

We provide English translations for the convenience of non-Japanese speakers. However, the Japanese shall always prevail over the English in case of any inconsistency.

January 18th, 2023

Dr. Tatsuo Ushiki, President of Niigata University

Dr. Masayuki Sekine, Associate Professor of Department of Obstetrics and Gynecology,
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Compliance Hotline of Misconduct in Research, Audit Office of Niigata University

**Request for Correction to Misidentification in Niigata
University's public relations article on the "Large epidemiologic
study to evaluate the efficacy and safety of HPV vaccination
against cervical cancer in Japan" (NIIGATA Study) and
Verification of the Cause of the Misidentification**

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Purpose of the Request

On September 12, 2022, Niigata University School of Medicine and Graduate School of Medical and Dental Sciences published a public relations article on their website titled "Demonstration of Preventive Effect of HPV Vaccine against cervical precancer - NIIGATA study: Higher preventive effect with vaccination prior to sexual debut"¹ (hereinafter referred to as "the article"). The article misleads its readers about the effectiveness of the HPV vaccine by misrepresenting the contents of the paper "Effectiveness of human papillomavirus vaccine against cervical precancer in Japan: Multivariate analyses adjusted for sexual activity" (hereinafter referred to as "the paper"). It was written by Research Associate Risa Kudo, Specially Appointed Professor Takayuki Enomoto and Associate Professor Masayuki Sekine of the Department of Obstetrics and

Gynecology, Niigata University Graduate School of Medical and Dental Sciences *et al.*². Therefore, we request the following from Niigata University:

1 Promptly edit the article and correctly explain on its website that according to the paper, an appropriate comparison of HPV vaccinated and unvaccinated groups failed to confirm the effectiveness of the HPV vaccine in preventing cervical precancer.

2 Promptly conduct a detailed investigation into why the article contained such unscientific and unfair content by interviewing its authors and checking for their conflicts of interest, and disclose the results of the investigation.

Reasons for the Request

1 Associate Professor Masayuki Sekine is the contact person for enquiries regarding this article. The beginning of the article is shown in Figure 1 below.

● 2022/09/12 研究成果

HPVワクチンによる子宮頸部前がん病変予防効果を確認 – NIIGATA study : 初交前接種でより高い予防効果 –

新潟大学大学院医歯学総合研究科産科婦人科学分野の工藤梨沙助教、榎本隆之特任教授、関根正幸准教授らの研究グループは、子宮頸部前がん病変（細胞診異常）に対してHPVワクチン²がどの程度の予防効果を示すかを検討しました。ワクチン接種者では子宮頸部前がん病変（高度扁平上皮内病変：HSIL以上）が有意に減少しており（ワクチン有効率64%）、特に初交前に接種した場合はHPV16/18型関連の細胞診異常を認めていませんでした。ワクチン接種歴を自治体データにて正確に確認し、初交年齢や経験人数など性的活動性で調整し、HPVワクチンの子宮頸部前がん病変予防効果を明らかにした日本において初めての研究です。

本研究の詳細はCancer Sci.2022 Jun 22. doi: 10.1111/cas.15471.(IF:6.518)に発表されました。

【本研究成果のポイント】

- ・ HPVワクチン接種を受けた20～26歳の女性では、子宮頸部前がん病変（高度扁平上皮内病変：HSIL以上）に対する有意な予防効果が認められた。
- ・ さらに初交前に接種した場合は、HPVワクチンの主標的型であるHPV16/18型に関連する細胞診異常を認めなかった。
- ・ 接種率が激減しているHPVワクチンであるが、HPV感染の予防効果に加えて、子宮頸部前がん病変の予防効果を示した、社会的インパクトの高い知見である。

Figure 1: Extracts from the beginning of the article (Emphasis added by Medwatcher Japan)

Here, the paper is introduced as showing that cervical precancers (high-grade squamous intraepithelial lesion (HSIL) or worse (HSIL+)) were significantly reduced in the vaccinated population (vaccine effectiveness rate 64%). Then, the results are described as "the first study in Japan to demonstrate the effectiveness of HPV vaccination against cervical cytological abnormalities, adjusted for sexual activity including age at sexual debut and number of previous sexual partners."

