Author's response to reviews

Title: Population based prostate cancer screening in north Mexico reveals a high prevalence of aggressive tumors in detected cases

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Author's response to reviews: see over
Monterrey, Mexico. December 7th, 2008

Mrs. Jenny Leigh  
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Subject: MS: 8071151072170864 - Population based prostate cancer screening in north Mexico reveals a high prevalence of aggressive tumors in detected cases

Dear Mrs. Leigh:

Enclosed you will find the point by point revised version of the manuscript “Population based prostate cancer screening in north Mexico reveals a high prevalence of aggressive tumors in detected cases” written by Gómez-Guerra LS., et al. We followed YOUR SUGGESTED FORMAT FOR responses and actions to reviewers’ recommendations of as described in the attached new list of changes.

We hope that you will find the article satisfactory for its publication.

Thanks a lot for all your attention. I remain

Sincerely yours,

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NEW LIST OF CHANGES

Reviewer's report

Title: Population based prostate cancer screening in north Mexico reveals a high prevalence of aggressive tumors in detected cases.

Version: 1  Date: 23 September 2008

Reviewer: Stacy Loeb

Reviewer's report:

General:

- Is the question posed by the authors well defined? Yes-- they ask what is the prevalence of prostate cancer in men from Nuevo Leon Mexico in 2004-2006.

- Are the methods appropriate and well described? Methods are appropriate, but further description would be helpful for several issues.

- Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes.

- Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes.

- Do the title and abstract accurately convey what has been found? Yes.

- Is the writing acceptable? Yes, the article is very well-written.

Major Revisions:

1. What were the exclusion criteria, if any? For example, did they exclude men with symptoms suggestive of active urinary tract infection or men taking finasteride (which lowers PSA)? If these are not known or were not excluded, this should be mentioned in the limitations.

   Response: There were no exclusion criteria, all attending subjects were screened. Our questionnaire asked for personal antecedents of PCa, but we did not record any case of a previously diagnosed patient.

   Action: In page 4, line 8, we added: “no exclusion criteria were considered for this study”.
2. More description of the study population-- was this the 1st PSA test all of these men ever had, or had some been serially screened on the outside? Had any of these men undergone a prior prostate biopsy? These will affect the interpretation of the high proportion of aggressive tumors. If prior screening/biopsy status is unknown, would mention this in the Limitations.

Response: As far as we know, this was the first screening ever for most of the subjects. There are no previous reports of PCa screening for open population in our city.

Action: In page 8, line 1 we added: “most of the participants do not have antecedents of PSA screening neither prostate biopsy for cancer detection”.

3. Are the data sound? The data are sound but have significant limitations, as follows:

- Biopsy was only performed for a PSA >4 ng/ml or abnormal DRE. Unlike the PCPT, empiric biopsies were not performed in men without a clinical indication--as such, we do not know the “true prevalence” of PCa in Mexican men, in particular those with PSA levels <4 ng/ml and normal DRE. This should be discussed in the limitations section.

Response and action. We did not perform empiric biopsies as stated in page 10, line 7. We did not consider undergoing empiric biopsies in this open screening program, because this invasive procedure is very costly and by the opposite, researchers are focused in the search for markers to decreases “unnecessary biopsies” due to the negative impact of this procedure in the patients.

- We also do not really know the “true prevalence” of PCa in Mexican men who do have PSA levels >4 ng/ml and/or abnormal DRE since only 55 of 125 men with an indication for biopsy actually complied with the biopsy recommendation. The 44% compliance rate is low and should be given greater emphasis in the Limitations section. It would also improve the quality of the manuscript if the authors performed a statistical analysis showing whether demographics were similar between men who did and didn't comply with the biopsy recommendation (I suspect there are systematic differences between these 2 groups, some of which may not be possible to capture in this type of study). The potential biases due to the fact that the majority of men did NOT proceed for biopsy should be mentioned.

Response and action: We emphasize this low compliance for the biopsy procedure in page 10, line 9, and compared it with the historical data of compliance in the Urology Service of our University Hospital, which is also low.

