1–17.3	5	5.7	1.9–12.8
HPV-16	3	3.3	0.7–9.3	1	1.1	0–6	1	1.1	0–6.2	1	1.1	0–6.2	3	3.4	0.7–9.6
HPV-18	1	1.1	0–6	0	0	0–4	0	0	0–4.2	1	1.1	0–6.2	1	1.1	0–6.2
HPV-31	1	1.1	0–6	1	1.1	0–6	1	1.1	0–6.2	4	4.6	1.3–11.4	0	0	0–4.1
HPV-51	3	3.3	0.7–9.3	1	1.1	0–6	0	0	0–4.2	2	2.3	0.3–8.1	1	1.1	0–6.2
HPV-52	0	0	0–4	1	1.1	0–6	1	1.1	0–6.2	4	4.6	1.3–11.4	0	0	0–4.1
HPV-56	1	1.1	0–6	0	0	0–4	0	0	0–4.2	0	0	0–4.2	0	0	0–4.1
HPV-58	1	1.1	0–6	2	2.2	0.3–7.8	0	0	0–4.2	0	0	0–4.2	0	0	0–4.1
HPV-59	1	1.1	0–6	3	3.3	0.7–9.4	1	1.1	0–6.2	0	0	0–4.2	0	0	0–4.1
HPV-66	0	0	0–4	1	1.1	0–6	0	0	0–4.2	1	1.1	0–6.2	0	0	0–4.1
HPV-73	0	0	0–4	0	0	0–4	0	0	0–4.2	1	1.1	0–6.2	0	0	0–4.1
Any low-risk HPV	7	7.7	3.1–15.2	0	0	0–4	8	9.2	4.1–17.3	4	4.6	1.3–11.4	3	3.4	0.7–9.6
HPV-6	1	1.1	0–6	0	0	0–4	0	0	0–4.2	0	0	0–4.2	2	2.3	0.3–8
HPV-26	0	0	0–4	0	0	0–4	1	1.1	0–6.2	0	0	0–4.2	0	0	0–4.1
HPV-40	1	1.1	0–6	0	0	0–4	0	0	0–4.2	1	1.1	0–6.2	0	0	0–4.1
HPV-53	0	0	0–4	0	0	0–4	0	0	0–4.2	1	1.1	0–6.2	0	0	0–4.1
HPV-61	0	0	0–4	0	0	0–4	1	1.1	0–6.2	0	0	0–4.2	0	0	0–4.1
HPV-62	4	4.4	1.2–10.9	0	0	0–4	1	1.1	0–6.2	2	2.3	0.3–8.1	1	1.1	0–6.2
HPV-67	0	0	0–4	0	0	0–4	1	1.1	0–6.2	0	0	0–4.2	0	0	0–4.1
HPV-70	0	0	0–4	0	0	0–4	1	1.1	0–6.2	0	0	0–4.2	0	0	0–4.1
HPV-81	1	1.1	0–6	0	0	0–4	0	0	0–4.2	0	0	0–4.2	0	0	0–4.1
HPV-83	0	0	0–4	0	0	0–4	1	1.1	0–6.2	0	0	0–4.2	0	0	0–4.1
HPV-84	2	2.2	0.3–7.7	0	0	0–4	2	2.3	0.3–8.1	1	1.1	0–6.2	0	0	0–4.1
HPV-CP6108	0	0	0–4	0	0	0–4	2	2.3	0.3–8.1	0	0	0–4.2	0	0	0–4.1

95% CI, exact 95% confidence interval; LL, lower limit; UL, upper limit.
[a] Number of subjects whose cervical samples were tested.
[b] Number of subjects who underwent cervical sample testing in each age stratum.
[c] Number of subjects infected with a given HPV type.
[d] $c/b \times 100$.

aged at least 55 years, which again is consistent with global reports, where the mean age of women with cervical cancer caused by HPV-16 is 50.0 years.[6] However, further testing of the cervical specimens might be required to ascertain if these women have cervical diseases.

Analysis of the health-related behaviour questionnaire revealed that age at first marriage, number of lifetime partners, parity, and smoking status were not reported more frequently for HPV-16, HPV-18, or any HR HPV infection. A previously conducted two-series study by the International Agency for Research on Cancer observed no association between education level and HPV infection.[19] Although 19.9% (88/443) of women included in the present study had not received any formal education, HPV prevalence among these women was low (8%), while the prevalence was higher in those who had received primary, secondary, or post-secondary/university education (12.1%, 11.0%, and 9.7%, respectively); however, all 95% CI overlapped, thus strong conclusions on the difference cannot be drawn.

Data from the HPV awareness questionnaire indicated that few women (33.2%) had previously heard of HPV. These findings are consistent with previous studies that noted a low awareness of HPV and its link to cervical cancer amongst Egyptian women. Indeed, only about 1.5% of women from urban areas have routine Pap tests.[14] Of interest is that almost all women who completed the questionnaire expressed an interest in vaccination.