The article also explains in the "Key Points of the Study Results" section that "significant preventive effectiveness against cervical precancer (high-grade squamous

intraepithelial lesion: HSIL or worse) was observed in vaccinated women aged 20 to 26 years."

2 However, the paper reports that the comparison of the HPV vaccinated and non-vaccinated groups, adjusted for age and sexual activity, showed no statistically significant difference in the incidence of high-grade squamous intraepithelial lesion or worse (HSIL+), as shown in Figure 2 below. Therefore, the paper straightforwardly introduces its conclusion in its abstract: "However, analyses of all vaccinated women did not show significant effectiveness against cytological abnormalities." The main body of the paper also explains it as "In terms of effectiveness against HSIL+, VE was 64.0% (95% CI 19.4–83.9%; $P = 0.013$) in the univariate analysis, 54.1% (95% CI –21.0–82.6%; $P = 0.116$) in Model 1, and 41.1% (95% CI –53.0–77.3%; $P = 0.276$) in Model 2, with the multivariate analyses adjusted for age and number of sexual partners not showing significance."

Thus, the paper's results show no statistically significant difference in the incidence of HSIL+ in the vaccinated and unvaccinated groups. However, the article places special emphasis on the effectiveness of the HPV vaccine without mentioning these conclusions. This is an unscientific and unfair way of introducing a paper.

TABLE 3 Vaccine effectiveness against HPV infection and cytological abnormality

| | HPV 16/18 infection | | | HSIL+ | | |
|-----------------------------|---------------------|-------------|-------------|-------|--------------|-------------|
| Crude analysis ^a | | | | | | |
| OR (95% CI) | 0.06 | (0.03–0.13) | $P < 0.001$ | 0.36 | (0.16–0.81) | $P = 0.013$ |
| VE (95% CI) | 94.1 | (87.0–97.3) | | 64.0 | (19.4–83.9) | |
| Model 1 ^a | | | | | | |
| aOR (95% CI) | 0.09 | (0.04–0.21) | $P < 0.001$ | 0.46 | (0.17–1.21) | $P = 0.116$ |
| aVE (95% CI) | 91.4 | (79.5–96.4) | | 54.1 | (–21.0–82.6) | |
| Model 2 ^a | | | | | | |
| aOR (95% CI) | 0.11 | (0.05–0.27) | $P < 0.001$ | 0.59 | (0.23–1.53) | $P = 0.276$ |
| aVE (95% CI) | 88.8 | (73.4–95.3) | | 41.1 | (–53.0–77.3) | |

Note: Model 1: adjusted for age.

Note: Model 2: adjusted for age and number of lifetime sexual partners.

aOR, adjusted odds ratio; aVE, adjusted vaccine effectiveness; CI, confidence interval; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; HSIL+: HSIL or worse; OR, odds ratio; VE, vaccine effectiveness.

^aVaccinated vs unvaccinated (logistic regression test).

Figure 2: Table 3 in the paper. Model 1 shows the results of the vaccinated and unvaccinated groups, adjusted for age. No statistically significant difference in the incidence of HSIL+ was shown, as the 95% confidence interval crosses 1 and the p-value exceeds 0.05. Model 2 shows the results adjusted for sexual activity (number of previous sexual partners) in addition to age, and similarly no statistically significant difference was shown for the incidence of HSIL+.

To begin with, as is clear from Figure 2 above, the "vaccine effectiveness rate of 64%" cited by the article is merely a crude analysis that wasn't adjusted for differences between the two groups, and does not represent the conclusion of the paper.

Therefore, introducing the paper's conclusion in the article as if it has demonstrated a significant reduction in cervical precancerous lesions (highly squamous intraepithelial lesions (HSIL) or worse) in the HPV vaccinated group adjusted for age and sexual activity is completely false and leads to an apparent misconception about the effectiveness of the HPV vaccine.

