Title: Overexpression of CDC25B, CDC25C and phospho-CDC25C (Ser216) in vulvar squamous cell carcinomas are associated with malignant features and aggressive cancer phenotypes

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Please find enclosed the revised version of the manuscript "Overexpression of CDC25B, CDC25C and phospho-CDC25C (Ser216) in vulvar squamous cell carcinomas are associated with malignant features and aggressive cancer phenotypes." by Zhihui Wang, Claes G Tropè, Vivi Ann Flørenes, Zhenhe Suo, Jahn M Nesland and Ruth Holm.

We have revised the manuscript according to reviewers recommendations. The comments of the reviewers have been dealt with in the following way:

**Reviewer 1 (Yasuhiro Ito)**

**Reviewer's report:** Wang et al. investigated CDC25s in vulvar squamous cell carcinomas. Although interesting, several issues are present requiring a revision.

1. Tables and presentation in the Results are too messy. Specificity for antibodies should be presented at the beginning of the Results. Table 3 should be presented prior to Tables 1 and 2.

   *Specificity for antibodies has been presented at the beginning of the Results (page 12). Original Table 3 has been presented as Table 1 (Tables, page 1). Original Table 1 and Table 2 have been emerged into one--Table 2 (Tables, page 2-4), after data regarding to CDC25A, CDC25B and phospho-CDC25C expression in both cytoplasm and nuclei are removed.*

2. All normal tissues highly expressed CDC25A, whereas decreased CDC25A expression was seen in 49% of carcinomas. CDC25A expression did not relate to any clinicopathological features, including patient prognosis. That is all we know from their studies for CDC25A. The part of CDC25A should be deleted from Table 1. Authors should make a discussion why almost half of carcinomas showed decreased CDC25A expression in the Discussion.

   *The part of CDC25A has been deleted from the original Table 1 (Tables, page 2-4). Discussions addressed on why almost half of carcinomas showed decreased CDC25A expression were already presented in the Discussion (page 18, paragraph 3, sentences 6-8).*
3. Similar to CDC25A, little clinical and physiological significance could be found for CDC25B, because only 16% of carcinoma overexpressed it. Although expression level was directly linked to carcinoma differentiation, the incidence of CDC25B overexpression was still low at 28% in poorly differentiated carcinoma. Thus, data regarding CDC25B should also be deleted from Table 1.

Data regarding CDC25B has been deleted from original Table 1 (Tables, page 2-4).

4. In normal tissue, only a weak CDC25C and phospho-CDC25C could be seen in the cytoplasms. Data regarding CDC25C can be left as they are in Table 1. Although carcinoma tissues expressed phospho-CDC25C both in the nuclei and cytoplasms, authors should present data only about the cytoplasms and nuclei in Table 2.

Data regarding phospho-CDC25C expression both in the nuclei and cytoplasms has been deleted from original Table 2 (Tables, page 2-4).

5. Authors should emphasize the data about CDC25C and phospho-CDC25C in the Results and Discussion (also Tables) and condense or delete others. Otherwise, readers might miss the point authors want to emphasize.

Results regarding CDC25A and CDC25B were condensed by partly deletion from the Results (page 13, paragraph 2 and 3; page 14, paragraph 2 and page 15, paragraph 1 and 2).

We reduced the Discussion part regarding CDC25A and CDC25B (page 16, paragraph 1 and 2).

The language has been corrected.

Reviewer 2 (Barbara Tringler)

Reviewer’s report: The present, retrospective study by Zhihui et al. reports on the expression of CDC25 subtypes in vulvar squamous cell carcinomas. CDC25 has been described to play a crucial role in cell cycle regulation. The aim of this study was to evaluate the importance of CDC25 in the pathogenesis of vulvar cancer and to verify the prognostic value of CDC25 subtypes in this cancer type. The strength of this paper is that it is the first study ever focusing on the expression of CDC25 isoforms in a large number of vulvar cancer cases and correlating the results with malignant cancer features. The study is well designed, clearly constructed and the quality of the immunohistochemical staining is very high. Results have shown that CDC25C and phosphor-CDC25C (Ser216) overexpression was associated with advanced tumor stage, presence of lymph node metastasis, large tumor diameter and poor differentiation. However, CDC25A, CDC25B and CDC25s may not have potential to serve as a prognostic marker in vulvar carcinogenesis.

The reviewer reported no revisions needed.