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Abstract

Background: In Japan, the human papillomavirus (HPV) vaccination rate has dropped to nearly zero since the suspension of proactive government recommendations in 2013. Following the termination of vaccination suspension in 2021 and subsequent proactive vaccination recommendation in 2022, it is crucial to promote catch-up vaccinations for those who missed their initial opportunity.

Objective: This trial aims to evaluate the effect of video-based informational intervention on the uptake of catch-up HPV vaccinations among unvaccinated young adult women in Japan.

Methods: In this randomized, parallel, single-blinded, internet-based trial, we recruited women aged 18–26 years unvaccinated for HPV through an online research panel. The participants were randomly assigned (1:1) to receive either an educational leaflet containing information on the HPV vaccine and a short narrative video (intervention) or the leaflet alone (control). The primary outcome was the difference in proportion between both groups regarding the uptake of the free catch-up vaccinations at the follow-up survey after 3 months.

Results: We enrolled 4065 women in the trial and randomly assigned them to either the intervention (2274 women) or the control (2331 women) group. Of these, we excluded 2595 women (63.8%) who did not respond to the follow-up survey, resulting in 1017 and 993 women in the intervention and control groups, respectively, for the final analysis. At the 3-month follow-up, 11.3% (228/2010) of the participants received at least one catch-up vaccine dose. The intervention and control groups had 10.5% (107/1017) and 12.2% (121/993) uptake, respectively. The difference in proportions between both groups was -1.7% (95% confidence interval [CI]: -4.5–1.2%), and the adjusted difference was -1.6% (95% CI: -4.3–1.0%). In the subgroup analysis, the intervention group had a lower proportion of catch-up vaccination among sexually experienced women who had prior sexual intercourse experience (difference in proportion: -5%, 95% CI: -10% to -1%) and those who had undergone a Pap test within the past 2 years (difference in proportion: -11%, 95% CI: -20% to -1%). Women with lower educational levels had lower vaccination rates compared to those with higher educational levels (difference in proportion: -7%, 95% CI: -10% to -4%). In addition, women who had undergone a Pap test within the past two years had higher vaccination rates compared to those who had not.

Conclusions: Our study demonstrated that video-based interventions did not have a substantial impact on the uptake of catch-up

HPV vaccinations among young adults. It is desirable to explore effective interventions in real-world settings to remove the barriers to vaccination. Clinical Trial: Japan Registry of Clinical Trials jRCT1030230315; https://jrct.niph.go.jp/en-latest-detail/jRCT1030230315

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Conclusions: Our study demonstrated that video-based interventions did not have a substantial impact on the uptake of catch-up HPV vaccinations among young adults. It is desirable to explore effective interventions in real-world settings to remove the barriers to vaccination.

Trial Registration: Japan Registry of Clinical Trials jRCT1030230315; https://jrct.niph.go.jp/en-latest-detail/jRCT1030230315

Keywords: human papillomavirus (HPV); HPV vaccination; behavioral change; randomized controlled trial.

Introduction

Cervical cancer (CC) is a significant public health issue. Increasing the coverage of the prophylactic human papilloma virus (HPV) vaccine in the target population is essential for CC prevention. Globally, CC is the fourth most common cancer among women, with approximately 662,301 new cases in 2022 [1]. In Japan, approximately 10,000 women are diagnosed with CC, and 3,000 women die from the disease annually [2]. In addition, it is the third most frequent cancer among women aged 15–44 years [1]. Persistent infection with carcinogenic HPV is the cause of almost all CCs [3,4]. HPV vaccination substantially reduces the CC risk at the population level and plays a crucial role in eliminating CC [5–7].

Due to the suspension by of government recommendations between 2013 and 2022 , many women in Japan missed the opportunity to receive HPV vaccinations. HPV vaccinations were introduced in the fiscal year (FY) 2009 and were formally included in the National Immunization Program (NIP) in April 2013. However, reports of adverse events potentially linked to the HPV vaccine appeared in the Japanese media in May 2013, and this caused the Ministry of Health, Labor and Welfare (MHLW) to cease proactive HPV vaccine recommendations in June 2013. Consequently, the HPV vaccine coverage of the target girls (aged 12–16) dropped drastically to near zero [8]. This was referred to as a “vaccine crisis” [9,10]. A modeling study estimated that the vaccine crisis from 2013–2019 is predicted to result in an additional 24600–27300 cases of CC and 5000–5700 deaths over the lifetime of cohorts born between 1994 and 2007, compared with if the coverage had remained at around 70% since 2013 [7]. In November 2021, the MHLW finally announced the termination of their ‘temporary suspension’, and proactive vaccination recommendations began in April 2022, targeting girls born in or after FY2006 [11]. Thus, it is essential to promote catch-up vaccinations and encourage vaccination for women who missed the opportunity during this ‘temporary suspension’ period. Consequently, a catch-up vaccination program was started for women born between FY1997 and FY2007 who missed the recommended routine immunization [12]. A simulation study indicated that the catch-up immunization coverage among unvaccinated women needed to reach 90% by FY2022 to lower the risk to a similar level or below that of women born between 1994 and 1999 [13]. However, the HPV catch-up vaccination rate among unvaccinated women remained low (12–21%) at the end of the FY 2022 [14].

