SUMMARY & CONCLUSION
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Carcinoma of the uterine cervix is a major public health problem throughout the world and is the leading malignancy in women in the developing countries. India, alone accounts for approximately 16% of the global load which will increase to 1.6 fold in absence of any control programme. Annually, about one lakh women develop cervical cancer in India. The etiology of this cancer has been thought to be multifactorial. The development of this cancer is linked with the sexual behaviour. The promiscuity of either partner which suggests the possibility of an infecting agent(s) is a important risk factor for cervical cancer. Genital infections like HPVs, HSVs, Chlamydia and some of the non venereal agents like diet, smoking are also related to the development of cervical cancer.

'Glutathione (GSH), a non-protein thiol is found in all living cells. Its reduced form is involved in a variety of biological functions. The anticarcinogenic action of this molecule has been thought through its role in the detoxification of carcinogens and various toxic molecules via GST-and GPX-system. Therefore significant connection between GSH and carcinogenesis have attracted attention. The enzymes of glycolytic pathway, especially G6PD and 6PGD of pentose phosphate pathway have also received considerable attention in
carcinogenesis and the altered activity of these dehydrogenases have been used prognostically as a tumor marker. However, cancer of uterine cervix is very little studied for GSH-related as well as for glycolytic enzymes. Thus this report has studied the various GSH-related variables in the erythrocyte of women with cervical precancer and cancer in India where the incidence of this malignancy is the highest in the world. The broad objectives of this study is to find out any significant changes in the GSH related parameters and to explore the possibility to use these changes as a objective systemic biochemical marker(s) for early detection of cervical malignancy.

The present study encompasses the following salient findings -

1. The erythrocyte activities of GR and GPX enzymes were found to be reduced, however the activities of GST and the dehydrogenase enzymes viz G6PD & 6PGD of pentose phosphate pathway were observed to be increased in the erythrocytes of women with advanced cervical lesions. Further, the contents of GSH, GSSG and Se were also found to be altered in the precancerous as well as in invasive nature of uterine cervix.
2. The GSH content in the erythrocytes was noted to be decreased in CIN III and in invasive cancer as compared to controls (7.512 versus 8.232 umoles/gm and 5.925 versus 8.232 umoles/gm of Hb, respectively; p<0.05). The high content of GSH was found to be protective for CIN III and invasive cancer (chi-square=6.19, 12.25, respectively; p<0.005). Further the decrease for GSH content was consistent as the severity of the disease increased in this study.

3. The content of GSSG was noted to be increased in CIN III and in invasive cancer when compared with the content of normal women (0.033 versus 0.026 and 0.046 versus 0.026 umoles/gm of Hb, respectively; p<0.01). The odds ratio analysis showed the significant risk for high content of GSSG for invasive cancer (chi-square=11.3; p<0.05).

4. All the subjects of CIN III and of invasive cancer were found to have the lower plasma total GSH content as compared to normal women (0.724 versus 1.082 and 0.622 versus 1.082 respectively; p<0.001). It has also been observed that the content of total GSH was observed to be
decreased with the increasing severity of the cervical lesions. In the present study, the high content of TGSH was found to be protective for developing cervical cancer (chi-square=8.90; p<0.001).

5. The erythrocyte activity of GR was expressed as the ratio of activated (with FAD) to basal activity (without FAD), known as activation coefficient (AC) for all the participating subjects. The activated activity of GR was noted to be lower as compared to the basal activity. The AC values for CIN III and invasive cancer were found to be 1.5 and 1.7 respectively which were lower than the AC value for control women (1.1). This suggested the riboflavin deficiency in the advanced cervical lesions.

6. The present study also showed the elevated activity of GST enzyme in low grade CIN (9.35 IU/gm of Hb), high grade of CIN (11.14 IU/gm of Hb) and in invasive cancer (14.26 IU/gm of Hb) as compared to controls (8.00 IU/gm of Hb). The increase in the GST activity was found to be consistent with increasing severity of disease.
7. Erythrocyte Se was found to be associated with process of cervical carcinogenesis. The decreased Se content was observed in CIN III and in invasive cancer when compared with normal women (99.4 versus 126.5 ug/dl and 90.3 versus 126.5 ug/dl, respectively; p<0.001). No difference could be obtained for Se content between control and low grade CIN. However, the high content of Se was found to be protective for invasive cancer (chi-square=5.15, p<0.05). The protective role of Se in high grade of CIN and in invasive cancer might be due to its antioxidant role via Se-dependent GPX system.

8. Together with the decreased Se content in high grade CIN and in invasive cancer, the activity of the GPX enzyme was reported to be lower in CIN III and in invasive cancer as compared to the activity for controls (30.6 versus 39.2 and 27.9 versus 39.2 IU/gm of Hb, respectively; p<0.001). This study also showed the decreasing trend in the GPX activity with the increasing severity of the malignancy.

9. The present study illustrated the positive correlation between the GPX activity and the selenium content for all the study groups. The
positive correlation was also observed between GPX activity and the GSH content for controls and in precancerous state of uterine cervix, however such correlation was found to be disappeared in the invasive cancer group. It indicates that the decreased activity of selenium dependent GPX enzyme is somehow independent of GSH content.

10. An attempt was made to study the enzymes of PP-pathway viz. G6PD and 6PGD during cervical carcinogenesis. The results showed the consistent elevation in the G6PD activity in higher grade of CIN and in invasive cancer when compared with the activity for normal women (7.41 versus 4.56 and 9.35 versus 4.56, respectively; p<0.05). The increasing trend in the G6PD activity could also be noticed as the severity of the lesions increased.

11. The most of the control subjects were found to have the G6PD activity above the baseline activity (5.0 IU/gm of Hb). However, 52% of the subjects of CIN III group were found to have the G6PD activity above the baseline activity. On the other hand maximum subjects (75%) of invasive cancer group were reported to have the G6PD activity above the baseline activity.
12. The odds ratio analysis for low G6PD activity, based on the distribution of subjects above and below the normal G6PD activity showed that the lower activity of G6PD activity was protective to develop advanced cervical lesions.

13. The other dehydrogenase of the pentose phosphate pathway, 6PGD was also found to be elevated in high grade of CIN (CIN III) and in invasive cancer when compared with the activity for the normal women (7.92 versus 5.43 and 9.97 versus 5.43, respectively, p<0.001). An increasing trend in the 6PGD activity was also observed from control to preinvasive to invasive state of uterine cervix.

14. The results of multiple comparison analysis for the most of the GSH related variables have clearly indicated the similarity between biochemical and morphological grouping of two population groups i.e. low grade CIN and high grade CIN.

15. There was no difference in the GSH related data between CIN I and CIN II group. However, erythrocyte GSH related data of high grade CIN (CIN III) were significantly different from the data of low grade CIN and of normal women.
The changes in the erythrocyte GSH related indices, reported here for the first time in the Indian women having various grades of CIN and invasive cancer indicate an plausible association of GSH antioxidant system during cervical carcinogenesis. This study also suggests that low grade CIN which showed no changes in GSH related variables may have the infections or inflammatory lesions which are thought to be transient in nature. However, high grade of CIN i.e. (CIN III) which illustrated the significant changes in the GSH-related parameters is thought to be involved in ongoing neoplastic process and capable of progressing to invasive cancer. These changes in the GSH related enzymes represent the systemic biochemical markers for the epithelial preneoplastic and neoplastic lesions of uterine cervix and may be used as a tumor marker for during the process of cervical carcinogenesis.