RESEARCH ARTICLE

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Association between Prestored Smartphone Monitored Physical Activity and the Risk of HPV Infection and Cervical Cancer

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Abstract

Objective: This study was to determine the prevalence of HPV in non-vaccinated women from East China, and the association between prestored smartphone monitored physical activity and the risk of human papillomaviruses (HPV) infection and cervical cancer. **Methods:** We retrospectively reviewed medical records of unvaccinated women received first-time cervical HPV screening in the Affiliated Cancer Hospital of University of Chinese Academy of Sciences between March 2018 and December 2019. HPV genotyping was examined by the GenoArray. Physical activity defined by any movements at speeds of 0.5-2 m/s was obtained from smartphones. We collected prestored physical activity data for 6 months prior to the HPV screening. Logistic regression models were applied to determine the association between physical activity and the risk of HPV infection and cervical cancer. **Results:** A total of 11,730 women were initially included. Women with cervical cancer had significantly higher prevalence of infection with any high-risk (HR) HPV, or with individual HPV16, 18, 31, 33, 45, 52 and 58. Among them, 896 controls and 289 cervical cancer women had information of smartphone monitored physical activity. Multivariate logistic regression analysis showed that more daily physical activity time (or distance) was a protective factor for infection with any HR HPV, or infection with HPV16, but not other individual HPVs. Increased age, less physical activity time (or distance), and infection with any HR HPV (16, 18, 31, 52 and 58) were associated with a significantly increased risk of cervical cancer. In contrast, obesity was not associated with risk of HPV infection and cervical cancer. **Conclusion:** The high prevalence of HPV infection in unvaccinated women highlights the importance of prevention. More daily physical activity time (or distance) may help to reduce the risk of HPV infection and cervical cancer. Smartphone monitoring is an effective tool for recording physical activity.

Keywords: Cervical cancer- HPV- physical activity- age- obesity- smartphone

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Introduction

Cervical cancer ranks as the fourth most common malignancy, and lead to 311,000 deaths in women in 2018 worldwide (Arbyn et al., 2020). As the top two countries with the largest populations, China and India contribute to over a third of these new cases and cancer deaths (Arbyn et al., 2020). In the USA, cervical cancer continues to be the second leading cause of cancer death in women aged 20 to 39 years. Though its overall incidence has declined for decades, the disease at distant stage is increasing (Islami et al., 2019).

Almost all cervical cancer cases are linked to infection with high-risk human papillomaviruses (HPV), an extremely common virus transmitted through sexual contact (Munoz et al., 2003; Burchell et al., 2006). A large-scale epidemiological survey reported that 90% of American women experience HPV infection at least once in their life (Revzina and Diclemente, 2005). HPV is a double-stranded DNA virus without enveloped icosahedral capsids. More than 200 HPV genotypes have thus far been identified (Burd, 2016). Based on their capacity in cancer development, HPVs are commonly divided into high-risk (HR) or low-risk (LR). These HR subtypes include HPV16, 8, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68, causing more than 96% cervical cancers (Arbyn et al., 2014; Burd, 2016). Infection of LR genotypes, such as HPV6 and HPV11, causes benign or low-grade changes in cervix (Munoz et al., 2003). The most well-established protective factors are cervical cancer screening and vaccination HPVs. Identification of other modifiable risk factors is important to reduce the risk of cervical cancer and improve the management of the disease.

A few studies have presented the beneficial impact of physical activity on cervical intraepithelial neoplasia, a precancerous condition, has been reported in several studies (Lee et al., 2013; Chang et al., 2020). The metabolic equivalent of task (MET) is a unit to estimate

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caloric expenditure by the body. It is reported that regular leisure-time physical activity of ≥7.5 MET-h/week and sustained lifetime leisure-time physical activity ≥13.2 MET-h/week–year were associated with a reduced risk of cervical neoplasia (Chang et al., 2020). Another study enrolled a cohort of 543 normal, 382 women with cervical intraepithelial neoplasia and 300 women with cervical cancer. Compared with the low physical activity (<38.5 MET-h/week), medium (38.5-71.9 MET-h/week) and high physical activity (72 MET-h/week or more) was associated with reduced risk of cervical intraepithelial neoplasia 2/3 in Korean women after adjusting other confounders (Lee et al., 2013). Furthermore, prolonged sitting time was significantly associated with increased risk of cervical intraepithelial neoplasia (Chih et al., 2013; Szender et al., 2016). However, Szender et al reported no association between occupational-related physical inactivity and cervical cancer (Szender et al., 2016). The role of physical activity in the prevention of cervical cancer in women has not been well investigated.

Moderate physical activity has been associated with lower risk of several types of cancers and other chronic diseases (Patel et al., 2015; Marques et al., 2018; Bascioni et al., 2019; Patel et al., 2019; Matthews et al., 2020; Thomas et al., 2021) and the all-cause mortality (Patel et al., 2018; Lee et al., 2019). Smartphones have become popularized worldwide in the past decade which have many native features to automatically record the physical activity (Bort-Roig et al., 2014). This current study was to first examine the prevalence of HPV in unvaccinated women and then to determine the association between smartphone monitored physical activity and the risk of HPV infection and cervical cancer. Particularly, the smartphone monitored physical activity data was obtained a half year prior to subjects' participation in this study.

