

**COMMENT ON: LIFESTYLE, REPRODUCTIVE FACTORS AND RISK OF GALLBLADDER CANCER**

Dear Sir,

I have read with interest the recently-published article by Shukla et al in your prestigious journal.<sup>(1)</sup> I am raising here my comments to clarify some methodological and statistical pitfalls in it.

In the abstract and methods sections, the authors stated that their study was a “prospective case-control study”. They definitely erred, because collecting data on their study participants “over a period of five years” does not entitle their study to be a “prospective” study. In prospective studies, the risk factor of the disease is known and the researcher is following up on the cases to investigate the outcome or the disease.<sup>(2)</sup> In the current study, the researchers already knew the disease and investigated its risk factors. That means this was only a case-control study, where every case or control was seen only once, investigated for its risk factors and not followed up.

The results of the current study were presented in a weak and inconclusive manner. The authors started Table I without presenting the association of the disease with age and gender of the study participants. They erred by mentioning in their abstract and results section that “a Hindu preponderance was seen”, but the results in Table I showed no significant difference between the religion and cancer of the bladder.

The title of Table II implied more than it really presented. The “dose” profile was not clearly shown in the table, as dose means the product of quantity by duration, which was not stated. Moreover, the duration of tobacco consumption either for chewing or smoking showed no significant difference between the cases and controls. Additionally, the authors confused the reader in page 913, column 1, last four lines of the results section, where I think they meant to say that “any form of chewing tobacco” increased the odds of bladder cancer by 2.5 times, instead of “chewing tobacco” (as one of the forms in Table III), increased the disease likelihood by 2.71 times.

The authors also stated in the results section that, “statistically, there was an increased risk of carcinoma in patients who were smokers”. They erred in this statement because the confidence intervals of the odds ratio (OR) in Table III were all not significant. The authors also erred by mentioning in the discussion section that the risk of carcinoma “was particularly more in patients who started smoking lately”, as this was inconsistent with the results in Table II which showed no significant difference in this regard.

The data in Table IV seems ambiguous to me. I wonder which test of significance was used to derive the ORs. I also wonder how the authors compared the mean differences in age at menarche, age at marriage, number of childbirths, number of abortions, number of times pregnant, and age at first and last birth. The ANOVA or *t*-test is used to compare the mean of continuous variables, whereas the unadjusted OR could be calculated in a  $2 \times 2$  or a  $2 \times X$  matrix, where the variables are discrete. The adjusted OR is calculated via a binary or multinomial logistic regression.<sup>(3)</sup> To display the mean and standard deviation of the variables and present the ORs in Table IV is incomprehensible. Therefore, the authors should elucidate their statistical methods and the applied tests of significance in the methods section.

Lastly, I could not understand the last variable of “menstrual status”, nor its values and its ORs. Did the authors mean menstruating vs. menopausal women? Did they want to say that menstruation is protective against bladder cancer? Why then did they not associate the disease with age in both genders, since age is a strong confounder to menstruation in females? Where are the results of the multivariate analysis where all the variables could be introduced to get the robust significant risk factor(s)? Why are there two ORs for this variable? As it is a  $2 \times 2$  table, with menstruating and menopausal women as a risk factor in rows and cancer or gallstones in columns, can the authors explain how they have two ORs, one protective and the other risky? Why do the *n* differ in the two rows? I suggest that the authors present the results of their paper in a more meticulous way, commensurate with the time and effort spent in their study.

Yours sincerely,

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#### **REFERENCES**

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