Rather, the paper shows that having examined the government's project results of actively promoting HPV vaccination among young women nationwide, including those in Niigata Prefecture, they could not confirm the preventive effect of HPV vaccination against precancerous lesions of cervical cancer between the HPV vaccinated and unvaccinated groups. The paper should be viewed as one of the extremely important findings that will compel the government to reconsider its active recommendation for HPV vaccination.

3 To date, the article has been uncritically quoted in various media as having demonstrated the effectiveness of the HPV vaccine, as exemplified in Figures 3 and 4 at the end of this document. False information about the HPV vaccine has already been spread across society due to Niigata university's erroneous public relations activities.

The university should promptly edit the article and correctly explain on its website that according to the paper, an appropriate comparison of HPV vaccinated and unvaccinated groups failed to confirm the effectiveness of the HPV vaccine in preventing precancerous cervical lesions.

It should also promptly conduct a detailed investigation into why the article contained such unscientific and unfair content by interviewing its authors and checking for their conflicts of interest, and disclose the results of the investigation.

4 Therefore, we would appreciate your reply in writing within one month of receipt of this document regarding the university's response to this matter.

実証！HPVワクチンの前がん病変予防効果



新潟大学大学院産科婦人科学分野の工藤梨沙氏、主任教授の檀本隆之氏、准教授の関根正幸氏らの研究グループは、ヒトパピローマウイルス（HPV）ワクチンによる子宮頸部前がん病変（細胞診異常）の予防効果を検討。ワクチン接種者では子宮頸部前がん病変〔高度扁平上皮内病変（HSIL以上）〕が有意に減少しており、特に初交前に接種した場合はHPV16/18型関連の細胞診異常を認めなかったとの結果を[Cancer Sci \(2022; 113: 3211-3220\)](#) に報告した。初交年齢や性交経験人数など性的活動性で調整し、HPVワクチンの子宮頸部前がん病変予防効果を明らかにしたのは日本初の成果だ。

Figure 3: September 14, 2022, Jiji Press website article³

ニュース

【子宮頸がん】HPVワクチンは効果が高いことを確認 初交前に接種すると予防効果は78%に上昇 広くアピールする必要がある

いいね! 7 シェアする ツイート

2022年10月03日

地域保健 女性の健康 学校保健 母子保健 特定保健指導 産業保健 調査・統計

新潟大学は、子宮頸がんの前がん病変(細胞診異常)に対して、HPVワクチンがどれくらいの予防効果を示すかを調査した。

2014～2020年に新潟市内で、子宮頸がん検診を受けた20～26歳の女性4,553人を対象に調査した。

その結果、ワクチン接種を受けた女性では、子宮頸がんの前がん病変(高度扁平上皮内病変)が有意に減少しており、ワクチン有効率は64%に上がることが分かった。

とくに初交前に接種した場合は、ワクチン有効率は78.3%に高まることも示された。

「HPVワクチンの接種を検討している女性に対して、ワクチンの効果を強くアピールしていく必要があります」と、研究グループでは述べている。

研究は、ワクチン接種歴を自治体データで正確に確認し、初交年齢や経験人数など性的活動性で調整し、HPVワクチンの子宮頸部前がんの予防効果を明らかにした日本ではじめてのものとしている。



Figure 4: October 3, 2022, Japan Medical & Health Informatics Laboratory website article⁴

¹ https://www.med.niigata-u.ac.jp/contents/info/news_topics/209_index.html (Accessed on December 10, 2022)

² Kudo R, Sekine M, Yamaguchi M, Hara M, Hanley SJB, Kurosawa M, Adachi S, Ueda Y, Miyagi E, Ikeda S, Yagi A, Enomoto T. Effectiveness of human papillomavirus vaccine against cervical precancer in Japan: Multivariate analyses adjusted for sexual activity. *Cancer Sci.* 2022 Sep;113(9):3211-3220. doi: 10.1111/cas.15471. Epub 2022 Jul 11. PMID: 35730321; PMCID: PMC9459348.

³ <https://medical.jiji.com/news/54203> (Accessed on December 10, 2022)

⁴ <https://tokuteikenshin-hokensidou.jp/news/2022/011575.php> (Accessed on December 10, 2022)