Materials and Methods

Patients and methods

We reviewed medical records of participants underwent HPV screening at the Affiliated Cancer Hospital of the University of Chinese Academy of Sciences between March 2018 and December 2019. The detailed inclusion criteria were: (1) aged 18–85, physically and psychologically competent; (2) unvaccinated with no previous HPV screening; (3) sexually active; (4) cervix intact, (5) cervical specimen adequate for HPV DNA testing and pathological diagnosis. Exclusion criteria included: (1) prior history of gynecological cancers; (2) cervical intraepithelial neoplasia; (3) a chronic disease such as renal failure or cardiovascular disease. Cervical specimens were collected by a gynecological practitioner using plastic cervical brushes (Xing et al., 2021). Diagnosis of cervical disease was based on the 2015 American Society of Gynecological Oncology (SGO) and American Society of colposcopy and cervical pathology (ASCCP) interim guidelines for cervical cancer screening. Based on BMI cutoff value for Chinese women (Zhou and Cooperative Meta-Analysis Group of the Working Group on Obesity in, 2002), subjects were defined into underweight (<18.5 kg/m^2), normal (18.5-23.9 Kg/ kg/m^2), overweight (24~27.9 kg/m^2) and obesity (>28.0 kg/kg/m^2).

HPV detection and genotyping

DNA extracts from Exfoliated cervical cells were prepared with the QIAamp DNA Blood Mini kit 3 (Qiagen, Inc., Shanghai, China). The HPV GenoArray Test kit (HybriBio Ltd., Chaozhou, China) was used to genotype 13 HR HPV genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) and 7 LR HPV genotypes HPV6, 11, 42, 43, 44, 53, 66 and cp8304) following the manufacturer's instructions (Tao et al., 2012). Quality controls were performed throughout the experiments, including DNA extracting, amplification and hybridization. Both positive and negative controls were applied for PCR reactions.

Acquisition of smartphone monitored physical activity

Physical activity of these women with HPV screening was acquired based on their smartphone movements tracked by both GPS and wireless network base stations. The smartphone monitored movements were routinely recorded and stored in a cloud database. Physical activity was defined as any movements at speeds ranging from 0.5 to 2m/s (LaRoche et al., 2011). Both the time and corresponding distances of these movements were obtained. To avoid compromising privacy, no localization information was collected from the database. The data of the entire half year before the HPV screening was gathered to better represent participants' habitual physical activity.

The protocol was approved by the Ethics Committee of Zhejiang Cancer Hospital (approval no. IRB 2019 75). Written informed consent was obtained from all participants prior to the start of the study.

Statistical analysis

The Student T test was applied to compared means of continuous data between two groups. Categorical data were compared by Pearson $\chi 2$ or Fisher exact tests as appropriate. Linear regression was used to examine the correlation between averaged daily physical activity time and distance, and between averaged daily physical activity time and BMI, and between averaged daily physical activity distance and BMI. Univariate and multivariate logistic regression was applied to determine the correlation between variables and the risk of HPV infection or cervical cancer. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. The logistic regression model was applied to generate receiver-operating characteristic (ROC) curves and estimate the area under the ROC curve (AUC). Double-sided $P < 0.05$ was considered to be statistically significant. All data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Prevalence of HPV in unvaccinated women undergoing first-time HPV screening

A total of 11,730 women were enrolled in this study. Among them, 7383 (62.9%) were healthy controls and 4347 (37.1%) were diagnosed with cervical cancer.

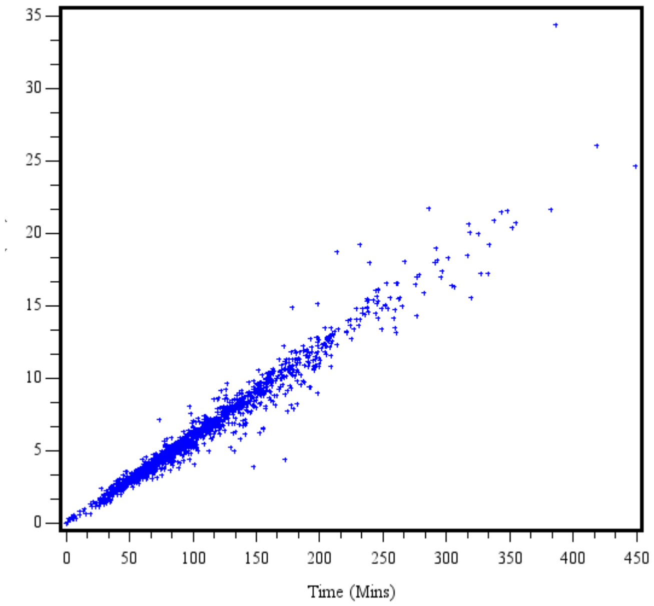

Figure 1. Linear Regression Analysis Showed Significant Correlation between Average Daily Physical Activity Time and Distance in Both Control and Women with Cervical Cancer (R^2=0.9348, P<0.0001)).

Their mean ages were 49.2 ± 11.4 and 53.1 ± 11.4 years (P<0.0001), respectively (Supplemental data Table S1). Healthy controls had a significantly higher proportion of participants at a younger age, and correspondingly less at older ages compared with women with cervical cancer (P<0.0001).

