Author's response to reviews

Title: From the set-up of a screening program of breast cancer patients to the identification of the first BRCA mutation in the DR Congo

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Author's response to reviews: see over
Point-by-point responses to reviewers’ comments

Dear Mrs Aguirre

We refer to your e-mail of February 6, 2014.

As requested, please find hereafter our point-by-point responses to the concerns of the 2 reviewers.

Sincerely yours

Prof C Van Ongeval
Comment to the reviewers

We want to thank the reviewers for the very interesting remarks. Because all women who consulted the hospital with large breast cancers first went to see a witchdoctor, the medical staff of the hospital wanted to start a campaign on breast cancer awareness. With the results of this work, we hope to sensitize the government for this problem of breast cancer in women and especially in young women.

1. Comment to the first reviewer

Abstract

- Some information on the breast cancer awareness campaign should be mention in the methods paragraph

As a matter of fact the abstract did not contain information on the strategy. We corrected the abstract as follows: see lines 32-62.

Introduction section

- Data from Globocan 2012 or another more updated source should be used when presenting the age adjusted annual incidence and mortality rates for breast cancer
- Specific information about breast cancer in Democratic Republic of Congo (DRC), which can be also obtained from Globocan 2012, is needed

We included the information from Globocan 2012. Unfortunately, on the Globocan website, no information on the specific situation of breast cancer in the DRC is available.

We added following data (lines 67-74):

Globocan 2012 reports an age-adjusted breast cancer incidence rate worldwide of 43.3 Age Standardised Rate (ASR) per 100,000 women and a mortality of 12.9 ASR per 100,000, while in Europe the incidence of breast cancer is 94.2 per 100,000 and the mortality 22.4 ASR per 100,000. [1] In contrast with Europe the incidence is 25.5 per 100,000 in Sub-Saharan Africa (SSA) and the mortality 19.3 per 100,000, showing a 3.7 times lower incidence but comparable mortality rate. Occurrence of breast cancer increased from 19 per 100,000 to 25.5 per 100,000 in 2012. [1, 2] But so far, no data on breast cancer in the DRC are available. [1]

Methods section

- The section is not well structured. It should be indicated that the study design was built up according to the WHO framework but then put more emphasis on the study design, the setting, the strategy, the recruitment procedures, inclusion and exclusion criteria if any...

Thank you for this important remark. As the description by the WHO framework for the setup of a breast cancer awareness program lacks practical guidelines for the implementation in a low income country as DRC, we looked for better descriptions. Your article on the breast cancer awareness program in Ghana (IJC, 2013 by Mena et al.) made us aware of the existence of “The Breast Health Global Initiative (BHGI)” as an organization which also described implementation strategies of early detection of breast cancer in LMICs. This organization provided more details about the introduction of such a program and defined different levels of early detection, adjusted to the financial situation. In ‘BMC Health Services Research’ Bridges et al. described a more comprehensive framework for national breast control strategies, based on a survey done in different LMICs.
This discussion on the strategy is included in the background and method section, more specifically in the strategy section. Because the text underwent a major revision, I included for each section the lines which were added to the paper:

**Background:** lines 102-132  
**Methods:** lines 144-155  
**Strategy:** lines 160-183

1. **The program needs to be explained with more details. How were recruited the health care staff and the women from the general population to participate in the study? Were the health care workers from some specific centers? Which was the duration and contents of the training?**

The initiation of the program was done by the medical staff of the General Hospital in Kinshasa. The whole awareness program started in Kinshasa. We described the formation of an expert group and an awareness group. The information on the education programs, not only organized in the hospital but also organized outside the country (Belgium), was described. In each awareness group women with a history of breast cancer were included. To illustrate this, a flow diagram of the organization was added (Figure 1).

2. **The authors explain that the “breast awareness” education was realized by the use of posters on which breast self-examination was explained, but also that one of the channels was the radio, where the participants are not able to see the poster…clarification on this point and more details on how the content of the message given to the participants is needed**

To clarify this, we added (lines 210-213):

> “On the radio the breast cancer awareness campaign was always presented by a radiologist who described the different early signs of breast cancer, the importance of breast self-examination and the difference between diagnosis and therapy in hospitals compared to witchcraft.”

3. **The sessions organized for couples need to be explained with more details, what were the men taught about?**

The sessions were not only organized for couples. When inviting the women, their husbands were also advised to come to the sessions: in total one fourth to one fifth of the people attending the sessions were men. Because the subject “cancer” is one of the items explained on the posters, not only images of breast cancer were shown but also of prostate cancer. Therefore, some questions about cancer were also asked by men. We added this in the paper in the following sentences (lines 202-206):

> “The awareness group not only focused on meetings for women but also on groups in which men are participating. Some sessions were even organized for couples: in total one fourth to one fifth of the people attending the sessions were men. These men also asked questions related to cancer occurring in the male population.”