Developing effective communication strategies to enhance voluntary vaccine uptake after this period of unacceptance is critical to promote vaccination behavior among the target generation of the catch-up vaccination. The factors influencing vaccine hesitancy are complex and depend on context [15]. There have been numerous intervention trials targeting parents of the vaccination generation, and our group has accumulated evidence in this field [16,17]; however, fewer interventions target young adults. Current evidence on the effects of the interventions on young adults indicates that multi-component and dialogue-based interventions, such as the involvement of religious or traditional leaders, social mobilization, social media, and mass media are the most effective strategies to address vaccine hesitancy [18]. Reportedly, video-based informational interventions have positive effects on promoting voluntary vaccination, although they do not necessarily translate into positive behavioral outcomes of increased vaccination rates [19–21]. However, no study has targeted the generation Z (Gen Z) born between the late 1990s and the early 2000s [22]. Gen Zs are genuine digital natives, having been exposed to the internet, social networks, and mobile devices from a very young age, and digital media has a greater influence on their attitudes than the previous generation [23]. Therefore, the effectiveness of video interventions on Gen Z may differ from that of the previous generations of young adults.

This randomized controlled trial aims to address this knowledge gap by assessing the effect of video-

based informational intervention on the uptake of catch-up HPV vaccinations among unvaccinated Gen Z women living during the period of suspension of proactive government recommendations of HPV vaccination.

Methods

Trial design and setting

We conducted this randomized, controlled, parallel, single-blinded, purely web-based trial targeting women aged 18–26 years eligible for catch-up HPV vaccinations. This trial was conducted from August 28, 2023, to September 6, 2023, as a pre-survey, and from December 7, 2023, to December 20, 2023, as a follow-up survey. Participants were randomly assigned in a 1:1 proportion to a control group (those who solely read a leaflet on free catch-up vaccinations) and an intervention group (those who additionally watched a brief interventional video), with the primary outcome of accepting HPV vaccine assessed at 3 months.

The Yokohama City University Ethics Committee approved this study (No. F230706002).

Participants and trial procedures

Women aged 18–26 years who missed the opportunity to receive the HPV vaccine during the NIP (ages 12–16) and had not been vaccinated for HPV at the time of this study were recruited from the registered members of the Nippon Telegraph and Telephone (NTT) Com Online Marketing Solutions Corporation (Tokyo, Japan) research panel. Inclusion criteria included the ability to use a computer and access the internet. We excluded women whose HPV vaccination status was unknown. This panel is used for customer satisfaction evaluations, promotional strategies, and academic studies and about 53,000 individuals in Japan have enrolled in this research panel [24]. Prior to participation, all eligible individuals were provided with a detailed explanation document and informed consent form. The document outlined the purpose and significance of the study, procedures and duration, voluntary participation and the right to withdraw without penalty, data handling and confidentiality, potential risks and benefits, and contact information for inquiries. We randomly assigned participants using the year of birth in three-year increments (FY1997–1999, FY2000–2002, and FY2003–2005) as a stratifying factor. The NTT Com Online Marketing Solutions Corporation data center generated random numbers using computers and performed simple randomization within each stratum. The allocation information was not disclosed to the participants (single-blinded). After responding to the initial online survey, participants were asked to view a leaflet issued by the MHLW regarding free catch-up HPV vaccination [25]. The leaflet provided information on the availability of the HPV vaccine for women born between FY1997 and FY2006 who missed the opportunity to get vaccinated. The leaflet explained what the HPV vaccine is, the types of HPV it protects against, and the importance of getting vaccinated to prevent CC. It also included details on the potential side effects of the vaccine and emphasized the importance of regular CC screenings for women > 20 years old. This pre-survey gathered comprehensive data, including their age, year of birth, residential area (by prefecture), household and personal income, highest educational attainment, reasons for not receiving the HPV vaccine, whether they had undergone a cervical cytology screening in the past 2 years, sexual intercourse experience, intention to receive the HPV vaccine within the next 3 months, and their communicative and critical health literacy (CCHL) scores [26]. It also assessed their awareness with specific questions such as:

- Were you aware that you are eligible for the free vaccination against HPV since 2022?
- Were you aware that the infection of the cervix with HPV can cause CC?

- Were you aware that CC screenings are recommended every 2 years for individuals ≥ 20 years?

After viewing the leaflet, those in the intervention group were required to watch a brief, approximately 50 s intervention video featuring two female medical students discussing the catch-up HPV vaccination and its safety [27]. In the video, one student expressed her mother's concerns about potential side effects. In contrast, the other student explained that millions of women around the world have received the vaccine and she was vaccinated without any issues. After 3 months, a follow-up survey was administered online to evaluate outcomes. This survey obtained information on whether participants had received catch-up vaccinations, the type of vaccine administered (bivalent, quadrivalent, or nonavalent), the subjective understandability of the leaflet, CCHL scores, and their awareness of HPV and HPV-related cancers, using questions such as:

- Were you aware that HPV can cause cancers in men as well (for example, in the throat, penis, and anus)?
- Were you aware that the HPV vaccine is administered to young boys and men in some countries?
- Were you aware that in Japan and abroad, there has been a significant reduction in pre-cancerous lesions among young women who were vaccinated with the HPV vaccine?