In 2006, the Middle East Cancer Consortium published statistics from four Middle Eastern countries (Egypt, Jordan, Cyprus, and Israel) on population-based registry data.[20] The Tanta registry for Egypt (1999–2001) reported an age-adjusted standardized incidence rate of 2.7 for cervical cancer compared with the higher rates of 5.3 in Israeli Jews and 3.7 in Cypriots and the lower rates of 2.6 in Jordanians and 2.5 in Israeli Arabs (per 100 000 females).[20] Data from Globocan estimated the age-standardized incidence and mortality rates per 100 000 females for cervical cancer in Egypt as 1.6 and 1.3, respectively, as compared with 6.6 and 4.0, respectively, in North Africa and 9.0 and 5.8, respectively, in the Eastern Mediterranean region.[21] Although these data indicate that the rates of incidence of cervical cancer and the associated mortality are lower in Egypt than in some of the neighbouring countries,[20,21] cervical cancer indeed causes a substantial disease burden in Egypt. In addition, since the detection rate of cervical cancer at an early stage (stage I and/or II) in Egypt is much lower (36%) as compared to that in the USA (60%),[22] there is a possibility of some cervical cancer cases and deaths not being reported or diagnosed. Therefore early detection and preventive strategies are necessary to reduce the disease burden of cervical cancer in Egypt.

Both the bivalent and quadrivalent vaccines provide protection against HR HPV-16 and HPV-18 and have been reported to provide cross-protection against non-vaccine HR HPV-31, 33, 45, 52, or 58.[7–12] Since we found additional HR HPV types circulating in the country, cross-protective properties of these vaccines might protect Egyptian women from cervical cancers and pre-cancer lesions.

Our study had some limitations. Firstly, the study was cross-sectional, and as HPV infections may be transient and resolve on their own, the prevalence of HPV might therefore change over time. Secondly, since the cervical samples were collected only from women attending routine gynaecological visits, there is a possibility of selection bias. Lastly, since the number of women positive for HPV infection was indeed low ($n = 46$), our results need to be interpreted with caution.

Despite these limitations, the study had several strengths. The high quality DNA testing at a single laboratory using a standardized test for all samples ensured the collection of robust data while avoiding variability across different laboratories. Also, this was a multicentre study conducted in three large hospitals. The participating hospitals were tertiary university hospitals

Table 4
Awareness of HPV infection among subjects ($N = 443$[a])

Characteristics	Categories	n[b]	%[c]
How frequent is cervical cancer in women?	Very frequent	71	16.0
	Frequent	94	21.2
	Rare	210	47.4
	Not sure	67	15.1
	Missing	1	0.2
What do you think is/are the main reasons for cervical cancer?[d]	Abnormal cells growing inside the body	79	17.8
	Bacterial infection	54	12.2
	Viral infection	144	32.5
	None	52	11.7
	Not sure	114	25.7
Which among these can cause cervical cancer?[d]	Persistent infection with HPV	44	9.9
	Rous sarcoma virus	13	2.9
	Hereditary/genetic factors	242	54.6
	None	37	8.4
	Not sure	107	24.2
What do you think can turn into cervical cancer[d]	Genital warts	88	19.9
	Bacterial infection	43	9.7
	Viral infection	113	25.5
	Fungal infection	41	9.3
	None	51	11.5
	Not sure	107	24.2
Apart from avoiding unwanted pregnancy, what would you think can happen with the use of contraceptive pills[d]	Protects against cervical cancer	79	17.8
	Increases the risk of cervical cancer	68	15.3
	No ill effect at all	66	14.9
	Not sure	230	51.9
Did you hear about HPV before?	Yes	147	33.2
	No	296	66.8
If yes[d]	General physician	33	7.4
	Friend or family member	41	9.3
	Internet	32	7.2
	TV/magazine/newspaper	41	9.3
How is HPV transmitted?[d]	Contaminated food/water	80	18.1
	Mosquito bite	32	7.2
	Sexually	98	22.1
	None	38	8.6
	Not sure	192	43.3
How is cervical cancer diagnosed?[d]	Pap smear test (Papanicolaou test)	30	6.8
	Colposcopy	22	5.0
	Biopsy sample testing (histological)	186	42.0
	All above	43	9.7
	None	18	4.1
	Not sure	144	32.5
Is it possible to prevent cervical cancer?	Yes	125	28.2
	No	167	37.7
	Not sure	151	34.1
If yes[d]	Through cancer vaccine	25	5.6
	Through responsible sexual behavior	22	5.0
	Through cervical screening	47	10.6
	Through condom use	31	7.0
If the vaccine against cervical cancer was available, would you be interested in getting vaccinated?	Yes	441	99.5
	No	2	0.5

HPV, human papillomavirus;
[a] Number of subjects whose cervical samples were tested.
[b] Number of subjects in the specified category for whom the questionnaire data were collected.
[c] Percentage of subjects in the specified category for whom the questionnaire data were collected.
[d] Subjects could have selected more than one option.

which treated the population living in the region. Finally, the questionnaires were completed by all enrolled women and therefore provided a good dataset for analysis.

In conclusion, the results from our study provide important reference data for public health officials when formulating future strategies, including vaccination programs, to prevent HPV-associated complications in Egypt. Further analysis on the potential health and economic impact of preventive actions will be necessary to complement our data.

Trademarks

Cervarix is a trademark of the GlaxoSmithKline group of companies. Gardasil is a trademark of Merck & Co., Inc. Thinprep is a trademark of Hologic, Inc. Linear Array HPV Genotyping Test is a trademark of Roche Molecular Systems, Inc.

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Author contributions: MFS, HNS, MA, FM, HH, AI, and MES were involved in the conception and design of the study. HR has collected the data. KG was involved in the collection of data and in collaboration with, RD performed the analysis and interpretation of the study results. All authors have had access to data, reviewed and approved the final manuscript before submission.

Conflict of interest: Authors MFS, FM, HNS, and MES received fees from GlaxoSmithKline group of companies for the conduct of the study; KG and RD are employed by the GlaxoSmithKline group of companies and RD has stock options; MA, HH, AI, and HR have no conflicts of interest to declare.

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