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RESEARCH PAPER

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Time-dependent changes of the intention of mothers in Japan to inoculate their daughters with the HPV vaccine after suspension of governmental recommendation

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ABSTRACT

In Japan, the trend for cervical cancer at younger ages has been increasing. As a countermeasure, the HPV vaccine was introduced as a routine vaccination in April 2013. However, the Ministry of Health, Labour and Welfare (MHLW) announced a "Suspension of its active inoculation recommendation for HPV vaccine" in June 2013. In 2016, 32 months after that suspension, we conducted survey via Internet and compared the results with our previous ones conducted at 9 and 23 months after suspension (in 2014 and 2015, respectively). We examined the 'time-dependent change' of the 'intention of mothers to inoculate their daughters with the HPV vaccine' in terms of efficacy of external decision-making support. 17.5% of mothers in the first survey replied that they would inoculate their daughters under the current circumstances, 12.1% in the second survey, and 6.7% in the third, showing a consistent decrease in willingness over time ($p = 0.03$, $p < 0.01$). If the government recommendation were to be reintroduced, 22.5% of mothers in the first survey replied they would inoculate their daughters, 21.0% in the second survey, which indicated no significant difference ($p = 0.65$) over the first interval; however, this was significantly decreased to 12.2% in the third survey ($p < 0.01$). Our study revealed that the intention to inoculate their daughters has been declining among Japanese mothers over time triggered by the suspension.

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Introduction

The age at which cervical cancer, including carcinoma in situ (CIS), is being detected in Japan is trending downwards.[1] In 1985, the peak age of onset of cervical cancer (including CIS) was over age 40. This contrasts with a recent dramatic shift, of the peak age of onset to women in their twenties.[1] In addition, there has been a notable increase of more than 4 years, from 26.4 years to 20.7 years, in the mean age at which Japanese females first give birth,[2] combined with a rapid increase in the incidence rates of cervical cancer (including CIS) before first birth, putting national fertility at even greater risk. As a new dire contributing factor, the cervical cancer screening rate in Japanese females is unusually low for advanced countries, at less than 40%, compared to that in Europe and America, which is 60–80%.[3,4] In particular, the cervical screening rate among women in their early twenties is 10%.[5]

The Human Papillomavirus (HPV) vaccine against cervical cancer was expected to be a powerful preventive measure. So much so that subsidies in local governments for the HPV vaccination programs commenced in 2010 and it became vaccination with public expenditure grant in April 2013. However, repeated news reports regarding so-called adverse events such as chronic pain and motor impairment arose soon thereafter, stoking public doubts about the vaccine's safety. The MHLW responded by announcing a "Suspension of its active inoculation recommendation for the cervical cancer prevention vaccine" on June 14th, 2013.[6] As of March 2018, this

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suspension remains in place. Due to combined effect of both alleged adverse events and MHLW's consequential suspension of its active recommendation, the HPV vaccination rate among younger generation has sharply decreased, with the percentage for females born after 2002 being 1% or less.[7]

This is our third Internet survey conducted to date among mothers who had HPV-unvaccinated daughters. The girls were aged 9–12 in the 1st survey, and aged 12–16 in the 2nd one.[8,9] If the respondents had multiple eligible daughters, only answers for the eldest were collected. Because the first Internet survey was a pilot study, its target population was relatively small. We analyzed the intention of mothers to inoculate their daughters under three types of circumstances: (1) under current circumstances; (2) if the MHLW restarted their recommendation; and (3) if the MHLW restarted their recommendation upon reading vaccine recommendation messages.

In the first Internet survey, conducted in May 2014, nine months after suspension of the recommendation – regarding the intention of mothers to inoculate – 17.5% of mothers replied they would inoculate under the current circumstances, and 22.5% replied they would inoculate – if the recommendation was restarted. Furthermore, those replying that they would inoculate with the vaccine – if recommendation messages were posted – increased to 23.5%. Despite the respective increases in tendencies, no significant differences were observed ($p = 0.26$, $p = 0.90$). Moreover, it was revealed that a significant correlation was observed between the mothers' awareness of the risk of side-effects from the HPV vaccine and the inoculation action taken by their daughters, whereas no correlation was observed between the reactions of their daughters at the time of HPV vaccination and the decisions taken by their daughters about inoculation. Because it was revealed that the views of the mothers were more influential than those of their daughters regarding decisions about inoculation, it became clear that it was critical to provide correct and influential information to the mothers, in the event of a reintroduction of the recommendation. We therefore modified those messages.[8] We conducted a second internet survey in May of 2015, 23 months after the suspension of recommendation, where we examined the effect of these modified messages. As a result, while 12.1%, replied they would inoculate under the current circumstances, those replying they would inoculate – if the recommendation resumed – increased significantly, to 21.0% ($p < 0.001$). Furthermore, those who replied they would inoculate – if the modified messages were also posted – significantly increased, to 27.3%, indicating the definite effectiveness thereof of the modification ($p < 0.001$).[9]