For participants who had not received catch-up vaccinations, we inquired about their plans regarding future vaccination. In addition, among those who did not plan to receive catch-up vaccinations, we investigated the reasons behind their decision. Participants in the control group were given access to the brief video before responding to the follow-up survey to ensure equal opportunity.

Outcome measures

The primary outcome was the difference between the two groups regarding the uptake of free catch-up vaccinations at the follow-up survey. The secondary outcomes were as follows: the difference between the two groups at the follow-up survey regarding the uptake of the nonavalent HPV vaccine, awareness about HPV or HPV-related cancer, the change in CCHL score, and the subjective understandability of the leaflet.

Statistical analysis

We hypothesized that the additional viewing of the video would show superiority to reading only the leaflet. Considering the potential intervention effect of participating in the study, including viewing the leaflet, we set the vaccination rate for the control group at 10% over 3 months. We defined the clinically meaningful minimum difference in vaccination rates between both groups as 5%, setting the vaccination rate in the video intervention group at 15%. Using Fisher's exact method with a two-sided significance level of 5% and a power of 80%, we calculated that 721 participants were needed per group. However, anticipating dropouts, we aimed for 2,000 participants, with 1,000 in each group. We included those who registered for the study and responded to all survey questions after randomization. Due to the nature of the online survey, those who did not respond to the follow-up survey were considered as not willing to participate.
Categorical variables were defined in specific terms. The year of birth was categorized into

three periods: 1997-1999, 2000-2002, and 2003-2005. The residential region was divided into eight distinct areas: Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, Shikoku, and Kyushu. Household income was segmented into five levels, each representing a quartile within the analysis population. The highest educational attainment was classified into two main categories: higher education, which includes graduate school, university, and junior college, and lower education, encompassing all other educational backgrounds. Awareness about HPV or HPV-related cancer was scored based on the number of questions they answered: “Yes” (0, 1, 2, and 3). The subjective understandability of the leaflet was categorized into two levels: "Understandable," which includes the responses "Somewhat agree" and "Strongly agree," and "Not Understandable," which includes the responses "Strongly disagree," "Disagree," and "Neutral."

The difference in proportions between the two groups was estimated using Fisher’s exact test. Wald's confidence interval was employed to calculate the confidence intervals for the difference in proportions between the two groups. Yates' continuity correction was applied to enhance the accuracy of approximating the binomial distribution to the chi-squared distribution in small sample sizes.
R version 4.3 (The R Foundation for Statistical Computing) was used for statistical analysis and report generation. The significance level for tests was set at a two-sided 5%.

For the primary outcome, we calculated the proportion and difference between the intervention and control groups regarding taking up the vaccine during the study period. We also conducted multiple regression analysis to adjust for potential confounding factors, including year of birth, sexual experience, residential area, highest educational attainment, household income, reasons for having not accepted the HPV vaccine ever, whether a cervical Pap cytology screening test was conducted in the past 2 years, intention to get the HPV vaccine in the next 3 months, and CCHL scores in the pre-survey. The analysis employed robust variance estimation for estimating standard errors [28]. Subgroup analyses were conducted to evaluate the heterogeneity of the intervention effect. The subgroups included the year group, sexual intercourse experience, residential region, educational background, household income, the reasons for not being vaccinated, knowledge of HPV, Pap-test history in the last 2 years, intention to be vaccinated in the following 3 months, and CCHL score in the pre-survey. This involved calculating the difference in the primary outcome between the two groups within each stratum, along with their 95% confidence intervals (CI). Multiple regression analyses were applied to the control group, the intervention group, and the entire study participants while adjusting for potential confounders to explore the effects of various factors on the catch-up vaccination behavior. Robust variance estimation was used in this analysis. The factors included the year group, educational background, household income, intercourse experience, knowledge of HPV, Pap-test history in the last 2 years, and CCHL score in the pre-survey (supplementary table 1).

We conducted analyses for the secondary outcomes as follows: We calculated the proportion of participants in the two groups who received the nonavalent HPV vaccine with the same method as the primary outcome. The crude and adjusted differences in the proportions of participants between the two groups with awareness about HPV or HPV-related cancer in the follow-up survey were calculated with their 95% CIs. We also calculated the crude and adjusted differences of the CCHL scores between the follow-up survey and pre-survey, along with the average differences between the two groups and their 95% CIs. The adjusted differences were calculated using multiple regression analysis. We applied similar potential confounders used in

the primary outcome of these analyses. Furthermore, to explore the characteristics associated with the subjective understandability of the leaflet, multiple regression analyses were applied to the entire study population while adjusting for similar potential confounders used in the analyses of factors affecting catch-up vaccination behavior (supplementary table 1). Robust variance estimation was used in this analysis.

