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June 11, 2018.

Opinion on Sadao Suzuki's paper on the Nagoya City Cervical Cancer Immunization Survey

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1 "Nagoya City Cervical Cancer Immunization Survey" and Suzuki paper

A paper titled "No association between HPV vaccine and reported post-vaccination symptoms in Japanese young women: Results of the Nagoya study"ⁱ (hereinafter referred to as "the Suzuki paper") by Professor Sadao Suzuki of Nagoya City University was published in the journal *Papillomavirus Research* in 2018. The paper is an analysis of the Nagoya City Cervical Cancer Immunization Survey, which was conducted by the city of Nagoya in 2015ⁱⁱ (hereinafter referred to as "the survey").

On December 14th, 2015, the City of Nagoya released a Preliminary Report of Analysis of Nagoya City Cervical Cancer Immunization Program Survey (hereinafter referred to as "the preliminary report"). In response to this, Medwatcher Japan submitted a "Statement on the 'Preliminary Report of Analysis of Nagoya City Cervical Cancer Immunization Program Survey'ⁱⁱⁱ (hereinafter referred to as "the 2015 opinion") to the Mayor of Nagoya, pointing out problems with the survey. The preliminary report was criticized by people other than Medwatcher Japan and was later retracted by the city of Nagoya^{iv}.

The Suzuki paper is an article that Professor Suzuki, who was in charge of the analysis of the preliminary report, submitted this time to an academic journal. In his conclusion, he says, "The results suggest that there is no causal relationship between the vaccine and the reported symptoms or adverse reactions." However, there are still serious problems with the Suzuki paper, so we believe that there are reasonable grounds to state that its conclusion is incorrect.

2 Limitations of the survey - not suitable for inferring causality

The survey is highly significant as it is the first large-scale survey of adverse reactions to the HPV vaccine reported in Japan by vaccinated and non-vaccinated people. However, as mentioned in the 2015 opinion, due to its design, it has various limitations as follows:

- 1) Since it is a sample survey in the form of a questionnaire whose responses depend on factors such as the respondents' intentions, it is possible that the sample (respondents) may be biased against the population (all survey targets).
- 2) The symptomatic group is likely to be more active in answering than the asymptomatic group. This tendency is expected to be more pronounced in the non-vaccinated group (those who have not been vaccinated and are not symptomatic are much less interested in answering), and may result in a higher estimate of the incidence of symptoms in the non-vaccinated group.
- 3) The respondents' answers varied. Some said that they filled out the questionnaire themselves (27.1%), others said that they filled it out in consultation with their guardians (29.5%) and others said that their guardians filled it out (43.4%). It is possible that this caused some variability in the responses.
- 4) No physician was involved in determining the presence or absence of symptoms, and responses may vary from person to person for similar conditions.
- 5) The older the respondents were, the more they were required to give answers based on what they remembered about their symptoms over a longer period of time. Therefore, it is conceivable that the accuracy of these respondents' answers varied depending on the respondents' age.
- 6) Since people who are in poor health are likely to avoid vaccination, there may be a bias in the population itself, with that more people in the non-vaccinated group are in poor health. As a result, the comparison between the vaccinated and non-vaccinated groups may not simply be a comparison of status, in other words vaccinated or non-vaccinated, but rather a comparison of the incidence of symptoms in two groups with different health statuses.
- 7) Rare adverse reactions in vaccinations are so infrequent that any statistical significance is difficult to detect.

While giving due consideration to the above limitations of the survey, we do not deny the usefulness of conducting exploratory analysis to obtain clues for further investigation. However, a part of the Suzuki paper contains an analysis method that lacks sufficient consideration of these limitations to test the statistical significance of the vaccinated group and the non-vaccinated group, and makes inferences about causality based on the results of the test, which is highly inappropriate.

3 No rationale for age-adjustment is provided

In the preliminary report, the data before age-adjustment showed that there were 4 symptoms where "symptomatic" was significantly more frequent in the vaccinated group. After age-adjustment, however, none of these symptoms were found, and conversely, 15 of 24 symptoms became significantly less frequent in the vaccinated group. In relation to this, the 2015 opinion pointed out the error of age-adjustment as a serious problem with the preliminary report.

Although age-adjustment was also used in the Suzuki paper, the paper only states that "[a]ge ... confounded the association between HPV vaccination and reported symptoms, therefore we decided all analyses should be age-adjusted," without providing any specific rationale for age-adjustment.