4. Are the discussion and conclusions well balanced and adequately supported by the data? Although I generally agree with their conclusions (that a high proportion of the cancers diagnosed in this population were
high-grade), these should be carefully tempered by the fact that this is based upon only 15 detected prostate cancers.

**Response and action:** In page 8th, line 14, we added “Only 15 cases of PCa were detected in the screenings. We are aware that this number may be affected by the compliance for biopsy in suspected subject, and additional factors, as the threshold criteria for serum PSA”.

5. Are limitations of the work clearly stated? No-- The limitations warrant further discussion, as described above (low compliance, no empiric biopsies, etc.).

**Response and action:** We added the description of the study limitations at the end of the Discussion (end of page 9 and beginning of page 10).

6. Would also mention that this study used a higher PSA threshold than is used in many US/European centers, and some men had only 6 biopsy cores (10-12 cores are typically performed currently), so the study design/biopsy protocol can also affect the "prevalence" and aggressiveness of PCa detected.

**Response and action:** We are aware on the fact that the “sextant” technology for prostate biopsy is a limitation in our study. In page 4, line 18 we describe that this method is the usual approach for diagnostic prostate biopsy in Mexico. In page 10, line 3 we added “An underestimation of cancer diagnosis in the biopsies may be due to the use of the sextant biopsy technique, the standardize method used in screening cancer programs in Mexico. It has been showed that increased numbers of biopsy cylinders per biopsied patient improve the chance for detection of prostate malignancies in suspected individuals [14-16]”.

**Minor Revisions:**

1. Table 2 mentions that PSA couldn't be measured in 25 men-- why? Might discuss why not in the Limitations.

**Response and action:** The explanation was included in the corrections (table 2). These men samples were insufficient for PSA detection.

2. It is noteworthy that the population included men up to 98 years old! Many groups suggest discontinuing prostate cancer screening after age 75 or in men with less than 10 years life-expectancy. How many men in their 80's and 90's were included here? Do the authors have any thoughts about the appropriate age to discontinue screening for Mexican men based upon their experience?

**Response and action:** Figure 1 was included to discriminate age ranges in all biopsied patients. The last two lines of page 6 and the first two lines of page 7
describe the age distribution of men > 75 y.o. and the percentages of men
diagnosed with cancer among the biopsied participants above and below the
threshold of 75 y.o., as stated: “98 screened patients were older than 75 years
(10.07%). The age distribution of subjects that underwent biopsy (Figure 1)
shows that PCa was diagnosed in 12/37 subjects from 40 to 74 years old
(32.43%), while this tumor was diagnosed in 3/6 subjects older than 75 years old
(50.0%)”. In Discussion (page 8, lines 5 to 13) we dissert about the utility of
PCa screening in older men and wrote: “The U.S. Preventive Services Task
Force (USPSTF) Recommendation Statement established a threshold of age at
75 for PCa screening; USPSTF recommends against routinely providing the
screening to asymptomatic patients because found at least fair evidence that
screening is ineffective or that harms outweigh benefits [7]. In Mexico, there is
no experience about the impact of harms/ benefit for early detection screening of
PCa in men older than 75 years. In our study, a total of 98 patients were older
than 75 years and PCa was diagnosed in 3/6 subjects that underwent biopsy
(50%). This reflects the higher incidence of PCa in older men, and accordingly,
we do not oversee the benefit of the screening for PCa in this group of men”.
This paragraph states our agreement on the scarce utility of the screening in men
> 75 y.o.

3. The abstract might clarify that 125 men had a PSA/DRE indication for
biopsy but that of those men, only 55 received a biopsy-- otherwise, the
denominator from which PCa detection rates are calculated is not entirely
clear.

Response and action: In Abstract (page 2nd, line 16) we clarified this point as
stated: “Prostate biopsy was recommended to 125 men based on PSA values and
DRE results, but it was performed in only 55 of them. 15 of these biopsied men
were diagnosed with PCa, mostly with Gleason scores ≥ 7”.