Finally, among women who had not received a catch-up vaccination at the time of the follow-up survey and indicated that they did not plan to receive the HPV vaccine in the future, we descriptively summarized their reasons for this decision. The categorization for this summary was based on classifications from previous studies on vaccine hesitancy [29].

Results

Trial population

We enrolled 4065 women in the trial from August 28, 2023, to September 6, 2023, and randomly assigned them to either the intervention group (2274 women) or the control group (2331 women). In the intervention group, 1257 women did not answer the follow-up survey, leaving 1017 women to be analyzed for the primary outcome. In the control group, 1338 women did not answer the follow-up survey, leaving 993 women to be analyzed for the primary outcome. Therefore, 2595 women (63.8%) were excluded from the study population because they did not answer the follow-up survey, which left 1017 women in the intervention group and 993 women in the control group for the final analysis (Figure 1). The median age was 22 years (interquartile range: 20–24) for both groups, and other baseline characteristics were similar (Table 1).

Table 1. Characteristics of the participants at baseline.

Characteristic	**Control**, N = 993[a]	**Intervention**, N = 1,017[a]	**p-value**[b]
Age	22 (20, 24)	22 (20, 24)	0.755
Region			-
Hokkaido	36 (3.6%)	38 (3.7%)	
Tohoku	70 (7.0%)	84 (8.3%)	
Kanto	356 (36%)	360 (35%)	
Chubu	165 (17%)	172 (17%)	
Kinki	194 (20%)	221 (22%)	
Chugoku	57 (5.7%)	53 (5.2%)	
Shikoku	19 (1.9%)	17 (1.7%)	
Kyushu	96 (9.7%)	72 (7.1%)	
Household income (×10000 Yen)	400 (200, 700)	400 (200, 600)	0.856
Educational background			0.643
High (junior	368 (37%)	366 (36%)	

college level or above)			
Low	625 (63%)	651 (64%)	
History of sexual intercourse			0.054
Yes	430 (43%)	480 (47%)	
No	424 (43%)	427 (42%)	
Unsure	139 (14%)	110 (11%)	
Intention to receive HPV vaccine in the next three month			0.266
Yes	89 (9.0%)	102 (10%)	
No	631 (64%)	666 (65%)	
Unsure	273 (27%)	249 (24%)	
CCHL score in the pre-survey	3.20 (3.00, 3.80)	3.20 (3.00, 3.80)	0.986
[a]Median (Interquartile range); n (%)			
[b]Welch Two Sample t-test; Fisher's exact test			

Primary outcome

Regarding the primary outcome, overall, 11.3% (228/2010) of the participants had received at least one catch-up vaccine dose by the 3-month follow-up survey (Table 2). This proportion was 10.5% (107/1017) and 12.2% (121/993) in the intervention and control groups, respectively. The difference in proportions between the groups and its 95% CI was -1.7% (-4.5 to 1.2). After adjusting for potential confounding factors, the adjusted difference in proportion was -1.6% (-4.3 to 1.0).

Figure 2 shows the subgroup analysis results. The proportion of catch-up vaccination was lower in the intervention group among women who had intercourse experience (difference in proportion: -5%, 95% CI: -10% to -1%) and those who had undergone a pap test within the past two years (difference in proportion: -11%, 95% CI: -20% to -1%). No significant differences were observed in the intervention effect for other factors, including age, residential area, educational background, household income, the reason for not being vaccinated, knowledge of HPV, intention for being vaccinated in the following 3 months, and CCHL score in the pre-survey.

Table 2 The results of the primary and secondary outcomes.

Outcome	Overall,	Control,	Intervention,	Difference in proportion[c]	Mean difference	p-value[5e, f]	Adjusted difference in proportion (95% CI)[g]	Adjusted mean difference (95% CI)[g]
	N = 2,010[a, b]	N = 993[a, b]	N = 1,017[a, b]	(95% CI)[d]	(95% CI)[e]			
Primary outcome								
Vaccinated (2-, 4- or 9-valent)	228 (11.3%)	121 (12.2%)	107 (10.5%)	-1.7% (-4.5 to 1.2)	-	0.26	-1.6% (-4.3 to 1.0)	-
Secondary outcomes								
Vaccinated (9-valent)	68 (3.4%)	36 (3.6%)	32 (3.1%)	-0.4% (-1.2 to 2.1)	-	0.622	-0.7% (-2.1 to 0.8)	-
Awareness on the questions								
Awareness on Q1[h]	568 (28.6%)	288 (29.0%)	280 (27.5%)	-1.5% (-5.5 to 2.6)	-	0.488	-2.5% (-6.3 to 1.2)	-
Awareness on Q2[i]	370 (18.4%)	182 (18.3%)	188 (18.5%)	+0.2% (-3.3 to 3.6)	-	0.954	-0.6% (-3.9 to 2.7)	-
Awareness on Q3[j]	550 (27.4%)	278 (28.0%)	272 (26.7%)	-1.3% (-5.2 to 2.7)	-	0.548	-1.8% (-5.5 to 1.9)	-
Change in CCHL score	-0.028	-0.041	-0.017	-	0.024 (-0.057 to 0.105)	0.558	-	0.083 (-0.070 to 0.086)

[a]n (%)

[b]Mean change

[c]the subtraction of the vaccinated proportion in the control group from

the vaccinated proportion in the intervention group.