4. **Ethical issues: No informed consent was required from the participants?**

For the 4,315 women to whom the problem “cancer” and “breast cancer” was explained, no informed consent was available. Only the women who went to the hospital for a radiological evaluation and a biopsy, a questionnaire together with an informed consent was given: by signing this questionnaire,
they agreed upon the anonymous collection and reporting of their data. For women who could not read, a health care worker assisted them to complete the questionnaire and the informed consent. This is included in the first section (lines 156-158):

“The study has been approved by the ethics committee of the GHK. All women who participated in this study have been informed about the procedures, filled out and signed the relevant questionnaire and informed consent.”

- **Were the health workers and women from the general population evaluated somehow in order to assess the gained knowledge? If not, that should be mentioned in limitations section**

The oncologist, the gynecologist and the radiologist of the expert group as well as one technologist who was trained in the technique of mammography were trained in Leuven (Belgium). The health care workers of the awareness group followed different conferences at the hospital in order to increase their knowledge. There was however no evaluation of the impact of the session on the awareness of cancer before and after the sessions. The increase of the number of women attending the conferences in the churches and the increase of churches who want to invite the awareness group is the only measurable result of the improvement on the knowledge of the women. Moreover, there is also an increase of the women visiting the mammography department. This is added as a limitation in the discussion section (lines 330-336):

“Another limitation is the absence of an evaluation of the impact of the breast cancer awareness campaign on the knowledge of cancer and of the early signs of breast cancer in the participating women. However indirectly the increase of the number of women attending the sessions in the churches and the increasing demand for new sessions suggest an improvement of the awareness in the population. Moreover, there is also a continuous and ungoing increase of the women attending the mammography department.”

**Results section**

- **Some results are already presented in the methods section and should be replaced in the appropriate section (e.g. case report);**

I agree with your comment: by including a case report describing the family, we wanted to report in a more detailed way on the background of this BRCA positive family, moreover as this is the first time reported in DRC. The diagnosis of this family was identified due to the organization of the awareness campaign: ie. with the evaluation of the daughter, the aunt also consulted the awareness group. The description of this family also demonstrated the problem of mastectomy in a woman in DRC as this is not accepted by the family or by the community. Because this is not the goal of the paper, we removed the case description from the paper as suggested, we only kept a short description in the methods and results sections.

- **It should be more specified where each group of women visited the campaign, how the counting of the participants was made**

The counting was not only necessary for the expert group in the hospital for the evaluation of the breast cancer awareness, but also for the churches who were inviting us and wanted to report on these sessions to their hierarchy. So, we added (lines 190-191):

“Before the start of the sessions, one person of the awareness group was appointed for the counting of the participants.”
• Regarding the objective 2, more demographic information about Kinshasa should be presented. Figure 2a and 2b are the maps of DRC and Kinshasa; in green, the Bas-Congo province is shown in which awareness campaigns were also started.

Discussion section
• The discussion should be separated from the results section. Most of the information presented in the conclusions sections should be replaced at the discussion section and conclusions thus should be shorter, just a summary of the main findings and message and recommendations that the authors want to give to the readers.

This was indeed not correct! We therefore added an additional conclusion section (lines 353-360):

“Introducing a breast cancer awareness campaign in the Democratic Republic of Congo, based on information by well-educated health care workers, breast self-examination and clinical breast examination, resulted in an increase of women looking for diagnosis and treatment in the hospital instead of consulting non-health care workers like witchdoctors. With an annual or bi-annual information day, knowledge on breast cancer can clearly expand to more women and with some financial involvement of the government more women can be diagnosed at an earlier stage.”

• The references are very few, and some not really updated ones. Recent papers on breast awareness strategies in Africa should be presented (e.g. Abruidis et al., The Lancet Oncology 2013, Mena et al., International Journal of Cancer 2103…) and discussed in relation to the results of the stud.

