

December 4, 2020

Finnish Cancer Registry

Dr. Tapio Luostarinen

Dr. Dan Apter

Dr. Joakim Dillner

Dr. Tiina Eriksson

Dr. Katja Harjula

Dr. Kari Natunen

Dr. Jorma Paavonen

Dr. Eero Pukkala

Dr. Matti Lehtinen

Questions regarding “Vaccination protects against invasive HPV-associated cancers” (2018)

Dear Drs. Luostarinen, Apter, Dillner, Eriksson, Harjula, Natunen, Paavonen, Pukkala, and Lehtinen,

We would like to express our respect for your continued effort to fight against cancers.

We are voluntary members of a group studying HPV vaccines of SHIN-IKYO (The New Japanese Medical Association).

The Japanese government, which continues routine HPV vaccination to date, says that HPV vaccines are expected to prevent cervical cancer. In addition, many organizations promoting HPV vaccination are also claiming that there is evidence that HPV vaccines prevent invasive cancer. One of the grounds they cite is the letter you sent to the editor of the International Journal of Cancer, “Vaccination protects against invasive HPV-associated cancers” (2018).

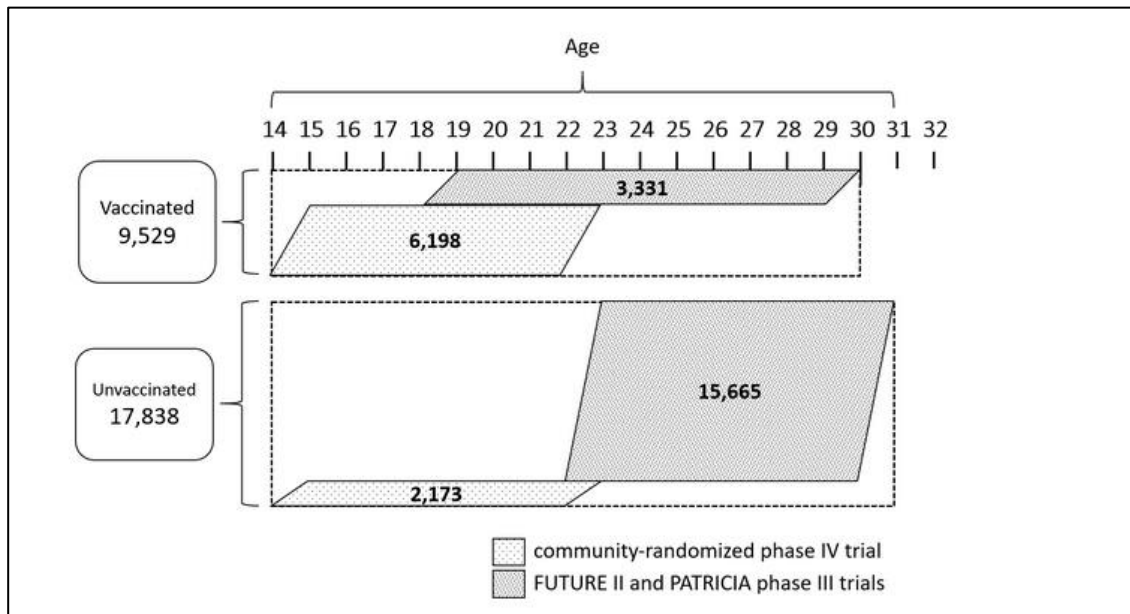
Thus, we examined the letter and found some medical and statistical questions.

The followings are our questions that we hope you would kindly answer:

1. We examined your letter but could not find any grounds that support “vaccination protects against invasive HPV-associated cancers,” the title. You also wrote in the end of the letter that the “follow-up of our intervention and non-intervention cohorts continues” and “analysis in 2019 is powered to provide HPV type-specific vaccine efficacy.” For two

years since you submitted the letter, we have been waiting for a subsequent report you planned to publish, but it has not yet been published. Could you clarify the reason for that?

- Based on the letter, we created the Figure 1 on the age groups of HPV-vaccinated cohort and unvaccinated cohort analyzed in the letter. It shows the distributions of age and number of women during the follow-up period by cohort.