[d]Wald interval

[e]Fisher's exact test

[f]Welch’s t-test

[g]coefficient of multiple regression analysis, with robust variance estimator

h” Were you aware that HPV can cause cancers in men as well (e.g., in the throat, penis, and anus)? ”

i” Were you aware that HPV vaccine is administered also to men in some countries? ”

j” Were you aware that in Japan and abroad, there has been a significant reduction in pre-cancerous lesions among young women who have been vaccinated with the HPV vaccine? ”

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Factors associated with vaccination behaviors

Figure 3 presents the differences in vaccination rates for each factor compared to the reference level after adjusting for confounding factors, in the entire study population. Compared to those born in 1997–1999 (24–26 years old), women born in 2000–2002 (21–23 years old) and 2003–2005 (18–20 years old) had lower vaccination rates at 3 months. Women with lower educational levels had lower vaccination rates compared to those with higher educational levels. In addition, women who had undergone a Pap test within the past two years had higher vaccination rates than those who had not. The CCHL score was not associated with vaccination behavior. When we restricted this analysis to the intervention and control groups, we observed similar trends in both groups (Supplementary Figure 1). However, in the intervention group, the confidence intervals for age and having a Pap test in the last 2 years crossed 0, indicating no statistically significant association.

Secondary outcomes

Table 2 shows the results of the secondary analysis. The proportion of participants who received the nonavalent HPV vaccine was 3.1% (32/1017) and 3.6% (36/993) in the intervention and control groups, respectively. The difference in proportions between the groups and its 95% CI was -0.4% (-1.2 to 2.1). After adjusting for potential confounding factors, the adjusted difference in proportion was -0.7% (-2.1 to 0.8). As for awareness of HPV and HPV-related cancers, or change in CCHL score between the pre-survey and the follow-up survey, we did not observe significant differences between the intervention and the control groups.

In the analysis of factors associated with the subjective understandability of the leaflet in the entire study population, lower age groups and higher household income were associated with higher subjective understandability (supplementary figure 2). In addition, there was almost no difference in subjective understandability between those who answered "yes" and those who answered "no" regarding sexual intercourse experience. However, those who answered "unsure" had lower subjective understandability. Similarly, those who answered "unsure" for the Pap test in the last 2 years had lower subjective understandability. Higher subjective understandability was also observed in groups with higher CCHL scores than those with lower CCHL scores.

Supplementary Figure 3 shows the reasons given by the 429 individuals who did not receive the catch-up vaccination and indicated that they did not plan to receive the HPV vaccine in the future. The most common reason was low perceived need or risk (36.1%, 155/429), followed by concerns about vaccine safety (30.3%, 130/429), fear of injections (16.3%, 70/429), information issues (7.5%, 32/429), and

influencers (4.4%, 19/429).

Discussion

In this randomized, controlled, internet-based trial, we found that approximately 10% of the participants in the follow-up survey received the catch-up HPV vaccination. However, we were unable to demonstrate an additional benefit of video-based intervention on catch-up vaccination behavior among young adults. Furthermore, women with higher educational levels, older women, or women who had undergone a Pap test within the past 2 years had higher vaccination rates.

The effects of interventions on HPV vaccine uptake among young adults have been inconsistent. There are numerous intervention studies on HPV vaccine uptake. However, most studies target parents of adolescents up to approximately 15 years old or healthcare professionals, with limited trials focusing on young adults. Furthermore, few interventions demonstrate significant effects on actual vaccine uptake. A randomized controlled trial (RCT) performed in the United States reported that a combined peer–expert vaccine decision narrative video doubled the vaccination rate at two months compared to the control group (22% vs. 12%) [30]. However, the same RCT found that an expert vaccine decision narrative video alone resulted in lower vaccination rates than the control group (6% vs. 12%). Other studies performed in the United States have shown that educational interventions while increasing vaccination intentions post-intervention, do not necessarily translate into actual vaccination behavior [31,32]. In this study, the narrative video featuring female peers did not increase vaccination rates at 3 months. Nevertheless, the fact that 12% of the control group received the vaccine at 3 months suggests that the knowledge-based leaflet itself may have had some intervention effect.

The necessary factor to change the behavior of Gen Z may not be the digital media but rather influencers whom they perceive as trustworthy. Gen Z, known as digital natives, are more influenced by digital media and social media influencers in shaping their attitudes than previous generations [23]. Therefore, we hypothesized that video interventions might have a different impact on this generation compared to earlier cohorts of young adults. However, our results indicate that the narrative video featuring female peers did not increase vaccination rates at 3 months within a Japanese culture. Reportedly, Gen Zs seek influencers who they feel are authentic and are genuinely pursuing interests that they share [33]. From this perspective, our intervention video might have been insufficient to make Gen Zs truly trust or want to follow it, particularly given the large gap of 9 years (2013–2022) of hesitancy by the government in recommending vaccination.

