Author’s response to reviews


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Version: 2 Date: 13 February 2015

Author’s response to reviews: see over
Version: 1 Date: 12 January 2015
Reviewer: Ahti Anttila
Reviewer's report:

The paper looks to cervical cancer mortality trends in Spain. As the quality of the original statistical data is very poor, the study has implemented a correction method that seems (and has been also earlier reported) to work rather well but not necessary as well as the high-quality original data would have been. The paper also extends data to most recent periods as well as reports unique findings by regions. Fortunately, the mortality data quality has improved towards more recent periods, even though it seems yet far from optimal. This means that the information on the recent mortality burden is already rather credible but the data system does not enable easily assessments of impact of interventions? Cervical cancer mortality is an important issue in the country - also in many other countries - because there is still much space for prevention. The paper is well written and analyzed; I have some remarks below how to make the data better comparable to other countries.

We want to thank the reviewer for his kind comments as well as for his thorough reading of the manuscript and helpful remarks that have helped us to improve the paper.

Major compulsory Revisions
None.

Minor Essential Revisions

1) Page 4, line 113 (and elsewhere in the manuscript where age standardized results are handled): could you add the age group 0-19 also (important particularly to the population denominator)? This would provide then a comparable estimate to standard statistics on cervical cancer mortality so that the estimates can be compared to data from other countries. Still, e.g. in the age-specific analyses that age group is not needed.

Age groups 0-4, 5-9, 10-14 and 15-19 were already included in age-standardized rates; our results are comparable from other countries. However, from the reviewer comment we detected a mistake in the text. Now it is clear that these groups are included in the computation of the rates. In table2 we have also added a note indicating only 11 cases was registered between 0 and 19 years for the whole study period.

2) Same "...by age group 20-44,...) and page 5 line 125 'five-year age groups'; I did not follow if the study used 5-year age groups throughout e.g. in the standardization and then just presented the results by the broader groups; or how did you do? Please specify.

We used the 5-year age groups to calculate all the rates, and the “broader age-groups” correspond in fact to truncated age-standardized rates for these categories, We have corrected the text to explain it better.
"We calculated crude and age standardized mortality rates (European standard population) for each quinquenium (1981-1986; through to 2006-2010) by Spanish Autonomous Community (Andalusia; Aragon; Asturias; Balearic Islands; Canary Islands; Cantabria; Castile-La Mancha; Castile & Leon; Catalonia; Valencian Region; Extremadura; Galicia; Madrid; Murcia; Navarre; Basque Country; La Rioja; Ceuta and Melilla), and also computed truncated age-standardized rates for the following age groups: 0-19, 20-44;45-64; >=65 years old."

3) Page 5 lines 132-136, and later: Often, in case of a decreasing trend, a loglinear shape of the trend is fitted, as it takes into account that the decrease can be first larger but then when time passes the trend approaches to the saturation level. Then no 'joint point' may be needed. However, when looking to the Figure showing age-specific and overall standardized rates it seems that the current modelling with lines trend and joint points works acceptably and almost comparably to log-linear modeling. There seemed to be in the results a clear 'joint point' in the year 2003, but it was not discussed in detail. It would be beneficial in the Discussion section to explain why such a 'joint point' was there. One likely explanation is that there may have been unchanged in the register data quality by decreasing the number of Uterus not otherwise specified? Are there any other possible reasons?

As the reviewer indicates, log-linear models are normally adjusted to study trends in rates. In our case, a simple log-linear model does not seem to fit well with our rates; they should draw a straight line in figure 1, which has a log-scale in y axis. Joinpoint analysis, which compares log-linear poisson models with and without change points, indicate that Spanish cervical cancer mortality presents a significant change of trend.

Joinpoint model suggests that the change of trend appears between 2001 and 2005, and in our opinion it is not probably due to differences on data quality; while it is true that the proportion of Uterus not otherwise specified has not changed markedly since 2000, it does not affect the total number of cases, which determines the rates; our sensibility analyses find the change of trend in the same period.

Why 2003? We really would like to have a clear answer for this question, but we do not have it. There have not been sudden changes in death coding or in screening at this date. As we state in the discussion, we think that the change of trend is a gradual consequence of the social changes on Spanish females’ sexual behavior, as well as the effect of demographic changes in the country which have increased the risk of exposure to VPH without having taken enough prevention measures to counteract it.

4) I was a little astonished that in the Conclusions there was no statement about the need to improve data quality on cervical cancers by increasing availability of validated population-based cancer registries in the regions, as well as improve the quality of the mortality data. I my understandingly such aspects would be important.

The reviewer is completely right. We should have included this comment. Now we have added this text, according with this suggestion.

"In addition, clear actions should be taken to strengthen cervical cancer surveillance: the lack of national cancer incidence registries as well as the present problems in the quality of
cervical cancer mortality data are also important issues that health authorities should address.

Discretionary Revisions
5) Abstract, lines 52-53 please delete words 'in the XXI century', it would make this better readable;

   OK

6) Background, page 3 line 69, "...especially in younger cohorts." The sentence needs reference(s). I understand that at least key references are given and discussed in detail later (in page 9) but some references could be mentioned here as well. Same reference(s) needed to be included also in page 7 line 205.

   Done

7) Page 7 lines 211 'ralentization', is it English? I did not understand the word, but google translator from Spanish suggested 'slow-down'.

   Thanks, we have changed the word.