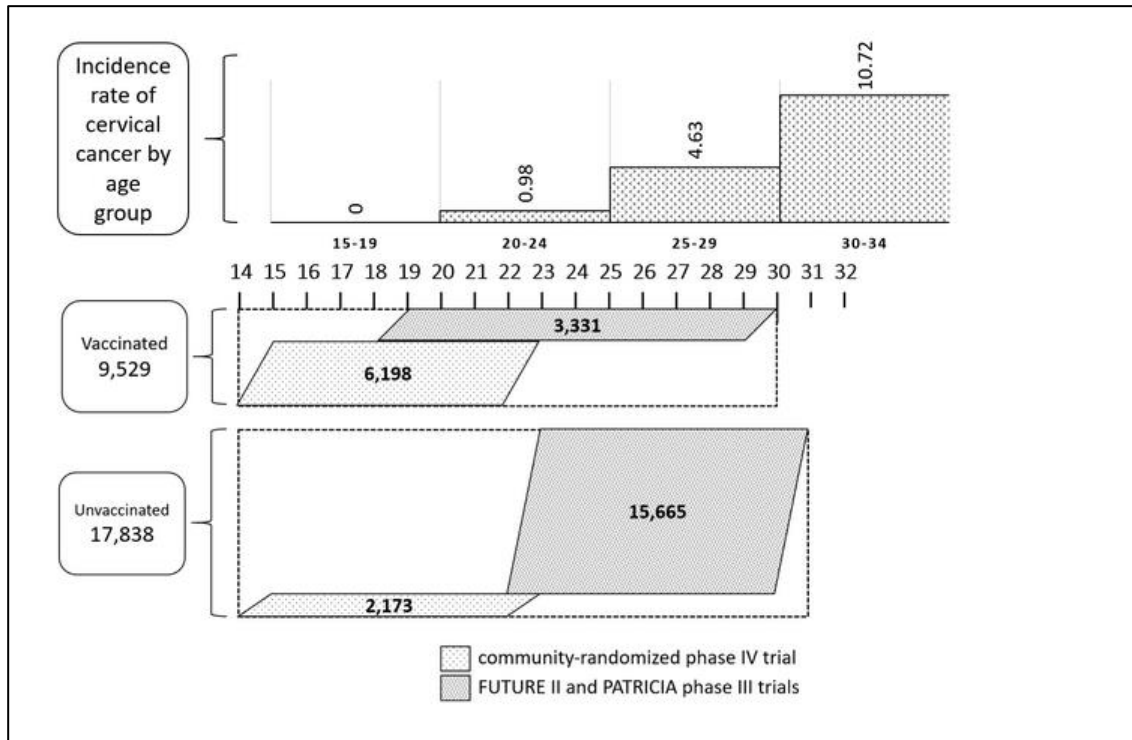


**Figure 1.** Distributions of age and number of women analyzed in the letter during the follow-up period

Figure 1 shows that, in the vaccinated cohort, 65% (6,198/9,529) of women were followed from age 14 to 23, and the remaining 35% (3,331/9,529) were followed from age 18 to 30. On the other hand, in the unvaccinated cohort, only 12% (2,173/17,838) were followed from age 14 to 23, while the remaining 88% (15,665/17,838) were followed from age 22 to 31. In short, the proportion of higher age group in the unvaccinated cohort is much larger than that in the vaccinated cohort, and the age is not matched between cohorts.

The incidence rate of cervical cancer depends on age; as people age, the risk of developing cervical cancer increases. According to the Finnish Cancer Registry, the incidence rate of cervical cancer per 100,000 persons in 2014-2018 was 0 in the age group of 15 to 19 years, 0.98 in the age group of 20 to 24, 4.63 in the age group of 25 to 29, and 10.72 in the age group of 30 to 34. In short, women of age 20 or younger will almost never develop cervical cancer, while the incidence rate for those of age 25 or over sharply increases.

In the Figure 2, we added a graph of these incidence rates to the Figure 1.



**Figure 2.** The incidence rate of cervical cancer by age group of the Finnish Cancer Registry (2014-2018) is added to Figure 1

When we look at the Figure 2, we see that the proportion of people under age 25, the age group whose incidence rate of cervical cancer per 100,000 persons is under 1, is high in the vaccinated cohort, while the proportion of people age 25 or older, whose incidence rate is 4.63 or more, is high in the unvaccinated cohort.

Nevertheless, you combined cohorts of three trials and compared the efficacy of vaccines with person-years. In order to justify the comparison of person-years, the incidence rate must not be varied depending on age.

We think that neglecting the age distribution of women followed and comparing with person-years lacks the validity from both medical and statistical perspectives.

3. Did you examine if there were any differences between cohorts in screening rates of cervical cancer or interval of screening? We think that the data are important in passive follow-up studies.

4. According to the Finnish Cancer Registry, the incidence rate of cervical cancer per 100,000 persons younger than age 25 is 0.98 or lower, and 4.63 or lower among those younger than age 30. Comparing them, the incidence rate of the unvaccinated cohort of your letter is considerably high (6.4 per 100,000 person-years). What could be the reason for this?

To date in Japan, your letter to the editor has been being cited saying as if HPV vaccines' preventive effects against cervical cancer were established. We hope to solve our questions as soon as possible and it is necessary to clarify the true effects of HPV vaccines. Therefore, we would like to have your answers by the end of February 2021.

Please be advised that this is an open letter and your reply will also be opened.

Your kind consideration would be highly appreciated.

Sincerely yours,



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