It is also necessary to remove the barriers between vaccine uptake intention and actual vaccination behavior. According to the theory of planned behavior, intention precedes action [34]. In various previous intervention trials, interventions have increased vaccination intention, but this has not translated into actual vaccination [19–21]. In this trial, we did not measure intention after the intervention; however,

individuals need to use the vaccination tickets sent by the municipality to make appointments with healthcare providers and go to the vaccination site to get vaccinated, and this may act as a barrier. In addition, since vaccination tickets are sent from the relevant municipality to the address where the individual is registered, it can be difficult for those whose actual residence differs from their registered address to get vaccinated. It may be important to establish a system that minimizes the barriers between intention and behavior, such as enabling immediate appointment scheduling and vaccination right after the intervention.

The barriers to HPV vaccination vary, and it is necessary to explore the optimal approach to address them. In this study, younger women (18–20 years, 21–23 years) had lower vaccination rates compared to older women (24–26 years), and women with lower educational levels had lower vaccination rates compared to those with higher educational levels. This suggests that educational leaflets may not be suitable for inducing behavioral change in these demographics. The reasons given by women who still expressed reluctance to consider vaccination include "low perceived need or risk" and "concerns about vaccine safety," which collectively accounted for two-thirds of the responses. Globally, both reasons are among the top reasons for vaccine hesitancy [29]. To overcome these barriers, it is essential to communicate the importance of the vaccine, the risks of not getting vaccinated, and objective facts about side effects in a manner that these women find convincing. Merely providing knowledge is likely insufficient to achieve true understanding and actual behavioral change among these women; therefore, dialogue-based interventions may be necessary [18].

This study had some limitations. First, there was a high dropout rate, which may have threatened the exchangeability between the two groups maintained at the time of random assignment, due to heterogeneity between those who dropped out and those who remained. In web-based intervention trials, nearly 50% of the participants often drop out [35,36], and this study was no exception. Second, applying the results from this experimental setting to the real-world is challenging. When implementing interventions to promote vaccination, the interventions must be integrated into the actual system. Achieving this at the population level, which includes people who have no intention of getting vaccinated, might be challenging. Furthermore, since the real-world environment can differ significantly from the trial setting, the effects of the intervention might also differ. Third, while we confirmed that the video was played on the participants' devices in this web-based intervention, we could not verify whether the participants actually watched it. If the actual viewership was low, the intervention effect might be underestimated. Finally, the primary outcome of this study was self-reported through an online survey, so we do not have concrete evidence that participants actually received the vaccination.

In conclusion, our study demonstrated that video-based interventions did not have a substantial impact on catch-up HPV vaccinations among young adults, particularly for Gen Z, who are digital natives. It is desirable to explore effective interventions in real-world settings to remove the barriers to vaccination.

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Authors' Contributions

All authors made substantial contributions to the study and manuscript preparation. TY analyzed data and drafted a manuscript. AG supervised the analysis, writing, and interpretation of the findings. EM was responsible for the study design, data collection, analysis, and interpretation. TY, AG, TM, YS and EM designed the trial. All authors have read and approved the final manuscript.

Conflicts of Interest

SK has served on advisory boards of both Merck and GSK and has received Merck and Roche lecture fees. SMG is a consultant for Merck and a member of their Global Advisory Board for HPV. She has also advised GSK. IIP has received lecture fees from Merck and Roche. MS received lecture fees from Merck & Co., Inc. and AstraZeneca. AY received lecture fees from Merck & Co., Inc. EM had honoraria and travel and support for attending meetings from Merck & Co., Inc.

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Abbreviations

CC: cervical cancer
CCHL: communicative and critical health literacy
CI: confidence interval
FY: fiscal year
Gen Z: generation Z
HPV: human papilloma virus
MHLW: ministry of health, labor and welfare
NIP: National Immunization program
NTT: Nippon Telegraph and Telephone
RCT: randomized controlled trial
AMED: Japan Agency for Medical Research and Development