The overall prevalence was 60.9% for any positive HPV, and 52.6% for any positive HR HPV infection (Table 1). In healthy controls, the prevalence of any HPV and any HR HPV infection was 37.9% and 36.8%, respectively. In contrast, all women with cervical cancer (100%) had infections with any HPV and 79.5% of them had infections with any HR HPV. The top common HPVs were HPV16 (25.4%), 58 (9.8%), 52 (6.5%), 18 (5%), 33 (3.4%) and 31 (2.6%). The prevalence of HPV16 (49.7 vs 11.1%), 18 (9.3 vs 2.4%), 31 (3.6 vs 2,0%), 33 (4.3 vs 2.8%), 45 (0.9 vs 0.5%), 52 (7 vs 5.8%) and 58 (12.3 vs 8.3%) was significantly higher in women with cervical cancer than in healthy controls (Table 1).

Multivariate logistic regression analysis showed that older age and infection with HPV16, 18, 33, 45, 52, 58 and 59 were significantly associated with an increased risk of cervical cancer. If any HR HPV infection was used as a risk factor, our result revealed that infection with HR HPV and older age were significantly associated with an increased risk of cervical cancer (Table 2).

Participants with physical activity information

Only 1185 of the participants had a smartphone that recorded half a year's physical activity before the screening. Among them, 896 women were healthy controls and 289 women had cervical cancer. Control women were significantly younger than cervical cancer women (47.4 ± 9.3 vs 51.5 ± 10.5 years, P<0.0001) (Table 3).

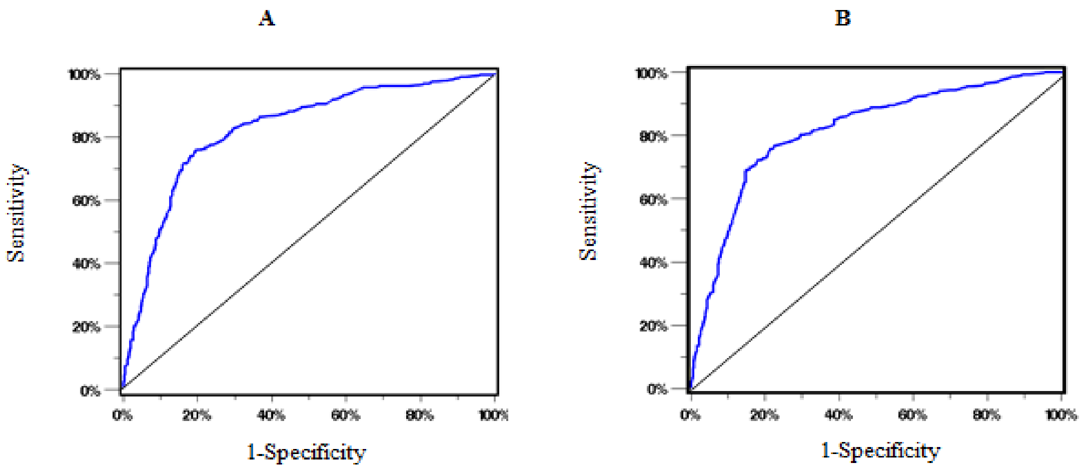

Figure 2. Receiver-operating Characteristic (ROC) Curve of Factors for Predicting the Risk of Cervical Cancer. (A), Plot for physical activity time as a risk factor with an AUC of 0.8258; (B), Plot for physical activity distance as a risk factor with an AUC of 0.8165.

Table 1. Prevalence of HPVs in Unvaccinated Women Undergoing First-Time Cervical Screening

Variable	Overall	Control women n (%)	Women with cervical cancer n(%)	P
Any HPVs				
Negative	4587 (39.1)	4587 (62.1)	0 (0)	<0.0001
Positive	7143 (60.9)	2796 (37.9)	4347 (100)	
Single positive	2960 (25.2)	2086 (28.3)	874 (20.1)	<0.0001
Multiple positive	4183 (35.7)	710 (9.6)	3473 (79.9)	
HR HPV				
Negative	5556 (47.4)	4664 (63.2)	892 (20.5)	<0.0001
Positive	6174 (52.6)	2719 (36.8)	3455 (79.5)	
Single positive	4739 (40.4)	2053 (27.8)	2686 (61.8)	<0.0001
Multiple positive	1435 (12.2)	666 (9)	769 (17.7)	
LR HPV				
Negative	11520 (98.2)	7250 (98.2)	4270 (98.2)	0.9055
Overall positive	210 (1.8)	133 (1.8)	77 (1.8)	
Single positive	204 (1.7)	130 (1.8)	74 (1.7)	0.7847
Multiple positive	6 (0.1)	3 (0)	3 (0.1)	
HPV16				
Negative	8748 (74.6)	6561 (88.9)	2187 (50.3)	<0.0001
Positive	2982 (25.4)	822 (11.1)	2160 (49.7)	
HPV18				
Negative	11148 (95)	7204 (97.6)	3944 (90.7)	<0.0001
Positive	582 (5.0)	179 (2.4)	403 (9.3)	
HPV31				
Negative	11425 (97.4)	7234 (98)	4191 (96.4)	<0.0001
Positive	305 (2.6)	149 (2)	156 (3.6)	
HPV33				
Negative	11337 (96.7)	7178 (97.2)	4159 (95.7)	<0.0001
Positive	393 (3.4)	205 (2.8)	188 (4.3)	
HPV35				
Negative	11659 (99.4)	7344 (99.5)	4315 (99.3)	0.1609
Positive	71 (0.6)	39 (0.5)	32 (0.7)	
HPV39				
Negative	11460 (97.7)	7208 (97.6)	4252 (97.8)	0.519
Positive	270 (2.3)	175 (2.4)	95 (2.2)	
HPV42				
Negative	11263 (99.4)	7024 (99.4)	4239 (99.4)	0.564
Positive	70 (0.6)	46 (0.7)	24 (0.6)	
HPV43				
Negative	11314 (99.8)	7060 (99.9)	4254 (99.8)	0.3798
Positive	19 (0.2)	10 (0.1)	9 (0.2)	
HPV44				
Negative	11290 (99.6)	7040 (99.6)	4250 (99.7)	0.3167
Positive	43 (0.4)	30 (0.4)	13 (0.3)	
HPV45				
Negative	11657 (99.4)	7347 (99.5)	4310 (99.2)	0.0156
Positive	73 (0.6)	36 (0.5)	37 (0.9)	
HPV51				
Negative	11460 (97.7)	7210 (97.7)	4250 (97.8)	0.6966
Positive	270 (2.3)	173 (2.3)	97 (2.2)	

