Author's response to reviews

Title: Tolerability of Breast Ductal Lavage in Women from Families at High Genetic Risk of Breast Cancer

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Author's response to reviews: see over
Thank you for considering our manuscript, “Tolerability of breast ductal lavage in women from families at high genetic risk of breast cancer” for publication in BMC Women’s Health. We have considered the reviewer’s comments and have addressed the issues within the manuscript. Specifically, we have included additional content as requested and clarified the limitations section of the manuscript. Please see below for a detailed explanation of our response to the reviewer’s report. All authors have reviewed the revised manuscript and agree with the changes made.

1. The authors should provide more detailed information about the validity of the markers available from the ductal lavage.......

The following content and references has been added to page 3 of the text:

However, obtaining adequate numbers of cells from DL samples for both cytological review and biomarker development has been a challenge [6]. Reliably obtaining NAF from all or most women studied, and acquiring samples with cell counts adequate for cytologic evaluation (>10 evaluable cells) from DL specimens has been problematic [1,7-19]. Neither NAF production nor 5-year Gail risk >1.7% [6,20,21] predicted atypia in DL specimens from high-risk women [9, 21]. It is possible to detect atypia in both NAF-yielding and non-NAF-yielding ducts from women at high-risk of breast cancer [6,7,9,12]; however, it is not known whether the atypia detected by DL will demonstrate an increased prospective risk of breast cancer in women at high genetic risk of breast cancer, and there is increasing evidence that reproducibility of cytologic diagnoses in benign duct epithelial specimens and in specimens with atypia found on DL is only fair-to-poor [6, 11, 13, 17].

Comments 2 (the potential variation in sampling) and 4 (a more in-depth comparison of previously published DL tolerability) were addressed by adding content on pages 13, 14 and 15:

Pain associated with DL has been evaluated by several groups [1,13,18,19]. Dooley et al., reported on 507 women who had DL performed on at least one breast; 291 had a prior history of breast cancer, 10 had a history of lobular carcinoma in situ, 199 were high risk due to a Gail Model risk of ≥ 1.7, 4 were not at high risk of breast cancer, and only 3 were BRCA1/2 mutation carriers. A median pain score of 28mm on a 0-100mm visual analogue scale which was administered immediately after DL was reported (1). However, 28% of subjects underwent the procedure in the operating room under general anesthesia and less than one percent of the subjects were cancer-unaffected, known BRCA1/2 mutation carriers. No comparison of pain scores between subjects who received general anesthesia versus those who did not was reported.
Mitchell et al. (20) employed a visual analogue scale (range 0-10) to record measurements of pain in 52 women with BRCA1/2 mutations. A similar rating of 2.8/10 was reported immediately after DL, and DL pain was described as similar to the pain experienced with mammography. As with the previous study (1), more than 50% of participants were breast cancer survivors. Neither group reported whether differences existed in measures of pain between women with a prior history of breast cancer and unaffected women. It is possible that women who are breast cancer survivors experience pain differently from women without a prior history of breast cancer. Neither group (1,18) reported the acceptance rate of future DL in their study populations.

DL tolerability was reported in a retrospective study in women at high risk of breast cancer who had been evaluated as part of a breast cancer screening study [19]. Twenty-two BRCA1/2 mutation carriers rated DL-related pain on a scale of 1 to 3 (1=minimal discomfort, 2=moderate discomfort, 3=maximal discomfort), and compared their experience with DL to breast MRI on a scale of 1 to 5 (1=much better, 2= somewhat better, 3= same, 4= somewhat worse, 5=much worse). BRCA1/2 mutation carrier participants more often rated DL as maximally uncomfortable versus MRI or mammogram, and the maximal discomfort ratings for DL vs. mammogram and MRI combined reached statistical significance (P=0.04). There was no difference in reports of pain between breast cancer survivors and unaffected women; however, the sample size was small (breast cancer survivors, n=13; unaffected, n=23), and mutation status was not reported. Future acceptance of DL was not reported in this study population.

The reliability and acceptability of DL in 69 women at high risk of breast cancer due to Gail Model score ≥1.66 (n=38), a family history of breast cancer (n=53), the presence of a BRCA1/2 (n=2), a personal history of abnormal breast biopsies (atypical hyperplasia, non-invasive or invasive breast cancer, n=20) or a prior history of breast cancer (DCIS/invasive breast cancer, n=11) was found to be less than ideal [13]. A visual analogue scale from 0-10 was employed to measure DL pain at visit one and six months later at the second visit. The mean pain score at visit one was 4 (range, 0-8) and the mean pain score at visit 2 was 3 (range, 0-9). After visit one, 70% of the women who underwent DL reported that they would have DL again, and if recommended, would undergo the procedure as part of routine early breast cancer detection. However, only 52% of these women returned for a second visit. There were insufficient numbers of known BRCA1/2 mutation carriers within this group of women to determine whether mutation carriers differ in measures of pain from other women at high risk of breast cancer.

Emotional distress might influence measures of DL pain and acceptance, since previous general population studies have suggested that women describing higher levels of emotional distress report greater mammogram-related discomfort [22-24]. Furthermore, unpleasant mammogram-related experiences have been associated with decreased likelihood of returning for annual breast cancer screening [24,25]. However, previous studies of DL tolerability [1,13,18,19] have neither assessed emotional distress nor analyzed its influence on DL pain and acceptance.

Comment 3 (limitations) is addressed by adding the following on page 16:

families or other healthy women in the general population who are at high risk of breast cancer. Therefore, our findings may not apply to a more general population of BRCA1/2 mutation carriers nor other women at high risk of breast cancer. However, we doubt that the presence of these highly-selected women in a study of DL tolerability specifically for woman from BRCA1/2 mutation-positive families biased the study’s findings.
I hope that this response will be considered adequate and that publication can now proceed. Please feel free to contact me if you have any further questions. I look forward to future publications with BioMed Central.

Best regards,

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