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Supplementary Files

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Figures

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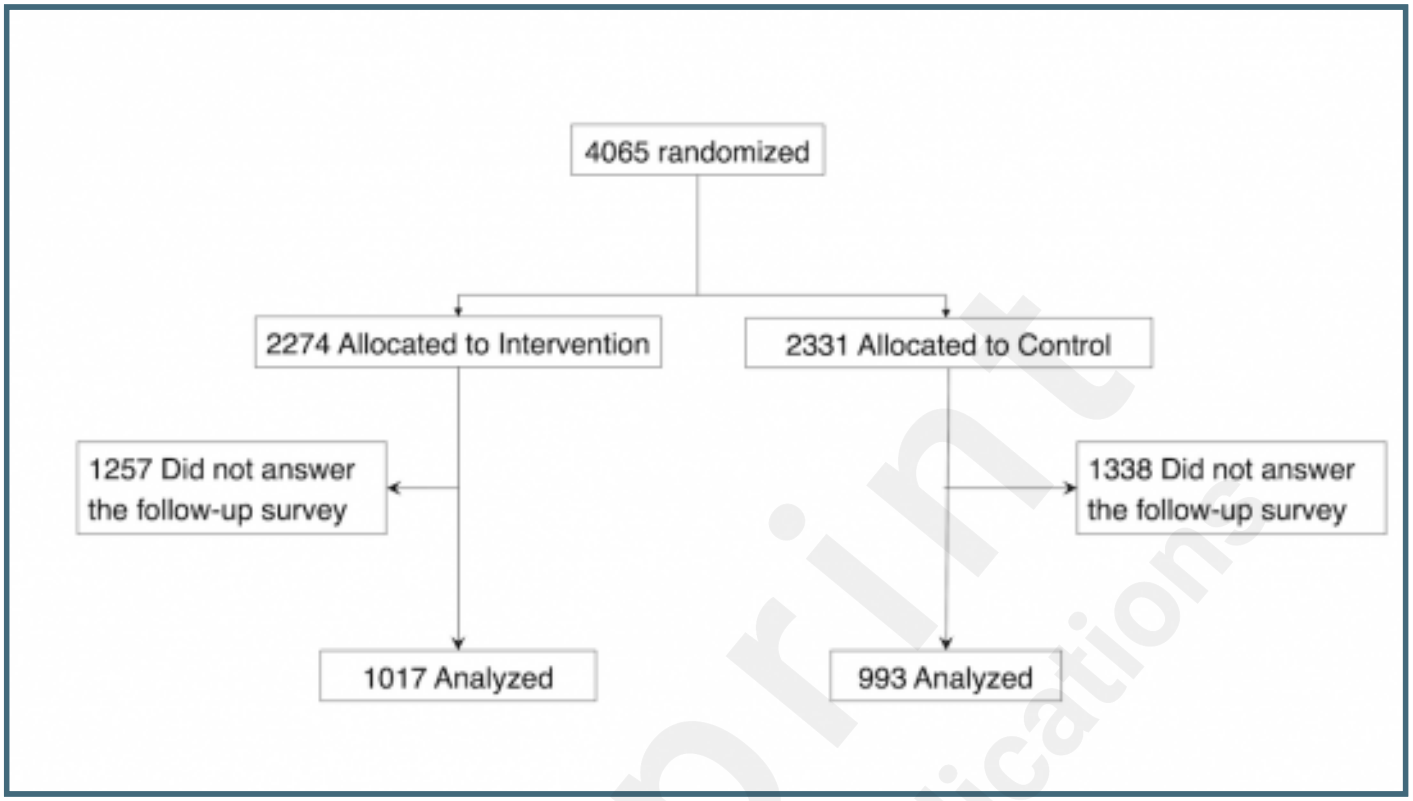
Flow diagram of the randomization.



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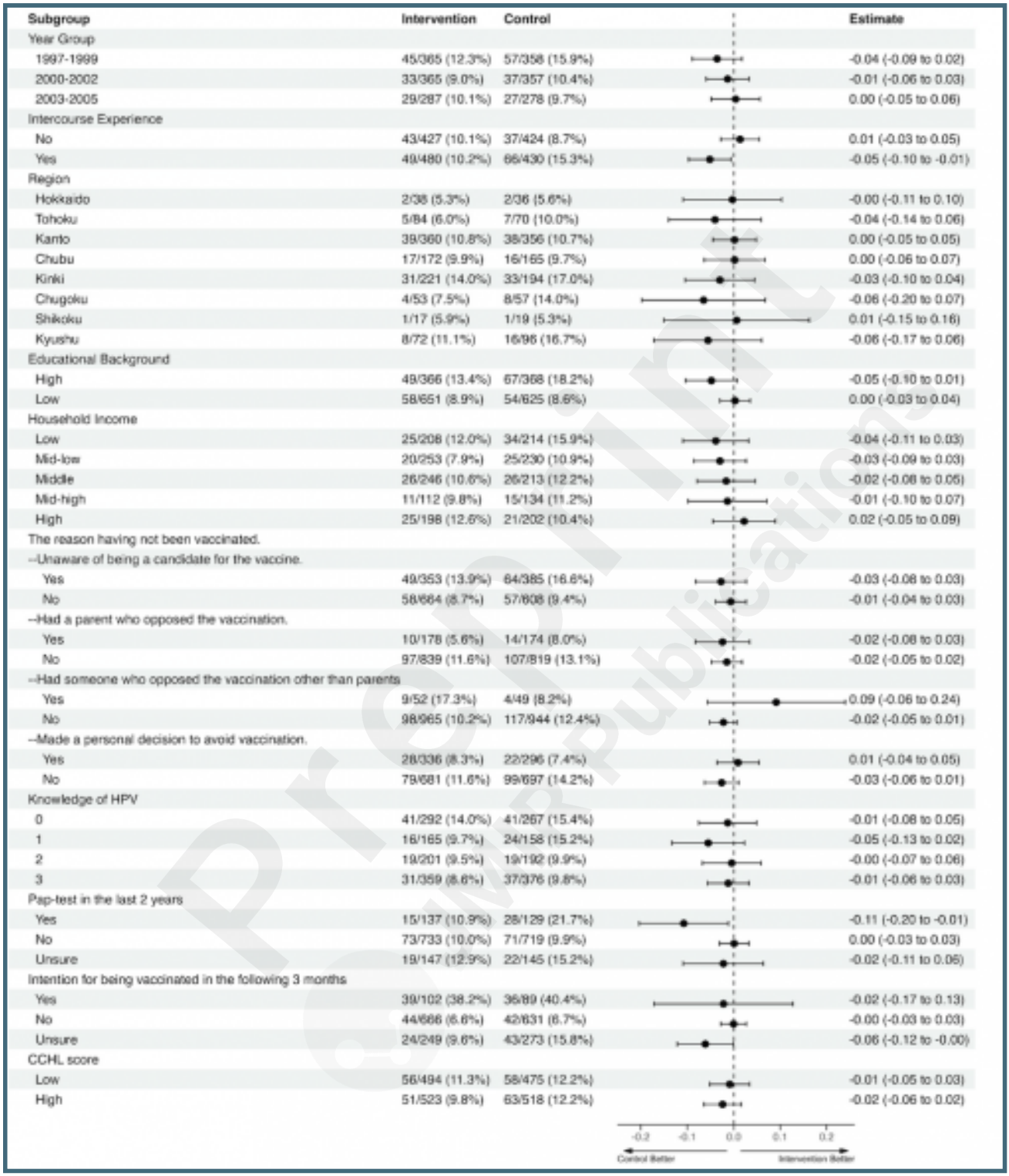
Subgroup analysis.