Discretionary Revisions:

1. What were the prostate sizes of these men on transrectal ultrasound? This
might be interesting to report given the relatively high prevalence of lower
urinary tract obstructive symptoms.

Response: We did not record the prostate sizes registered during the transrectal
ultrasound.
Action: no text was modified/added.

2. Do the authors have any statistics comparing socioeconomic factors
between Nuevo Leon and other areas in Mexico/Latin America? Would be
interesting to help the reader assess the generalizability of their findings to
other Latin American men.

Response: We do not know which social-economic indicators are relevant to
compare for this study in prostate cancer. The major issue is that reports on the
epidemiology of prostate cancer in Spanish-speaking Latin American countries are very scarce, including Mexico For example, we failed to find reports on screening for PCa programs in our region.

Action: no text was modified/added.

3. One place in the manuscript which might be slightly reworded for clarity: Page 5, sentence 1 of results says that 709 patients were "admitted"-- the authors probably mean "entered the study," but it might be confused with hospital admission.

Action: The word “admitted” was changed by “entered” (Page 5, line 4).

Level of interest: An article whose findings are important to those with closely related research interests.

Quality of written English: Acceptable.

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests.
Reviewer's report

Title: Population based prostate cancer screening in north Mexico reveals a high prevalence of aggressive tumors in detected cases.

Version: 1 Date: 25 September 2008

Reviewer: John K Gohagan.

Reviewer's report:

General:

The authors seek to determine the prevalence and grade of prostate cancers men from the urban population of Monterrey, Mexico. 973 men aged 40-98 years of age responding to public invitations via radio, TV and press were screened in three groupings (2004, 2005, 2006) following informed consent. 54% of the men presented with mild obstructive symptoms and 46% moderate to severe obstructive symptoms by the AUA-SI symptom index. Fifty-five of the 77 men with a PSA of 4ng/ml or above or with abnormal DRE underwent transrectal ultrasound guided biopsy, with a yield of 15 cancers, 14 of which were high grade (Gleason >= 7). Details of the findings test performance parameters are clearly presented. The authors observe that in many other screening settings (citing two European screening trials in which asymptomatic men were screened for comparison), prostate cancers detected tended to have lower Gleason score (Gleason 6 or lower) and state that for this difference they have no explanation while suggesting that it could be due to the lack of screening in the Mexican population they studied. The authors conclude that their series reflects low prevalence but high occurrence of high grade cancers.

The reported Mexican data should be reanalyzed in a population age-adjusted manner to draw conclusions about the prevalence of prostate cancer. The age distribution of subjects screened is not stated and prevalence among older men is substantially different than among younger men in all populations. In addition this was a symptomatic population which could affect their findings. It is not surprising that the authors reported higher Gleason grade than in the European comparisons cited, since prostate cancer progresses slowly to advanced stage with advancing age and they did not control for age or prior conditions whereas the Europeans did. A better comparison population for this project might have been the initial screening results reported for the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial reported in JNCI 2005;97:433 or other results from this trial, because there is substantial Hispanic participation in PLCO, especially at the Colorado screening center.

Response and action: We added a new figure (figure 1) to show the age distribution of biopsied men and some percentages of cancer in men below and above 75 y.o. We described than in these biopsied men, the percentage of PCa in
men older than 75 years is 50%, while this percentage in men below 75 is 32.43% (page 7, line 1). We also describe a diagnosis of PCa in 53.33 of the biopsied men above 70 y.o. (page 9, line 5).

This was the only comment from reviewer # 2.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** I declare that I have no competing interests.
Reviewer's report

Title: Population based prostate cancer screening in north Mexico reveals a high prevalence of aggressive tumors in detected cases.

Version: 1 Date: 30 September 2008

Reviewer: Wolfgang Horninger

Reviewer's report:

A clear and clean evaluation of screen detected prostate cancers. Results are written good, conclusions of the results are also discussed properly. I think it is a important paper for the clinically working urologists.

Reviewer #3 has did not suggest changes to the manuscript.

Level of interest: An article of outstanding merit and interest in its field.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests.