Author's response to reviews

Title: A descriptive study of variables associated with obtaining nipple aspirate fluid in a cohort of non-lactating women

Authors:

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Version: 2 Date: 11 July 2006

Author's response to reviews: see over
TO: BioMed Central Editorial  
Referees: Bonnie King, Edward Sauter  
FROM: Kimberly Baltzell  
RE: MS: 1538142018104106  
A descriptive study of variables associated with obtaining nipple aspirate fluid in a cohort of non-lactating women

Dear Drs. King and Sauter:

Thank you for your informative review of my manuscript. I am submitting a revised version based on your suggestions. Please find my responses to your concerns below.

Reviewer’s report
A descriptive study of variables associated with obtaining nipple aspirate fluid Title: in a cohort of non-lactating women  
Version: 1 Date: 7 June 2006  
Reviewer: Bonnie King  
Reviewer’s report:

1) The Materials and Methods section states that NAF collection was attempted on 3043 women, and then goes on to say that women diagnosed with breast cancer were excluded from the analysis. It appears that many of the statistical analyses were done on the entire group of 3043 women. Please clarify/confir specifically that the 3043 number does not include women who were diagnosed with cancer.

We have clarified this in the Materials and Methods section of the manuscript. The original cohort consisted of 3413 women and once all subjects who either had breast cancer or were diagnosed withing 6 months of initial visit with Dr. Sartorius were removed from the dataset, the number of eligible subjects remaining equaled 3043. All analyses were done ONLY on women without breast cancer.

2) The Discussion states that this study builds on the work of Wrensch (1990) and others, However, the paper is sparsely cited, and I think the interpretation of the data could be enhanced by referencing a more extensive body of literature. There is very minimal discussion relating to the potential biological significance of the findings relating to endocrine variables and tranquilizer use. In addition, no 2005 or 2006
references are cited, and there are recent papers that report on NAF collection in relation to clinical, reproductive, and endocrine variables.

References from 2005 and 2006 were added to the body of the manuscript. As for speculation on the biological significance of the findings relating to endocrine variables and tranquilizer use, there is scant literature on either of these topics so we felt it would not be prudent to speculate on reasons for the findings. We note that the composition of tranquilizers today is different than the composition of tranquilizers during the period subjects were seen by Dr. Sartorius, making a comparison even more difficult. However, given the statistical significance of our findings, it is an area that appears to warrant further investigation.

3) In the Results section ethnicity data was needs to be changed to data were. In the Discussion Instead, the data was needs to be changed to data were.

These changes have been made.

4) I’m not sure that breast fluid extraction is the best phrase to describe the NAF collection procedure.

Phrase was changed to “breast fluid collection”

5) The description in the Methods refers to the inner chamber of the Sartorius pump, without describing the device (which was double chambered in contrast to the aspirator currently used).

The description of the Sartorius pump was expanded, and additional information added to the Discussion section regarding current methods of NAF collection.

Discretionary Revisions (which the author can choose to ignore)

1) I thought the Introduction would be stronger if it focused on the potential of NAFs for risk assessment and reduction, and with less discussion on breast cancer detection.

Additional information was added to the introduction to reflect this excellent suggestion!

Reviewer's report
A descriptive study of variables associated with obtaining nipple aspirate fluid Title: in a cohort of non-lactating women
Version: 1 Date: 2 June 2006
Reviewer: Edward Sauter
Major compulsory revisions
Based on the first sentence under Materials and Methods, Dr Otto Sartorius, who attempted NAF collection on 3043 women it would appear that the initial cohort was 3043. The authors later state that women with breast cancer or women diagnosed with breast cancer within six months of their initial clinic visit were excluded. This would suggest that the population analyzed for this paper would be a subset of 3043. However, under results, the authors state that Fluid was obtained from 43% of women (1314/3043), which would suggest that the actual number of women, before excluding those with breast cancer, was more than 3043. Please clarify.

Please see response to referee above, who shared this concern. This has been clarified in Materials and Methods section.

Since the authors indicate that exogenous estrogen use was not a significant determinant of ability to obtain fluid, yet younger age was (in which estrogen and progesterone are generally at higher circulating levels than in postmenopausal women), please speculate on the scientific reasons for the apparent paradox between exogenous vs endogenous female hormone effects on NAF yield.

Additional information has been added to the Discussion section to further address the issue of endogenous vs. exogenous estrogen influence in NAF collection. An additional reference has been added with relevant findings. It seems likely that endogenous reproductive and menstrual hormones are partly responsible for the greater ability to obtain NAF in younger versus older women or in women with intact ovaries versus those with bilateral oophorectomy. However, at a certain age (which likely varies between women), aspects of senescence other than declining endogenous hormones also might influence breast physiology, the production of NAF, and the ability to obtain it. Greater understanding of these factors would be necessary to explain why exogenous estrogens do not appear to increase ability to obtain NAF.

In the current report, the authors report a success rate of NAF collection of 43%. In a 1973 paper (Jama 224: 825-27), Dr. Sartorius reported that for example, fluid was found in the breast aspirates of three-fourths of one series of 200 women who came to the clinic. The women ranged in age from 15-87 years, and the breasts of older women contained less fluid. And a bit later, using oxytocin, This work is still experimental, but already we find it gives almost double the yield of fluid and cells. We are now getting 90-95% cell yields. It would be helpful to reconcile the differences in success reported by Dr. Sartorius in the earlier publication with the present report, and clarify if the current cohort includes women who received preNAF oxytoxin. If it does, should these women be excluded?

After careful review of the records available to us, there is no indication that oxytocin was given to the 3043 women in this study. We have noted that a limitation of this study was that data were abstracted by a team of R.N.s and that information may not have been obtained on all potentially relevant factors. Additional information has been added to the Discussion section regarding reasons for differences in NAF collection rates.
An important question which needs to be addressed is whether the findings in the current report can be generalized. The finding reported are based on the use of a device developed by Dr. Sartorius in which he was the sole NAF collector, as I understand it. There are many other devices which have been developed and different NAF collection techniques. Others investigators have reported higher NAF collection success. It would be appreciated if the authors could address each of the following points (why different success rates, influence of device, influence of technique, and influence of person performing the NAF collection).

There is a statement in the Discussion section regarding the limited ability to generalize the findings based on the fact that women were from a breast clinic and may not represent the normal population. In addition, more information was added in response to points listed above by the referee. Overall it appears that there is a decline in the ability to obtain NAF after age 50, indicating this may be a technique of greatest use to a younger population of women.

Minor essential revisions
It would appear that the reference style is not that of BMC.

**Paper has been reformatted in BMC style.**

Thank you again for your helpful comments. I am looking forward to the publication of this manuscript.

Sincerely,

Kimberly Baltzell