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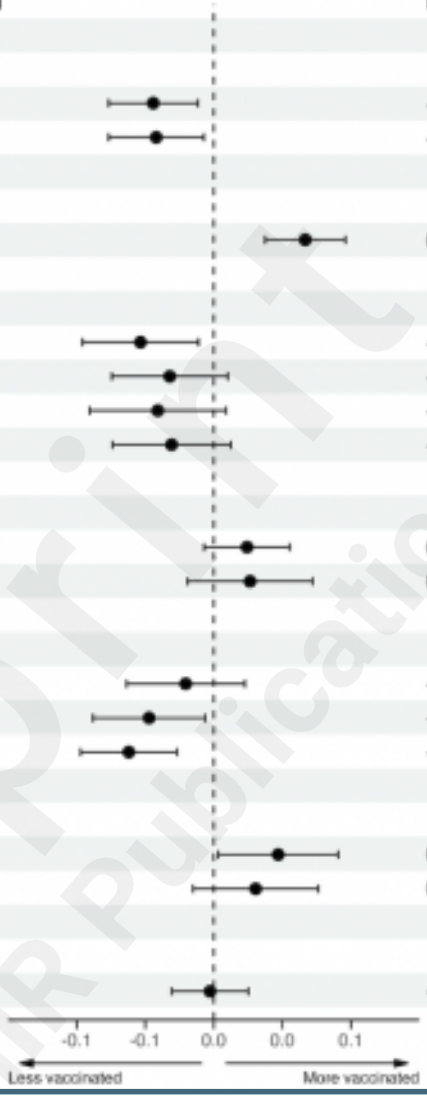
Factors associated with vaccination behaviors in the entire study population. HPV: human papillomavirus; CCHL: communicative and critical health literacy.

Factor	Vaccinated	Not vaccinated	Estimate
Year Group			
1997-1999 (Ref)	102	621	
2000-2002	70	652	-0.04 (-0.08 to -0.01)
2002-2005	56	509	-0.04 (-0.08 to -0.01)
Educational Background			
Low(Ref)	112	1164	
High	116	618	0.07 (0.04 to 0.10)
Household income			
Low(Ref)	59	363	
Mid-low	45	438	-0.05 (-0.10 to -0.01)
Middle	52	407	-0.03 (-0.07 to 0.01)
Mid-high	26	220	-0.04 (-0.09 to 0.01)
High	46	354	-0.03 (-0.07 to 0.01)
Intercourse experience			
No(Ref)	80	771	
Yes	115	795	0.02 (-0.01 to 0.06)
Unsure	33	216	0.03 (-0.02 to 0.07)
Knowledge of HPV and cervical cancer			
0(Ref)	82	477	
1	40	283	-0.02 (-0.06 to 0.02)
2	38	355	-0.05 (-0.09 to -0.01)
3	68	667	-0.06 (-0.10 to -0.03)
Pap test in the last 2 years			
No(Ref)	144	1308	
Yes	43	223	0.05 (0.00 to 0.09)
Unsure	41	251	0.03 (-0.01 to 0.08)
CCHL score			
Low(Ref)	114	855	
High	114	927	-0.00 (-0.03 to 0.03)



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Multimedia Appendixes

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Supplementary tables and figures.
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