However, when using statistical analysis methods such as age-adjustment, it is essential to check the status of the data to ensure that the analysis method is appropriate because if an inappropriate method is used, it will lead to wrong results. Nevertheless, the Suzuki paper presents results using the age-adjusted analysis method without indicating how the status of the data was checked, and concludes that vaccination does not increase adverse symptoms. This leaves us with no way of knowing if the results are correct or not.

4 Unreasonable result of significantly lower incidence in the vaccinated group - fundamental flaw in the paper

(1) Fundamental flaw in the Suzuki paper

In the age-adjusted analysis of the Suzuki paper, 14 of 24 symptoms were significantly lower in the vaccinated group than in the non-vaccinated group.

If the original health status of the respondents in the vaccinated and non-vaccinated groups were similar, and if age adjustment was appropriate for the data, such a result would not be possible. Therefore, it may have been caused by inappropriate age-adjustment.

In addition, if the health status of the vaccinated group and the non-vaccinated group were not similar, and the non-vaccinated group was in worse health than the vaccinated group (given the limitations of the survey e.g. 2), 6), this is quite possible), then the simple comparison of two groups with different health statuses would itself be problematic. This is not a problem that can be solved by age-adjustment.

Furthermore, it cannot be denied that the unreasonable results in the Suzuki paper, in which the incidence rate was significantly lower in the vaccinated group, may have been due to the fact that the non-vaccinated group was originally a group in poorer health, and the bias may have been more pronounced due to inappropriate age-adjustment.

Therefore, in any case, the Suzuki paper must be said to have made an inappropriate comparison. This is a fundamental flaw in comparative observational research, and no scientific conclusions can be drawn from the results.

(2) Comparing "multiple symptoms" is meaningless

The Suzuki paper also compared those who had multiple symptoms, and suggested that "there was no association between HPV vaccination and multiple symptoms." This seems to reflect the criticism in the 2015 opinion that simply comparing individual symptoms does not mean comparing symptoms after HPV vaccination, which is characterized by the multi-layered manifestation of symptoms in a single patient. However, in the comparison of "multiple symptoms" as the Suzuki paper calls it, the odds ratio for the occurrence of one type of symptom was 0.83 (95% confidence interval: 0.78 -0.88), two or more types of symptoms was 0.81 (0.76 -0.87), three or more types of symptoms was 0.80 (0.75 -0.86), four or more types of symptoms was 0.79 (0.73 -0.86), five or more types of symptoms was 0.77 (0.70 -0.84), and 10 or more types of symptoms was 0.76 (0.63 -0.93). Again, this shows an unreasonable result of the incidence rate being significantly lower in the vaccinated group. The results of the comparison of those who developed multiple symptoms shown here may also

be the result of inappropriate age-adjustment or differences in the original health status of the two groups, and therefore cannot be considered correct.

In the survey, because the presence or absence of each symptom over a long period of several years is asked, even if the respondents answered that they had more than one symptom, it does not necessarily mean that the symptoms developed in a multi-layered manner. Therefore, it should be added that this cannot be called "multiple symptoms."

5 Arbitrary considerations

In the "Results" and "Discussion" sections, the Suzuki paper is notable for its arbitrary descriptions and interpretations that lead to the conclusion that 'there is no causal relationship between the HPV vaccine and the reported symptoms.'

(1) For example, the preliminary report clearly stated that after age-adjustment, 15 of the 24 symptoms were significantly lower in the vaccinated subjects ("Nagoya City Cervical Cancer Immunization Survey Analysis Results (Preliminary) Summary" Table 4). However, the Suzuki paper only states in the "Results" section that "none of the 24 reported symptoms were significantly associated with an increased odds ratio after administration of the HPV vaccine," and does not present the fact that the incidence rate was significantly lower among vaccinated people in 14 symptoms, nor does it discuss the cause of this unreasonable result.

(2) The Suzuki paper also presents the results of a comparison between the presence or absence of hospital visits in symptomatic cases, after excluding cases that occurred before the first vaccination. This may have been in response to criticism of the preliminary report that it did not take into account the time of onset or the severity of symptoms. The results showed that the rate of hospital visits was significantly higher for 13 symptoms among those who were vaccinated. The Suzuki paper, however, states that there are three possible reasons for this: A) those who received the HPV vaccine had relatively more severe symptoms that required medical diagnosis/treatment, B) those who received the vaccine visited the doctor more frequently because they were more concerned about the causal relationship between the HPV vaccine and their symptoms, and C) the impression of the HPV vaccination was so strong that they mistook symptoms that existed before the vaccination as having occurred after the vaccination, suggesting that B) and C) rather than A) are the cause.