In this paper, we report on and compare the results of our third internet survey, conducted in February 2016, with those of the two previous internet surveys. We examined the 'intention of mothers to inoculate their daughters with the HPV vaccine' when we conducted the recommendation using messages in which we added further modifications to the second internet survey. In addition, we will explore the 'time-dependent change' of the 'intention of mothers to inoculate their daughters with the HPV vaccine' via a comparison with the past surveys and examine the efficacy of our external decision-making-support for the 'inoculation of their daughters' for mothers at the point when 32 months had passed from suspension of active recommendation.

Results

Characteristics of the responders to the present internet survey

Table 1 compares the characteristics of the subjects of the three surveys. The residential areas, as well as the educational backgrounds, of the responders roughly matched those of the National Census (Hokkaido/ Tohoku, Kanto, Chubu/Kinki, Chugoku/Shikoku, and Kyusyu).[10,11] No differences were observed in the three internet surveys regarding the characteristics of the responders, including age, residence area and education level (Table 1). The number of the responders was 200, 2060 and 2000, respectively, in the three surveys. Most of the responders were in their thirties and forties.

Results of the third internet survey

Regarding the inoculation intention of the mothers, 6.7% replied they would 'inoculate under current circumstances'. Those replying they would 'inoculate if the recommendation restarted' significantly increased, to 12.2% ($p < 0.01$), and those

Table 1. Characteristics of the internet survey responders.

		1st (Mar. 2014)		2nd (May. 2015)		3rd (Feb. 2016)	
Mothers with unvaccinated daughter		Number	Percent	Number	Percent	Number	Percent
Total		200	100.0%	2060	100.0%	2000	100.0%
Age	30-39	80	40.0%	488	23.7%	273	13.7%
	40–49	116	58.0%	1449	70.3%	1491	74.6%
	50–59	4	2.0%	119	5.8%	235	11.8%
	60-	0	0%	4	0.2%	1	0.1%
Residence area	Hokkaido/ Tohoku	23	11.5%	235	11.4%	218	10.9%
	Kanto	77	38.5%	714	34.7%	696	34.8%
	Chubu/Kinki	62	31.0%	754	36.6%	808	40.4%
	Chugoku/Shikoku	19	9.5%	157	7.6%	138	6.9%
	Kyusyu	19	9.5%	200	9.7%	140	7.0%
Education	Junior/Senior high-school	59	29.5%	712	34.6%	614	30.7%
	Junior/Technical college	84	42.0%	846	41.0%	838	41.9%
	University/Graduate school	57	28.5%	498	24.2%	545	27.3%
	Other	0	0%	4	0.2%	3	0.2%

Table 2. Intention for inoculation: Vaccinate without any specific conditions under suspension of active recommendation.

	Inoculate		Unsure	Won't inoculate
1st (Mar. 2014)	35	(17.5%)*1	165	(82.5%)
			114 (57.0%)	51 (25.5%)
2nd (May. 2015)	250	(12.1%)*1*2	1810	(87.9%)
			977 (47.4%)	833 (40.4%)
3rd (Feb. 2016)	133	(6.7%)*2 *3	1867	(93.4%)
			986 (49.3%)	881 (44.1%)

*1 $p = 0.03$ (Fisher's exact test).
*2 $p < 0.01$ (Fisher's exact test).
*3 $p < 0.01$ (Fisher's exact test) (compared to *6 in Table 3).

who replied they would 'inoculate if the recommendation restarted – and upon reading the messages' increased significantly further, to 24.9% from 12.2% ($p < 0.01$) (Tables 2, 3, 4). Regarding mothers, at 32 months, who replied they would not inoculate: 44.1% would not inoculate under the present circumstances, 32.5% would not inoculate even if the recommendation restarted, and 20.9% would not inoculate even if the recommendation restarted with added messages.