Table 1. Continued

Variable	Overall	Control women n (%)	Women with cervical cancer n(%)	P
HPV52				
Negative	10998 (93.8)	6955 (94.2)	4043 (93)	0.0097
Positive	732 (6.2)	428 (5.8)	304 (7)	
HPV53				
Negative	11018 (97.2)	6872 (97.2)	4146 (97.3)	0.8605
Positive	315 (2.8)	198 (2.8)	117 (2.7)	
HPV56				
Negative	11643 (99.3)	7329 (99.3)	4314 (99.2)	0.8657
Positive	87 (0.7)	54 (0.7)	33 (0.8)	
HPV58				
Negative	10581 (90.2)	6768 (91.7)	3813 (87.7)	<.0001
Positive	1149 (9.8)	615 (8.3)	534 (12.3)	
HPV59				
Negative	11613 (99)	7319 (99.1)	4294 (98.8)	0.0636
Positive	117 (1)	64 (0.9)	53 (1.2)	
HPV66				
Negative	11225 (99.1)	7000 (99)	4225 (99.1)	0.6003
Positive	108 (1)	70 (1)	38 (0.9)	
HPV68				
Negative	11574 (98.7)	7278 (98.6)	4296 (98.8)	0.2556
Positive	156 (1.3)	105 (1.4)	51 (1.2)	
HPV6				
Negative	11681 (99.6)	7356 (99.6)	4325 (99.5)	0.2549
Positive	49 (0.4)	27 (0.4)	22 (0.5)	
HPV11				
Negative	11701 (99.8)	7365 (99.8)	4336 (99.8)	0.9224
Positive	29 (0.3)	18 (0.2)	11 (0.3)	

HR HPV, high-risk HPV; LR HPV, low-risk HPV.

Averaged daily physical activity

Averaged daily physical activity time was 110.4 ± 62.4 mins, and physical activity distance was 6.6 ± 3.9 km for all participants. Control women had significantly more

Table 2. Risk Factors associated with Cervical Cancer

Variable	OR (95% CI)	P		OR (95% CI)
Model 1			Model 2	
Age (years)			Age (years)	
≤ 40	1		≤ 40	1
41~45	0.99 (0.84-1.16)	<0.0001	41~45	1.03 (0.88-1.2)
46~50	1.19 (1.03-1.38)	0.4103	46~50	1.23 (1.07-1.42)
51~55	1.38 (1.18-1.6)	0.0226	51~55	1.5 (1.3-1.74)
>55	1.79 (1.57-2.04)	<0.0001	>55	1.8 (1.58-2.05)
HPV16*	9.15 (8.28-10.1)	<0.0001	HR HPV*	6.48 (5.92-7.08)
HPV18	6.54 (5.38-7.95)	<0.0001		
HPV31	2.15 (1.66-2.78)	<0.0001		
HPV33	1.45 (1.15-1.83)	0.002		
HPV45	2.16 (1.28-3.62)	0.0037		
HPV52	1.37 (1.15-1.63)	0.0006		
HPV58	2.09 (1.82-2.4)	<0.0001		
HPV59	1.96 (1.3-2.96)	0.0014		