However, this is nothing more than a completely unfounded guess (or wish). For each symptom, the questionnaire asks the respondent to indicate whether the symptom is present or absent, and whether the respondent has visited a hospital for the symptom (yes or no), so the presence or absence of a hospital visit should be regarded as an indicator of the severity of symptoms. If this is interpreted as it is in the Suzuki paper, the meaning of asking about the history of medical visits would be lost.

Thus, the Suzuki paper makes a very arbitrary consideration in order to draw its conclusion based on the prejudgment that there is probably no causal relationship between the HPV vaccine and any symptoms.

(3) After such arbitrary considerations, it concludes by saying that "it has become clear that the HPV vaccines were not significantly associated with the occurrence of 24 reported symptoms, thus suggesting no causal association

between the vaccines and reported symptoms or adverse events."

Given the limitations of the survey and the fundamental flaws in the Suzuki paper as described above, it goes without saying that such a conclusion cannot be drawn. In the preliminary report, Dr. Suzuki himself did not link the results to a causal relationship, stating in his "conclusion" that "among the 24 symptoms surveyed this time, there were no symptoms that were significantly more prevalent among vaccinees." Rather, he said, "This is a statistical analysis, and we need to carefully judge the causality of each case." The conclusion seems to reflect his awareness that the survey had limitations and that he could not judge the causal relationship. It is also unclear why the Suzuki paper drew the conclusion that "[t]he results suggest no causal association."

6 Conflict of interests in the journal published

The journal *Papillomavirus Research*, in which the Suzuki paper was published, is a new online journal that was launched in 2015.

Xavier Bosch, the first editor-in chief of the journal, became an author on 9 out of 10 related papers due to his being a member of the PATRICIA study organized by GlaxoSmithKline, which manufactures and markets the HPV vaccine Cervarix. He is also a co-author on the clinical trial papers of Gardasil and Gardasil 9, which are manufactured and marketed by Merck^{v,vi}.

Bosch also allegedly received advisory board fees, speaker's fees, and travel grants from GlaxoSmithKline, Merck, and Sanofi Pasteur MSD, as well as unrestricted institutional research grants from GlaxoSmithKline and Merck, according to a 2016 paper^{vii}. He is also currently a member of the Program Committee of EUROGIN 2018, of which Merck is a platinum sponsor^{viii}. Thus, the editor-in-chief of the published journal has a strong conflict of interest with the HPV vaccine manufacturers.

Among the other editors and editorial board members of the journal, several (Jack Cuzick, Anna Giuliano, Joakim Dillner, Matti Lehtinen), including Ryo Konno, a professor at Jichi Medical University, have authored clinical trial papers on Cervarix and Gardasil.

Furthermore, in the editorial at the beginning of the first issue of the journal, Editor-in-Chief Bosch himself also mentions the importance of the HPV vaccine.

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Against this background, it can be inferred that the journal's editorial policy is to promote the HPV vaccine.

It can also be inferred that a strong conflict of interest on the editors' part contributed to the decision to publish the Suzuki paper in *Papillomavirus Research*, despite the limitations of the survey and the fundamental flaws in the analysis as pointed out in this opinion. As a result, there is a possibility that the paper was published without proper peer review.

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- ⁱ <https://www.sciencedirect.com/science/article/pii/S2405852117300708?via%3Dihub>
- ⁱⁱ <https://www.city.nagoya.jp/kenkofukushi/page/0000088972.html>
- ⁱⁱⁱ <https://www.yakugai.gr.jp/topics/topic.php?id=906>
- ^{iv} June 27, 2016, Chunichi Shimbun morning edition, June 27, 2016, Asahi Shimbun morning edition, etc.
- ^v From the description of conflicts of interest in the article <https://academic.oup.com/jid/article/199/7/926/853088>
- ^{vi} From the description of conflicts of interest in the article <http://pediatrics.aappublications.org/content/138/2/e20154387>
- ^{vii} Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis
<https://www.sciencedirect.com/science/article/pii/S2214109X16300997>
- ^{viii} <https://www.eurogin.com/2018/en/scientific-information/program-committee.html>
- ^{ix} <https://reader.elsevier.com/reader/sd/pii/S2405852115000087?token=7433FBA2D6A9CE949B5E8D7BA60B6BAA97DCE6B12BAD001D7AD0A9B2687F2739E53F50DA59C9B7494CEB5F832B248A84&originRegion=us-east-1&originCreation=20220110052831>