Reviewer2

Version: 1 Date: 1 February 2015
Reviewer: Marc Arbyn
Reviewer’s report:

GENERAL COMMENTS
The authors present a careful trend analysis of cervical cancer mortality after correction of the well-known certification for uterus-NOS (not otherwise specified). The correction of this certification might not be optimal by using age-specific proportions (cervix/corpus) from the Netherlands. However, the authors are aware of this and explain this in the discussion. Changes in trends are explained mainly as a consequence of exposure to HPV and screening. The authors make justified recommendations regarding future organized screening with use of HPV instead of cytology screening. A major problem is the error in the definition of ICD codes (explained below). These may be simple typing errors. These may be simple typing errors. If not, re-computation of corrected rates may be required.

   The reviewer is completely right. Thanks a lot for detecting our mistake. In our last version we mixed ICD codes- only in the text- and did not notice it. Fortunately, it was just a typo and we have corrected the paragraph.

SPECIFIC COMMENTS
Title
1) “Drop” of “decrease” would be better than “descent”

   Ok
ABSTRACT

BACKGROUND

2) Line 59-61. According to Arbyn Ann Oncol 2012, cervical cancer is the third most frequent female cancer and the fourth most frequent cause of death. This more recent ref can replace ref 4.

We have are using GLOBOCAN data in the first paragraph, and have also added this reference in Line 58. However, we have to maintain ref 4 (now reference 5) in the 2nd paragraph, because we refer to previous epidemiologic situation of cervical cancer mortality in Spain.

3) Line 62: change efficacy by effectiveness.

Done.

MATERIALS AND METHODS

4) There are errors in definition of the death causes.

Cervix cancer:
ICD-9: 179 is not cervix but uterus-NOS (not otherwise specified). The code for cervix in ICD-9 for cervix cancer is 180.

Uterus-NOS:
ICD-7: 173 is not uterus-NOS but uterus-other (a category for rare cancers such chorioblastoma) which can be omitted from the analysis. Inclusion or exclusion of this category will not have consequences for the analysis.
The authors can consult Ref 13 (Eur J Cancer 2009), for icd definitions.

Thank you for your comment, as we mentioned in the General Comments, we had a typo in ICD codes. In fact in the study period in Spain there were only two ICD in use: ICD-9 (1980-1998) and ICD10 (since 1999). Now the paragraph has this information:

Cervical cancer (ICD-9:180; ICD-10:C53); uterus corpus cancer (ICD-9:182.0; ICD-10:C54); and U-NOS (ICD-9:-179; ICD-10:C55),

5) Line 118

The joinpoint programme is not from SEER but NCI.

Thanks. We have changed the mention in the text; the reference was already correct.

6) Line 120.

“useful” would be a better adjective than “valid”.

Ok.

7) The fact that ACP models can only identify changes on top of linear trends but cannot attribute the linear drift to cohort or period (non-identifyability problem) could be explained better (see Arbyn Arch Publ Health 2000).
We have changed the paragraph, including two additional references (the suggested one and another from our group). Now it says:

“To overcome the problem of non-identifiability of model parameters arising from the exact linear dependence among age, period, and cohort [12], we adopted the approach proposed by Holford [13] and considered estimable functions of parameters, such as the curvatures in each effect and the sum of period and cohort linear slopes, also known as the net drift. We estimated the effects curvature and net-drift which are uniquely determined by the data and hence remain invariant irrespective of the particular approach used [14]. And we displayed graphically cohort and period effects. We also checked for extra-Poisson dispersion [15].”

8) RESULTS

It is recommended in the text to mention “—” when the trend is decreasing. For instance line 152: since 1995 around 2.6% per annum (95%CI: -3.6; -1.7). Put “—” before 2.6%. OK

9) Line 172: identify “post-war years”

Spanish civil war started in 1936 and ended in 1939. Now it says:

“Since the beginning of the 20th century, risk markedly declined with birth cohort until the Spanish early post-civil war years. At this time, around early 40’s...”

10) Line 176.

The instability for youngest cohorts is mainly due to small numbers.

We added this comment in the paragraph. Now it says:

“The fluctuating cohort effect in the last generations reflects the instability of the rates of these birth cohorts, represented here only for women in the youngest age-groups which have a very small number of deaths”

11) Line 190


Done. Now this reference is the number 18.

12) DISCUSSION

Line 191

Arbitrariness. “Possible non-representativity” is a better term.

Ok. Changed

13) Line 206

“Gynaecological revisions”. “Cytological screening” is a better term.
Ok. Changed

14) **Lines 205-7. A reference should be added demonstrating that women at higher risk tend to be better screened.**

We do not affirm that women at high risk tend to be better screened. We state that, according with the Spanish National Statistical Institute survey on sexual behavior (2003), in women born in Spain from 1954 to 1963, more conservative sexual behaviors (i.e. lifelong monogamy) were more common in females with primary educational level studies or lower than in those with university studies (80% vs 50%). In addition, women with higher study level do attend more screening programs.

Thus, in these cohorts, the opportunistic strategy pursued may have had a more relevant effect at a population level because, in the past, it might have unintentionally targeted the subgroup of women at higher risk. We have added part of this information to the text, with the references needed.

15) **Line 214.**

.. to further reduce the rates. “To compensate increased exposure to HPV” may be a better expression.

OK

16) **Line 279**

Better references (see ref 30) describing evidence regarding primary HPV-based screening are:


Done, we have changed reference 30 for these two new references.