*Negative as the reference. HR HPV, high-risk HPV

Table 3. Demographic Features of Women with Physical Activity Information

Variable	Overall	Healthy controls	Women with Cervical cancer	P value
Age (years)				
Mean ± SD	48.3 ± 9.7	47.4 ± 9.3	51.5 ± 10.5	<0.0001
Median (range)	48 (22-81)	47 (22-81)	51 (26-81)	
≤ 40	229 (19.3)	185 (20.7)	44 (15.2)	<0.0001
41~45	239 (20.2)	200 (22.3)	39 (13.5)	
46~50	259 (21.9)	211 (23.6)	48 (16.6)	
51~55	204 (17.2)	145 (16.2)	59 (20.4)	
>55	254 (21.4)	254 (17.3)	155 (34.3)	
Average daily physical activity time (Mins)				
Mean ± SD	110.4 ± 62.4	114.4 ± 63.4	98.1 ± 57.6	<0.0001
Median (range)	96.9 (5.2-448.8)	100.7 (5.1-448.8)	82.7 (5.2-327.2)	
≤ 60	248 (20.9)	164 (18.3)	84 (29.1)	0.0001
61~100	374 (31.6)	278 (31)	96 (33.2)	
101~150	294 (24.8)	235 (26.2)	59 (20.4)	
>150	269 (22.7)	219 (24.4)	50 (17.3)	
Average daily physical activity distance (km)				
Mean ± SD	6.6 ± 3.9	6.8 ± 4.1	5.8 ± 3.5	<0.0001
Median (range)	5.7 (0.3-34.4)	6.0 (0.3-34.4)	4.9 (0.3-20.6)	
≤ 3	168 (14.2)	112 (12.5)	56 (19.4)	0.0024
3.1~5	323 (27.3)	234 (26.1)	89 (30.8)	
5.1~8	354 (29.9)	277 (30.9)	77 (26.6)	
>8	340 (28.7)	273 (30.5)	67 (23.2)	
BMI				
Mean ± SD	23.3 ± 3.3	23.2 ± 3.2	23.4 ± 3.3	0.2236
Median (range)	22.9 (15.2-36.1)	22.8 (15.2-36.1)	23.1 (17.1-35.9)	
Underweight	52 (4.4)	41 (4.6)	11 (3.8)	0.6121
Normal	684 (57.7)	524 (58.5)	160 (55.4)	
Overweight	324 (27.3)	241 (26.9)	83 (28.7)	
Obesity	125 (10.6)	90 (10.0)	35 (12.1)	

BMI, body mass index

averaged daily physical activity time than cervical cancer patients (114.4 ± 63.4 vs 98.1 ± 57.6 mins, P<.0001), and correspondingly, more averaged daily physical activity distance (6.8 ± 4.1 vs 5.8 ± 3.5 km, P<.0001) (Tale 3). As expected, linear regression analysis revealed that averaged daily physical activity time was significantly associated with its distance in the whole cohort (R^2 = 0.9348, P<0.0001) (Figure 1).

Distribution of BMI

The averaged BMI was 23.3 ± 3.3 kg/m^2 for these participants. There was no significant difference in BMI between control women and cervical cancer patients (23.2 ± 3.2 vs 23.4 ± 3.3 kg/m^2, P=0.2236). The proportion of overweight or obesity was not significantly different between the two groups (P=0.6121) (Table 3).

Association between daily physical activity and BMI

Linear regression was applied to analyze the daily physical activity and BMI. Both averaged daily physical activity time and distance were not significantly associated with BMI. Their respective R2 squares were 0.002 (P=0.1031) and 0.02 (P = 0.1160) (Supplemental data Figure S2A and S2B).

Prevalence of HPV infection in women with physical activity information

There were significantly higher proportions of women with cervical cancer who had infections of any HPVs (85.1% vs 32.5%) or HR HPVs (84.8% vs 31.9%) compared with control women. HPV16 (55.7% vs 11.7%), 18 *7.6% vs 3.5%), 31 (4.5 vs 1.3%), 45 (1.4% vs 0%),52(9.7 vs 5.4%), 56 (1.4 vs 0.3%), and 58 (14.9 vs 5.7%) infections were also significantly increased in women with cervical cancer (Table 4)

Association between physical activity and HPV infection

Univariate analysis showed that increased age was significantly associated with the risk of infection with any HPV, or any HR HPV, or HPV16, or 18, or 58, or 52. Average daily physical activity time and distance were inversely associated with increased risk of infection with at any HPV, or any HR HPV, or HPV16, but only daily physical activity time was significantly and

Table 4. Prevalence of HPVs in Women with Physical Activity Information

Viable	Overall	Healthy control	Cervical cancer women	P
Any HPV				
Negative	648 (54.7)	605 (67.5)	43 (14.9)	<.0001
Positive	537 (45.3)	291 (32.5)	246 (85.1)	
Single	399 (33.7)	215 (24)	184 (63.7)	<.0001
Multiple	138 (11.7)	76 (8.5)	62 (21.5)	
Any HR HPV				
Negative	654 (55.2)	610 (68.1)	44 (15.2)	<.0001
Positive	531 (44.8)	286 (31.9)	245 (84.8)	
Single	399 (33.7)	215 (24)	184 (63.7)	<.0001
Multiple	132 (11.1)	71 (7.9)	61 (21.1)	
Any LR HPV				
Negative	1167 (98.5)	883 (98.6)	284 (98.3)	0.7358
Positive	18 (1.5)	13 (1.5)	5 (1.7)	
HPV16				
Negative	919 (77.6)	791 (88.3)	128 (44.3)	<.0001
Positive	266 (22.5)	105 (11.7)	161 (55.7)	
HPV18				
Negative	1132 (95.5)	865 (96.5)	267 (92.4)	0.003
Positive	53 (4.5)	31 (3.5)	22 (7.6)	
HPV31				
Negative	1160 (97.9)	884 (98.7)	276 (95.5)	0.0012
Positive	25 (2.1)	12 (1.3)	13 (4.5)	
HPV33				
Negative	1140 (96.2)	867 (96.8)	273 (94.5)	0.0753
Positive	45 (3.8)	29 (3.2)	16 (5.5)	
HPV35				
Negative	1179 (99.5)	893 (99.7)	286 (99)	0.143
Positive	6 (0.5)	3 (0.3)	3 (1)	
HPV39				
Negative	1167 (98.5)	884 (98.7)	283 (97.9)	0.3732
Positive	18 (1.5)	12 (1.3)	6 (2.1)	
HPV42				
Negative	1177 (99.3)	891 (99.4)	286 (99)	0.3862
Positive	8 (0.7)	5 (0.6)	3 (1)	
HPV43				
Negative	1183 (99.8)	894 (99.8)	289 (100)	0.4215
Positive	2 (0.2)	2 (0.2)	0 (0)	
HPV44				
Negative	1182 (99.8)	893 (99.7)	289 (100)	0.3247
Positive	3 (0.3)	3 (0.3)	0 (0)	
HPV45				
Negative	1181 (99.7)	896 (100)	285 (98.6)	0.0004
Positive	4 (0.3)	0 (0)	4 (1.4)	
HPV51				
Negative	1160 (97.9)	877 (97.9)	283 (97.9)	0.9636
Positive	25 (2.1)	19 (2.1)	6 (2.1)	
HPV52				
Negative	1109 (93.6)	848 (94.6)	261 (90.3)	0.009
Positive	76 (6.4)	48 (5.4)	28 (9.7)	