Time-dependent change

Nine months after suspension of the active recommendation by the MLHW, 17.5% of mothers replied they would inoculate in response to the question regarding whether or not they would inoculate in the future under present circumstances (first internet survey). This changed to 12.1% after 23 months (second internet survey), and 6.7% after 32 months (third internet survey), showing a consistent significant decrease in intention over time (17.5% v.s. 12.1%: $p = 0.03$, 12.1% v.s. 6.7%: $p < 0.01$) (Tables 2, 3, 4). Nine months after the suspension, 25.5% of mothers replied they would not inoculate, with this changing to 40.4% after 23 months, and 44.1% after 32 months.

Regarding the question of whether or not they would inoculate if the recommendation restarted, nine months after the suspension, 22.5% of mothers replied they would inoculate if the recommendation restarted. This changed only slightly, to 21.0%, after 23 months, indicating no significant difference (22.5% v.s. 21.0%: $p = 0.65$). However, this intent subsequently significantly decreased, to 12.2%, after 32 months (21.0% v.s. 12.2%: $p < 0.01$). Moreover, nine months after the suspension, 18.5% of mothers replied they would not inoculate, with this increasing to 24.7% (trending) after 23 months, and significantly, to 32.5%, after 32 months.

Table 3. Intention of inoculation: Vaccinate after restart of the recommendation.

	Inoculate		Unsure	Won't inoculate
1st (Mar. 2014)	45	(22.5%)*2	155	(77.5%)
			118 (59.0%)	37 (18.5%)
2nd (May. 2015)	433	(21.0%)*5*6	1627	(79.0%)
			1118 (54.3%)	509 (24.7%)
3rd (Feb. 2016)	244	(12.2%)*5*6	1756	(87.8%)
			1106 (55.3%)	650 (32.5%)

*2 $p = 0.65$ (Fisher's exact test).
*5 $p < 0.01$ (Fisher's exact test).
*6 $p < 0.01$ (Fisher's exact test) (compared to *3 in Table 2).

Table 4. Vaccinate after restart of the recommendation (After reading messages).

	Inoculate		Unsure	Won't inoculate
1st (Mar. 2014)	47	(23.5%)*7	153	(76.5%)
			113 (56.5%)	40 (20.0%)
2nd (May. 2015)	562	(27.3%)*7*8	1498	(72.7%)
			1071 (52.0%)	427 (20.7%)
3rd (Feb. 2016)	497	(24.9%)*8*9	1503	(75.2%)
			1086 (54.3%)	417 (20.9%)

*7 $p = 0.28$ (Fisher's exact test).
*8 $p = 0.08$ (Fisher's exact test).
*9 $p < 0.01$ (Fisher's exact test) (compared to *6 in Table 3).

Regarding the question of whether or not they would inoculate 'if the recommendation were restarted plus posted messages', nine months after the suspension, 23.5% of mothers replied they would inoculate, with this changing to 27.3% after 23 months, indicating an increasing tendency, but with no significant difference; however, this decreased to 24.9% after 32 months (23.5% v.s. 27.3%: $p = 0.28$, 27.3% v.s. 24.9%: $p = 0.08$). Nine months after the suspension, 20.0% of mothers, after reading the information messages, replied they would not inoculate, with this changing only slightly with time, to 20.7% after 23 months, and 20.9% after 32 months.

The results of the comparison of the mothers' intention to inoculate their daughters (inoculate versus unsure/won't inoculate) among three internet surveys were described above. We, then, performed sensitivity analysis, comparing mothers' intention to inoculate their daughters (inoculate/unsure versus won't inoculate), which did not reveal any significant differences in the above data.

Discussion

We have previously published our predictions for differences in infection rates for HPV types 16 and 18 upon turning 20 years of age, based on birth-year, as a direct result of the sharp decrease in the percentage of inoculations of the HPV vaccine.[12] As a result, if the percentage of inoculations does not soon recover – due to not restarting the active recommendation by the MHLW in 2016 – we predict that girls born in or after the year 2000 will soon exceed the eligible inoculation subject age and be unprotected.

