Author's response to reviews

Title: Prevalence of HPV infection among Greek women attending a gynecological outpatient clinic.

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Replies to the Editorial Team comments

We would like to thank the Editorial Team for the time they spent on our paper, as well as for the comments regarding our work. Our replies to their comments are:

1st Reviewer (Catterina Ferreccio)

Point 1. Needs better description of the study area, and the base population attending this hospital, how representative is of the Greek maternity population.

Answer: Thank you for your comment. Patient’s recruitment was made by the outpatient gynecological clinic of “Elena Venizelou” hospital. “Elena Venizelou” hospital is a tertiary maternal hospital responsible for the greater region of Athens, the capital of Greece [This is now stated in the text (page 4, paragraph 2, lines 4-5)]. However, since the number of the participants as well as the age range in our study sample was relatively limited, the results of the present study can not be extrapolated to the total female population of our country (this is stated in the limits section: page 13, paragraph 1).

Point 2. State selection criteria, refusal rate, are pregnant women included?, or women with a recent delivery?

Answer: Thank you for your comment. However, as it is stated in page 4, paragraph 2, lines 1-3, the study population was consisted of a sample of 225 consecutive women attending the gynecological outpatient clinic for regular gynecological control. Pregnant women or women with a recent delivery were not enrolled into the study (This is now stated in the text: page 4, paragraph 2, lines 5-6). The refusal rate was very low; only 2 women did not take part in the study (This is now stated in the text: page 4, paragraph 2, lines 6-7).
**Point 3.** Did they sign an informed consent?

**Answer:** Yes, indeed, all the study participants gave their written informed consent (page 5, paragraph 2, line 2).

**Point 4.** Who interviewed the patients?

**Answer:** Thank you for your comment. A study nurse interviewed the patients. This is now stated in page 4, paragraph 3, line 3.

**Point 5.** DNA detection: should list the HPV types studied

**Answer:** Thank you for your comment. All the HPV types studied are now listed in the text (page 6, paragraph 3, lines 1-3).

**Point 6.** Figure 1 will benefit if sample size of each age category is included

**Answer:** Thank you for your comment. The sample size of each age category is now included to figure 1 (HPV + / total).

**Point 7.** It may also benefit of a confidence interval in the bars or a p value for the differences by age.

**Answer:** The figure gives us information regarding the prevalence of HPV-16, HPV-18 and HPV-53 according to the different age groups. The addition of confidence intervals as well as P-value for the differences by age will not add additional information to the findings of the present study. Therefore, we believe that it is not necessary to include them to the figure.
Point 8. Should compare the type of subjects included in the various HPV studies they mention with theirs. In particular the differences between convenience samples like theirs with population-based random samples.

Answer: In the discussion section, results from studies in different populations regarding HPV prevalence are given. The population of each study is now mentioned in the text (page 10, paragraph 2, lines 8-16).

However, since these populations are different, regarding the geographic region as well as the history or not of cervical cancer, the comparison with the results of the present study will not offer additional information.

Point 9. Should try to interpret the results of the comparisons.

Answer: As it is mentioned above, since the existing studies used different populations (regarding the geographic region as well as the history or not of cervical cancer) no direct comparison with the results of the present study can be done. Therefore, it is difficult to interpret the different results regarding the prevalence of the HPV types.

Point 10. It is unclear the statement ” since the outpatient clinic is a referral one they give us important information regarding the prevalence of HPV infection among young and middle aged women...” explain

Answer: An important limitation of the present study is the small size of the study population. As it is mentioned (page 12, paragraph 2, lines 3-7), the results of the present study can not be extrapolated to the total female population of our country. However, since the outpatient clinic is a referral one the present study might give us important information regarding the prevalence of HPV infection in this group of women.
**Point 10.** Do not repeat the results “The number of sexual partners and alcohol consumption were the most significant risk factors for HPV infection, followed by young age and poor income...”

**Answer:** The above sentence includes the results of the statistical analysis that show us the main risk factors for HPV infection in our study population. Therefore, in our opinion, it is important to mention them at the conclusion.
2\textsuperscript{nd} Reviewer (Jennifer Smith)

**Point 1.** Throughout the entire text, please confirm what you mean by newly diagnosed cases. This definition is not clear. Please clarify the distinction between the overall and “newly diagnosed” cases.