Table 4. Continued

Viable	Overall	Healthy control	Cervical cancer women	P
HPV53				
Negative	1152 (97.2)	869 (97)	283 (97.9)	0.3998
Positive	33 (2.8)	27 (3)	6 (2.1)	
HPV56				
Negative	1178 (99.4)	893 (99.7)	285 (98.6)	0.043
Positive	7 (0.6)	3 (0.3)	4 (1.4)	
HPV58				
Negative	1091 (92.1)	845 (94.3)	246 (85.1)	<.0001
Positive	94 (7.9)	51 (5.7)	43 (14.9)	
HPV59				
Negative	1175 (99.2)	887 (99)	288 (99.7)	0.2873
Positive	10 (0.8)	9 (1)	1 (0.4)	
HPV66				
Negative	1174 (99.1)	891 (99.4)	285 (98.6)	0.1596
Positive	11 (0.9)	5 (0.6)	4 (1.4)	
HPV68				
Negative	1173 (99)	887 (99)	286 (99)	0.9604
Positive	12 (1)	9 (1)	3 (1)	
HPV6				
Negative	1183 (99.8)	895 (99.9)	288 (99.7)	0.3986
Positive	2 (0.2)	1 (0.1)	1 (0.4)	
HPV11				
Negative	1182 (99.8)	894 (99.8)	288 (99.7)	0.7179
Positive	3 (0.3)	2 (0.2)	1 (0.4)	

HR HPV, high-risk HPV; LR, low-risk.

inversely associated with HPV58 infection. Average daily physical activity time or distance was not significantly associated with infection with HPV18 or 52. There was no association between obesity and infection with these

Table 5. Risk Factors associated with HPV Infection in Multivariate Analysis

Variable	HR HPV OR (95% CI)	HPV16 OR (95% CI)		HR HPV OR (95% CI)	HPV16 OR (95% CI)
	Model 1			Model 2	
Age			Age		
≤ 40	1	1	≤ 40	1	1
41~45	0.71 (0.48-1.05)	0.67 (0.41-1.11)	41~45	0.71 (0.48-1.05)	0.66 (0.4-1.09)
46~50	1.65 (1.15-2.37)*	1.16 (0.75-1.81)	46~50	1.65 (1.15-2.36)*	1.16 (0.74-1.8)
51~55	1.93 (1.32-2.84)**	1.89 (1.21-2.95)**	51~55	1.91 (1.3-2.81)**	1.87 (1.2-2.92)**
>55	2.27 (1.58-3.28)**	1.72 (1.12-2.63)*	>55	2.26 (1.57-3.26)**	1.7 (1.11-2.61)*
Physical activity time (mins)			Physical activity distance (km)		
≤ 60	1	1	≤ 3	1	1
61~100	0.8 (0.6-1.2)	0.79 (0.55-1.15)	3.1~5	0.85 (0.58-1.25)	0.89 (0.59-1.36)
101~150	0.6 (0.4-0.9)*	0.62 (0.41-0.93)*	5.1~8	0.59 (0.41-0.87)**	0.56 (0.36-0.86)*
>150	0.5 (0.4-0.8)**	0.55 (0.36-0.84)**	>8	0.51 (0.35-0.75)**	0.51 (0.33-0.79)**
BMI			BMI		
Normal	1	1	Normal	1	1
Underweight	0.9 (0.5-1.7)	1.31 (0.68-2.51)	Underweight	0.92 (0.52-1.66)	1.28 (0.67-2.46)
Overweight	0.8 (0.6-1.1)	0.89 (0.64-1.23)	Overweight	0.83 (0.63-1.09)	0.89 (0.64-1.24)
Obesity	1.1 (0.7-1.6)	1.22 (0.78-1.91)	Obesity	1.08 (0.73-1.6)	1.23 (0.78-1.93)