Thank you for informing us on these very interesting papers. We included them in the discussion section as follows (lines 299-314):

In the work of Abruidis et al., in which an awareness program in Sudan, for both men and women, was implemented in different villages in Soudan, 10,309 women were screened by CBE [20] and 138 women were identified with breast abnormalities and were referred to the hospital for further diagnosis, but only 118 women were diagnosed, 101 were found with benign lesions, 8 with DCIS and in 9 with invasive carcinoma. In comparison, the campaign in Kinshasa and Bas-Congo resulted in a higher detection rate of breast cancer in the group of women with a palpable lump (CBE). The main reason for this difference is probably the better training of the health care workers in the awareness group of Kinshasa. Information on cancer and BSE together with BCE resulted in a better recognition of the early signs of breast cancer. This is in accordance with the findings of Mena et al. Ghana, who reported that the knowledge of the referent group on breast cancer appearing as a painless lump was only 53.3%, compared to the 82.3% of the intervention group, moreover the latter participants obtain significantly higher knowledge scores (odds ratio = 2.1, 95% confidence interval = 1.14-3.85) and realize better BSE (odds ratio = 12.29, 95% CI: 5.31-28.48). [21]
2. Comment to the second reviewer

- **the material on brca1 is beside the point and should be removed, adds nothing of importance**

I agree with your comment. The diagnosis of this family was identified due to the organization of the awareness campaign: once breast cancer was diagnosed in one young member of the family, the aunt also consulted the awareness group. The description of this family also demonstrated the problem of mastectomy in a woman in DRC as this is not accepted by the family or by the community. Because this is not the goal of the paper, we removed the description of the case report. But, as the detection of this mutation is the result of the dedicated work of the awareness group and is part of the study of the local etiology, a short description of this mutation is still kept in the method and result sections.

We changed this as follows:

Lines 244-247 (Method section): “c. Genetic analysis: The genetic analysis was performed as described by Michils et al. [18] During the data collection blood samples from the 29-year old patient with breast cancer, her affected mother and her aunt were taken for mutation analysis of the BRCA1 and BRCA2 genes.”

Lines 278-280 (Result section, Genetic analysis): “Genetic analysis revealed the presence, in the heterozygous state, of the c.2389_2390 delGA mutation in the BRCA1 gene in all 3 members. (Figure 5). The mutation leads to a frame shift at codon 797 of the BRCA1 gene (p.Glu797fs).”

- **the nature of the awareness screening program needs to be better described**

The organization of the awareness program was indeed not sufficiently explained. The WHO provides a description on how a breast awareness program should be organized in low income countries, but a more practical organization scheme is not available. The BHGI, on the contrary, clearly defines different steps in the organization, taking into account the financial situation of the country. Bridges et al. also described a comprehensive framework for national breast cancer control strategies, based on interviews in different low income countries and this resulted in the description of different steps for the organization of a breast awareness campaign. As this was also an important remark of the first reviewer, the paper has been changed accordingly. Therefore, we include here lines for each section we have changed:

Abstract: lines 35-48

Background: lines 102-132

Methods: lines 144-155, lines 163-183

- **of the malignant lesions how many were palpable, mammographically detectable only, both**

All the women who were referred to the hospital and investigated with mammography and ultrasound had palpable masses, therefore all malignant lesions were palpable. The organization chart of the breast cancer awareness campaign has been added to the paper in figure 1.

- **need the information on stage at presentation. this is very important**

Indeed, breast cancer is often detected at late stage disease. It is important to describe the stage at which the breast cancer is found. As there is often no surgery done after diagnosis, a pathological TNM classification was not possible. Often clinical elements for the clinical staging were not correct, we used a different definition for the staging of diagnosed breast tumors. Therefore, we included the definition in table 1 and added the results of the stages of the breast tumors in the result section.
In the methods section "For the TNM staging, only the clinical and radiological information could be used as the status of the lymph nodes was not always available and most of the surgical excised lesions were not all histologically investigated, therefore pathological staging was not possible. [16, 17] For the clinical staging, the diameter of the tumor was recorded for all patients, and in order to compensate for the absence of pathological information, the radiological measurements were included in the staging. Due to the above-mentioned problems, the description of the stages of the patients diagnosed in the DRC was different compared to the international TNM code (Table 1)." has been added (lines 226-234).

In the results section “The clinical stage distribution for the 87 invasive tumors was: 1 at stage 0 (1%), 2 at stage 1 (2%), 19 at stage 2 (22%), 65 at stage 3 (75%). (Table 3)” has been added (lines 274-276).

Furthermore, in the discussion section, we have added (lines 320-322): "Studies, conducted in Libya, Nigeria and Tanzania showed a more frequent presentation of breast cancer in stage III women, as also presented in our study. [24, 25]"

- **is there any historical information about stage at presentation for comparison group.**

No, in this study there was no referent group. The only knowledge on the situation before the campaign is the situation as it was seen in the hospital before 2010: only women with stage IV cancers consulted the hospital.