**Answer:** Newly diagnosed cases are women without history of a previous HPV infection while overall cases are referring to the total number of women with HPV infection (Page 8, paragraph 2, lines 1-3).

The corrected percentage of the newly diagnosed women with HPV infection is 17.3%. This is now stated in the text
- Page 8, paragraph 3, lines 1-3.
- Page 10, paragraph 2, line 3.

**Point 2.** Statement p.3 Background: “The impact of an HPV vaccine will be related to HPV 16 and 18...in the different population”. This really depends on the outcome to be prevented. I am concerned about this statement. It is important to differentiate HPV prevalence results found in the population, versus those found in LSIL lesions, versus those found in HSIL and those found in ICC. HPV prophylactic vaccines target the oncogenic HPV types that are most common in ICC. Thus, it is misleading to conclude that if HPV 16 and 18 are not the most common types in HSIL, LSIL or within the population that the vaccine efficacy will be compromised. Based on global review, HPV types 16 and 18 are found to be the most common types in ICC in all geographical regions surveyed. In actuality, the number of HPV types identified in each stage of cervical disease decreases with increasing grade of cervical disease, thus being lower in ICC than in HSIL or than in LSIL.

**Answer:** To avoid any confusion it is stated clearly in the text (page 3, paragraph 2) that the development of HPV vaccines against HPV types 16 and 18 prevents a great amount of cervical cancer cases worldwide. However, the impact of the HPV vaccination in different geographical regions, obviously, will be related to the prevalence of HPV types 16 and 18 in the different populations. Therefore, the knowledge of the prevalence of the different types
of HPV is of great epidemiological importance. That was the purpose of our study; to estimate the prevalence of HPV infections, especially with oncogenic HPV types, in our country.

**Point 3. Add references ie the validation of the biogenomics HPV assay for CIN-2 or greater.**

Add reference for the CFTR gene.

Please list HPV types that are detected.

**Answer:** All the HPV types studied are now listed in the text (page 6, paragraph 3, lines 1-3). In addition, the required references were added to the text:

- page 5, paragraph 3, lines 7-8
- page 6, paragraph 4, lines 1-3

**Point 4. P.8, Cut the top paragraph on the sociodemographics factors among the HPV positive women.**

**Answer:** Thank you for your comment. The above paragraph was cut by the text.

**Point 5. Please define newly diagnosed.**

**Answer:** Newly diagnosed cases are women without history of a previous HPV infection while overall cases are referring to the total number of women with HPV infection (Page 8, paragraph 3, lines 1-3).

**Point 6. Risk factors—please eliminate the p values from the text.**

**Answer:** Thank you for your comment. The p values were eliminated by the text.
**Point 7.** Please clarify throughout which populations are being screened for HPV: i) invasive cervical cancer cases, ii) high-grade cervical lesions, iii) low-grade cervical lesions, and iv) population-based samples. The distribution of HPV 16 and 18 will differ by stage of cervical disease and this needs to be taken into consideration for the discussion section. For example, reference (11) is among invasive cases. P.11, please be careful about making comparisons across studies that do not test the same population (invasive, high grade, low grade or population based).

**Answer:** Thank you for your comment. Indeed, the present study is a population-based study and cannot be compared with the study among invasive cases (reference 11). The different studies populations are now mentioned in the text

- page 10, paragraph 2, lines 8-9
- page 10, paragraph 2, lines 12-13
- page 10, paragraph 2, lines 13-14
- page 10, paragraph 2, line 14

**Point 8.** Please check English in the discussion section, last two sentences on page 12.

**Answer:** Thank you for your comment. The correction was made (page 12, paragraph 2, line 5).

**Point 9.** Please edit the text on “health conscious females”. Please define what is meant by this. Given that HPV is so commonly transmitted, I do not see how being more health conscious may reduce risk per se.

**Answer:** Thank you for your comment. The above sentence has been deleted by the text.

**Point 10.** Table 1: Please add 95% confidence intervals.

**Answer:** The 95% confidence intervals were added in table 1.
**Point 11.** Table 2: Please add referent groups to the ORS to clarify what the comparison groups are. We do not understand clearly for example, whether higher incomes or lower incomes are associated with a greater disease risk.

**Answer:** Yes, indeed, the comparison groups needed to be clarified. The correction has been made to the table 2. Also, the results, which are described in table 2, are fully explained in the text on page 9, paragraph 3.