HR HPV, high-risk HPV; * P <0.05 and ** P <0.01

Table 6. Factors associated with Cervical Cancer in Multivariate Analysis

Variable	OR (95% CI) Model 1	OR (95% CI) Model 2	OR (95% CI) Model 3	OR (95% CI) Model 4
HPV16	10.98 (7.82-15.42)**	10.86 (7.74-15.25)**		
HPV18	3.36 (1.78-6.37)**	3.33 (1.75-6.31)**		
HPV31	4.54 (1.83-11.24)**	4.49 (1.81-11.13)**		
HPV52	2.12 (1.2-3.76)**	2.08 (1.18-3.67)**		
HPV58	10.98 (7.82-15.42)**	3.52 (2.12-5.86)**		
HR HPV			11.69 (8.13-16.8)**	11.62 (8.09-16.69)**
Age				
≤ 40	1	1		1
41~45	0.65 (0.38-1.11)	0.65 (0.38-1.11)	0.64 (0.38-1.1)	0.64 (0.38-1.1)
46~50	0.62 (0.37-1.04)	0.61 (0.36-1.04)	0.55 (0.33-0.93)	0.55 (0.33-0.92)**
51~55	1.07 (0.64-1.8)	1.06 (0.63-1.77)	1.06 (0.63-1.76)	1.04 (0.62-1.74)
>55	1.88 (1.17-3.04)**	1.86 (1.16-3)**	1.67 (1.04-2.71)*	1.67 (1.03-2.69)**
Time (Min)				
≤ 60	1		1	
61~100	0.71 (0.47-1.08)		0.68 (0.45-1.02)	
101~140	0.6 (0.38-0.95)*		0.62 (0.4-0.97)*	
>140	0.45 (0.28-0.73)**		0.48 (0.3-0.77)**	
Distance (km)				
≤ 3		1		1
3.1~5		0.77 (0.48-1.23)		0.74 (0.47-1.18)
5.1~8		0.67 (0.41-1.08)		0.63 (0.39-1.00)
>8		0.53 (0.32-0.86)*		0.53 (0.33-0.86)*
BMI				
Normal	1	1	1	1
Underweight	0.79 (0.35-1.78)	0.79 (0.35-1.76)	0.86 (0.39-1.9)	0.86 (0.39-1.9)
Overweight	1.12 (0.78-1.61)	1.13 (0.78-1.62)	1.25 (0.88-1.79)	1.26 (0.88-1.8)
Obesity	1.18 (0.7-1.99)	1.2 (0.71-2.02)	1.34 (0.82-2.2)	1.35 (0.82-2.21)

HR HPV, high-risk HPV; * P <0.05 and ** P <0.01

HPVs (Supplemental data Table S2).

Since the daily physical activity time was significantly and positively associated with daily physical activity distance, we analyzed them in separate multivariate logistic regression models. Our results showed that older age (>55 years) and less averaged daily physical activity time or distance, were significantly associated with increased risk of infection with any HR HPV, or HPV16, but not other individual HPVs (Table 5 and supplemental data Table S3).

Association between physical activity with cervical cancer

Result of multivariate logistic regression analysis showed that age, HPV16, 18, 31 52 58, and average daily physical activity time were significantly associated with the risk of cervical cancer (Table 6 Model 1). The predicting model using these variables showed excellent ability to predict the cervical cancer (AUC = 0.8258) (Figure 2A). A similar finding was observed if daily physical activity distance was used instead of daily physical activity time (Table 6 and Figure 2B). If HR HPV instead of individual HPV were used as a risk factor, our data showed that age, infection with any one or more HR HPVs, and average daily physical activity time (or distance) were also significantly associated with the risk of cervical cancer. In contrast, BMI was not associated the risk of cervical cancer (Table 6).

Discussion

Cervical cancer is mainly caused by infection with HPV, which can be a preventable disease, with screening and HPV vaccines. It is of clinical significance to identify other modifiable factors to reduce HPV infection and consequently the risk of cervical cancer. This study first compared the prevalence of HPV infection between healthy controls and cervical cancer women in a large cohort and then determined the impact of smartphone monitored physical activity on the risk of HPV infection and cervical cancer. Our results revealed that there was a high prevalence of HPV infection, and HPV16, 58, 52, 18, 33 and 31 were the top commonly infected viruses in these unvaccinated women. Increased age and infection with at least one HR HPV or these top common HPVs were positively correlated with the risk of cervical cancer. Smartphone monitored physical activity, either average daily physical activity time or distance, was inversely associated with the risk of HR HPV or HPV16 infection, and cervical cancer. However, BMI was not associated with risk of HPV infection or cervical cancer.

This study revealed a high prevalence of HPV infection in women from Zhejiang province in East China. All women with cervical cancer had at least one HPV infection, and 79.5% of them had infection with at least one HR HPV. Even in healthy control women, 37.9% of them had at least one HPV infection and 36.8% had at least one HR HPV infection. It is noted that it was the first HPV screening in these unvaccinated women. Similar to this finding, high prevalence of HPV infection in control women and its further increase in cervical cancer was reported in women from other regions of China (Sun et al., 2010; Wang et al., 2016; Ma et al., 2018; Zhao et al., 2018). The high prevalence of HPV infection highlights the importance of cervical screening and vaccine use, and in identifying other modifiable risk factors to reduce the viral infection.