In Japan, various approaches for improvement of the rate of cervical cancer screenings have been taken, for example, the free screening coupon program. However, the overall medical examination rate is currently only 37.7% in women aged 20 to 69, with the lowest rate for females in their twenties.[3] Therefore, Japanese females remain very vulnerable to the threat of what was once a highly preventable malignant HPV virus infection, and cervical cancer.

Past surveys revealed that it was the will of mothers, not their daughters', that most influenced the decision regarding HPV vaccination.[8] More specifically, in terms of spreading the word on the HPV vaccine, it is believed important to see how mothers come to a decision and therefore, how recommendations are made. In this comparison of time-dependent changes in mother's attitudes, regarding the question "Would you inoculate your daughter if the active recommendation was restarted by the MHLW?", after nine months (first internet

survey), 22.5% of the mothers replied they would inoculate their daughters, with this changing to 21.0% after 23 months (second internet survey), indicating no significant decrease ($p = 0.65$) and suggesting that a certain number of mothers exist with the intention of inoculating their daughters. However, after 32 months, mothers who replied they would 'inoculate their daughters if the recommendation restarted' had significantly decreased, to 12.2% (third internet survey) ($p < 0.01$). These results suggest that the passage of time has a serious negative impact on the decision-making of mothers regarding the HPV vaccination, potentially impacting on the uptake of the HPV vaccine even if the MHLW restarted its active recommendation.

Furthermore, even if messages encouraging recommendation were included, regardless of the modification of the messages in each survey, the intention to inoculate in response to the question "Would you inoculate your daughter, if the active recommendation were restarted by the MHLW?" showed an increasing tendency, but with no significant change, between 9 and 23 months after suspension; however, a decreasing tendency was indicated after 32 months. Going forward, as more time passes, the intention to inoculate is likely to continue to decrease, even if messages encouraging recommendation are included.

This study revealed that, under the present circumstances of ongoing suspension of the recommendation by the MHLW, the intention of mothers to inoculate their daughters with the HPV vaccine has been decreasing significantly over time. Even assuming restarting of the recommendation, the intention of mothers to inoculate their daughters is decreasing with every passing month. In practice, in the case of a restart of the national governmental recommendation, mothers nationwide should receive a letter of recommendation encouragement from their local government.

To our knowledge, this is the first demonstration of time-dependent changes occurring in Japan, regarding mothers' intentions to inoculate their daughters with the HPV vaccine, following the government's suspension of its active recommendation for it. However, there are limitations to this study. For example, the age of the daughters of mothers targeted in this current survey was different from the prior two surveys; additionally, the number of the targeted mothers was relatively small in the first survey.

There was evidence that an improvement in the intention to inoculate increased significantly after reading the messages in the third survey (6.7% to 12.2%). Although we can expect that providing information in the form of developed messages and colored illustrations/captioned drawings will result in a level of increase in the intention to inoculate, we believe that this increase will be limited and that it is necessary to develop new approaches to support decision-making. Providing information that incidence and mortality of cervical cancer has been significantly increasing in Japan because of the lack of mass population vaccinations might be effective for mothers to make a decision regarding the HPV vaccination. It may also be important to better educate the public about the significant risks from cancer to health, life and fertility. Further studies are required regarding support for the decision-making processes for mothers and the inoculation of their daughters.

Methods

The third internet survey

We conducted a third internet survey, this time 32 months after the suspension of active recommendation. We used one of the most biggest internet research companies that offer online research panels. This survey was conducted among mothers who had HPV-unvaccinated daughters aged 12–16. 2000 mothers were included nationally. As with the past two internet surveys, this survey was conducted following a screening survey to select representative mothers. In the screening survey, we asked questions regarding the sex of the responder, device used to reply, occupation, educational background, household income, whether or not they have a daughter, grade of the daughter, and prevention vaccination status of the child (periodical inoculation/voluntary inoculation/HPV vaccine). If they had multiple daughters, the answers for only the eldest daughter were collected.