Our data discovered that HPV16, followed by HPV58, 52, 18, 33 and 31 were the most common viruses in these women. Similarly, Sun et al., (2010) reported that the most common genotypes were HPV16, 58, 52, 33, 53, and 31 in the Northeast region of China. Zhao et al., (2018) reported that the five most predominant genotypes were HPV16, 52, 58, 18 and 81 in women from Southern China. Other studies found that HPV52, 16, and 58 were the three most common types (Wang et al., 2016; Zeng et al., 2016). Conversely, HPV16 and 18 were the most common infection in Western countries (Koutsky, 1997; Usubutun et al., 2009; de Sanjose et al., 2010; Kose and Naki, 2014). The geographical differences in the most common viruses emphasizes the importance of HPV screening and applying the proper vaccines correspondingly.

Based on multivariate logistic regression analysis, infection with these top most common HPV16, 58, 52, 18, 33, 31, 45 and 59, or any HR HPV was associated with a significantly increased risk of cervical cancer. The multivariate logistic regression model suggests that concurrent infection with multiple HPVs will dramatically increase the risk of cervical cancer. Prevention of concurrent infection with multiple HPVs may possibly reduce the risk of cervical cancers. To date, there are four HPV vaccines available to protect against HPV (Joura et al., 2015). Our data support the nonavalent vaccine (HPV16/18/6/11/31/33/45/52/58) which covers the top common HPVs may be more protective for Chinese women (Zhao et al., 2018).

One intriguing finding of this study was that more averaged daily physical activity time or distance was significantly associated with the reduced risk of infection with any HR HPV. For individual HPV infection, more averaged daily physical activity time (distance) was significantly associated with a reduced risk of HPV16 infection, but not other viruses. Consequently, this study also demonstrated that physical activity is a protective factor for cervical cancer. Averaged daily waking time > 150 minutes (vs 60 minutes or less), led to 55% reduction of the risk to develop cervical cancer. Averaged physical activity distance over 8 km (vs 3 km or less) was associated with 47% reduced risk of cervical cancer. These findings are consistent with the previous studies (Lee et al., 2013; Chang et al., 2020). The beneficial effect of physical activity has been correlated with improving immune function and lowering the levels of sex hormones, insulin and growth factors (Winzer et al., 2011; Aleksandrova et al., 2017; Nieman and Wentz, 2019). These data suggest that physical activity is one of the modifiable risk factors in the prevention of HPV infection and cervical cancer.

Notably, smartphone movement was monitored through both GPS behavior data and wireless network base stations. The set of data was objectively pre-stored in the cloud database and was collected six months prior to the HPV screening. This approach essentially avoids possible recall, social desirability and other biases if the data is collected after subjects know their participation in a study (Bort-Roig et al., 2014; Sylvia et al., 2014; Schrack et al., 2017; Dowd et al., 2018). The objectively collected data may more closely reflect participants' life time or habitual physical activity. It is known that physical activity in the distant past or over the life span may be more etiologically relevant for cancers. This unique way of collecting physical activity data may partially explain our positive findings which has the potential to be translated into the public health recommendation. On the other side, the cloud databases have numerous data of smartphone monitored physical activity. This study establishes an example for utilizing this type of data in future related studies.

Previous studies showed that obesity was associated with an increased risk of cervical cancer (Lee et al., 2013). In contrast, we observed no significant association between obesity and the risk of HPV infection or cervical cancer. It is noted that the criterium used for obesity is 28 kg/m2, instead of 30 kg/m2. The proportion of subjects with obesity is very close to the prevalence of obesity in Chinese women reported in recent studies (Wang et al., 2020; Pan et al., 2021), but is much lower than the prevalence in many Western countries (Fryar, 2020). The BMI is also correlated with food intake and genetic factors. Our data indicated that physical activity was not significantly associated with BMI in these women. These may partially explain that physical activity, but not obesity, is associated with the risk of HPV infection or cervical cancer in these Chinese women.

This case-control study has several limitations. Information of many other risk factors, such as economic status, career and number of sex partners, was not available. A very recent study indicates that higher leisure-time physical activity reduces, whereas higher occupational physical activity increases, the risk of adverse cardiovascular events and all-cause mortality risk (Holtermann et al., 2021), suggesting their differential effect. This study defined physical activity based upon the movements within a speed range. It did not differentiate leisure physical activity from occupational physical activity. Our data are not enough to establish the optimal physical activity time and distance for its best protective effect. These subjects were unvaccinated women who underwent first-time HPV screening in a cancer hospital. Our findings may be generalizable to women visiting cancer hospitals. Among all enrolled women, less than 10% of them had the available physical activity data, which may bring a possible selection bias. The strength of this study is that physical activity was objectively collected for six months prior to their enrollment in the study.

In conclusion, more effective approaches are needed to reduce the high prevalence of HPV infection in women. physical activity may have a beneficial effect on the reduction of certain high-risk HPV infections and the risk of cervical cancer. BMI is not correlated with the risk of HPV infection and cervical cancer. Smartphone monitoring is an alternative approach to monitor physical activity.

Author Contribution Statement

AY and JX are responsible for the original concept of the study and, with all co-authors, designed the study. JX, TZ, JZ, WY and AY were responsible for data collecting, processing and analysis. JX drafted the manuscript which was revised by AY. All authors have read and approved the final manuscript.

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Ethical Declaration

Each participant provided written informed consent prior to the start of the study. The protocol was approved by the Ethics Committee of Zhejiang Cancer Hospital (approval no. IRB-2019-75).

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no competing interests.

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