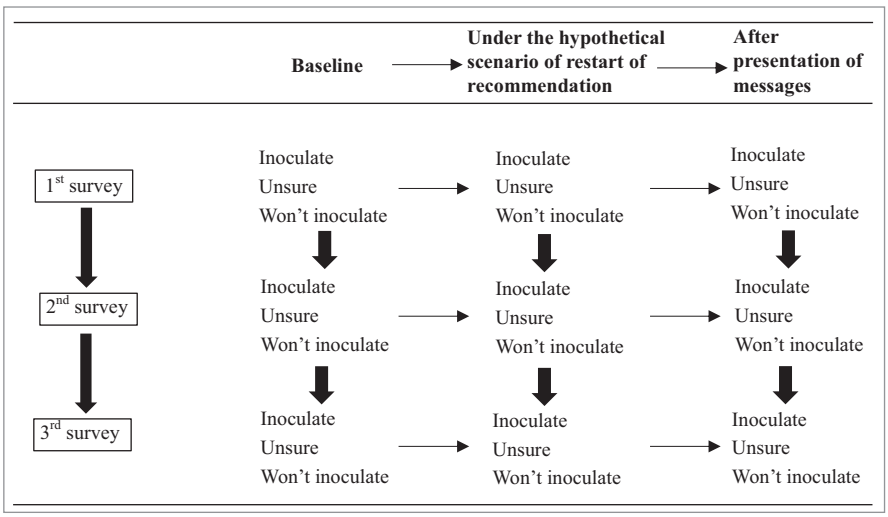

Figure 1. Survey for the mothers' intentions towards HPV vaccination for daughters.

We analyzed the answers to the following three questions: (1) Would you, or would you not, inoculate your daughter with the HPV vaccine under the current circumstances?; (2) Would you, or would you not, inoculate your daughter if the MHLW restarted the recommendation?; and (3) Would you, or would you not, inoculate your daughter if the MHLW restarted the recommendation, and upon reading vaccine recommendation messages?.

Regarding the presentation of messages, materials were created using messages on the "susceptibility and seriousness of cervical cancer," and "safety," "effectiveness" of the vaccines as follows: (1) Invasive cervical cancer in younger women has doubled, compared to 20 years ago, (2) Hysterectomy is usually needed for invasive cervical cancer, even if it is found at an early stage, and afterwards the patient can't conceive, (3) The vaccine is effective in preventing cervical cancer in the future, with a probability of 60–70%, (4) HPV vaccine is given safely in about 99.993% of vaccinations, and so on. Additional material was displayed on the Web screen; it included colored illustrations and explanatory drawings, provided in a comprehensible way, and a story which was created based on an actual clinical case, including illustrations of a female who underwent a hysterectomy, with the fetus still *in utero*, due to the detection of early cervical cancer during a prenatal checkup.

Analysis of the time-dependent change of the intention of mothers to inoculate their daughters with the HPV vaccine (comparison with past surveys)

We compared our current survey results with the internet surveys conducted 9 months and 23 months after suspension of active recommendation (Figure 1). Taking mothers who had HPV unvaccinated daughters as the subjects, the past two internet surveys were conducted among 200 mothers the first time and 2,060 mothers the second time, using the same survey methods each time.

We compared answers to the following three questions, over time, which we asked in each survey: (1) Would you, or would you not, inoculate your daughter with the HPV vaccine under the current circumstances?; (2) Would you, or would you not, inoculate your daughter if the MHLW restarted the recommendation?; and (3) Would you, or would you not, inoculate your daughter if the MHLW restarted their recommendation, and upon helpful messages being posted, and reading the messages? Message modification was conducted for the second and third surveys.

Regarding the three questions described above, the rate of mothers who replied they would inoculate was compared between the 1st and 2nd surveys, and between 2nd and 3rd ones, respectively. Especially in the 3rd internet survey, the inoculation intention of mothers who replied they would inoculate was compared between the three circumstances described above.

Statistics

Background characteristics in the three internet surveys were analyzed by the Wilcoxon rank sum test with Bonferroni correction. Fisher's exact test was used for the statistical analysis of mothers' intention to inoculate their daughters (inoculate versus unsure/won't inoculate). Sensitivity analysis was conducted by comparing mothers' intention to inoculate their daughters (inoculate/unsure versus won't inoculate). The level of statistical significance was set at $p = 0.05$.

Informed Consent and Approval

This study was approved by the ethics committees of the Osaka University Hospital. Informed consent was obtained by clicking an "I agree" button by all participants in this study.

Abbreviations

CIS	carcinoma *in situ*
HPV	human papilloma virus
MHLW	the Ministry of Health, Labour and Welfare

Disclosure of potential conflicts of interests

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