LETTER to the EDITOR

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# Challenges in Methodology and Data Reporting: Reflections on a Cholangiocarcinoma Study

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## Dear Editor

The recently published article "Social Determinants of Health Associated with Cholangiocarcinoma Risk in High-Risk Areas of Thailand: A Case-Control Study" by Khuanthong P. et al. [1], shows the association between the social determinants of health (SDH) and the risk of cholangiocarcinoma (CCA). The article serves as a crucial reminder that treating complicated medical conditions calls for an all-encompassing strategy. However, the article has methodological and reporting issues affecting the conclusion of the study and it needs further discussion.

In the method section, the authors' statement "In Step 1, the top four districts with the highest liver cancer and CCA mortality rates were selected using simple random sampling. In Step 2, the top four sub-districts with the highest mortality rates within Kham Khuean Kaeo District in 2021 were selected using simple random sampling." The selection of the top four districts/subdistricts acts as a limitation to the use of simple random sampling method, and it shows ambiguity.

The authors' statements in the method section "The inclusion criteria of the case had the following histories: (2.1) Examination for OV eggs in feces (OV+), (2.2) Family members with a history of illness or death from CCA, (2.3) Abdominal ultrasound examination showing abnormalities, i.e., detected with Grade II or higher cholangitis (PDF2), or having the history of any one of items (2.1-2.3) together with Item (2.4) Consuming alcoholic beverages.", and result section "Over the past year, all participants underwent fecal examination for OV eggs, with OV eggs detected in 100.00% of cases and 90.34% of controls.", are in contradiction to each other. Further, considering the fact that only 40% of women and only 11% of men as non-drinkers in Thailand [2], it is an uphill task to get subjects enrolled in the control group, as stated in the inclusion criteria 2.4 by the authors. An in-depth explanation of the recruitment of cases and control by the authors is essential for the replication of the study and hence scientific credibility.

The author statement "Survey-based research design: A total of 496 subjects were recruited between September 15, 2022, and September 29, 2022, from the HosXP PCU database. Verbal screening forms were used to select the sample." This limits our understanding of the recruitment process, considering the brevity (14 days) of window of recruitment period, lack of details of the screening protocol, and database characteristics. It is challenging to assess the reliability and validity of the sample selection process fully. Further, it is unclear how the top four districts/subdistricts selection is related to the subject recruitment from the HosXP PCU database. The authors' classification of the individuals into cases and controls after they were recruited, and recruitment of an unequal number of cases and controls, raises concern about the protocol followed by authors in the study.

The statement in method section "Univariate analysis was performed to investigate the relationship between individual exposures and CCA risk using McNemar's Chi-square test. Variables exhibiting a significant association with CCA risk in the univariate analysis ($p<0.05$) were subsequently included in a multivariate analysis." This differs from common statistical practices, as the chi-square test can only be used in a bi-variate analysis. Additionally, the authors' bi-variate analysis in tables 1 and table 2 suggest that SDH had $p <0.05$, but table 3 (regression analysis) included several factors that were either not stated in tables 1 and 2 or had $p > 0.05$, which contradicted the authors' claim in the statistical analysis description under the method's section.

The result section of the abstract mentions that, "48.00% of participants were at risk for CCA, with 32.06% having a history of liver fluke eggs detected in their faces" [1] This appears to be inconsistent, as controls are typically expected not to be at risk. In the result section, the main document states that "Over the past year, all participants underwent fecal examination for OV eggs, with OV eggs detected in 100.00% of cases and 90.34% of controls". [1] Both statements counter each other and therefore question the credibility of the research. Further, it raises questions about the study method that has defined cases as at risk of CCA and controls as not at risk of CCA. In the abstract result, the absence of comparison between cases and controls makes it less comprehensible. The monthly income was presented as mean ± SD, however considering the high SD value, the data seems to be skewed and should have been presented with Median and IQR.

The last phrase of the first sentence "Cholangiocarcinoma (CCA), particularly within the Greater Mekong Sub-region [1-3], which is among the poorest regions in Asia [4].", cannot be attributed to ref 4 [3] as no such statement given in the original source. The statements quoting ref. 6 and ref. 7 are not verifiable as the web pages yield no such information. Further the statement in the introduction "The districts with the highest CCA mortality rates over the past five years include, with average rates of 65.83%, 44.23%,

30.09%, 26.09%, and 20.07%, respectively." [1], is poorly understood because, in a previous statement, it was expressed per 100,000 population and not in percentage.

In the abstract, the statement "Analysis of SDH among the cases identified significant challenges, including high levels of poverty (49.14%), food security (52.22%), social exclusion (48.82%), inadequate housing (50.22%), and overall SDH burden (53.42%). In contrast, relatively lower levels of health inequality (48.78%) and unfavorable working conditions (51.65%) were observed." [1] As rates slightly below 50% (e.g., health inequality at 48.78%) are stated as "lower" which is statistically negligible. And the risks underestimating their impact, as such rates remain significant and depict an unclear interpretation. Additionally, the lack of clarity for terms like "inadequate housing," "food security," and "social exclusion" renders the findings generic and thereby limiting their contextual relevance, and comprehensiveness of the abstract.

Despite the article presenting a pressing issue, the methodology makes it less meaningful and further explanation would improve the credibility of the information presented in this article.

*Manuscript details*

This letter is in response to the article Khuanthong P. et al., titled "Social Determinants of Health Associated with Cholangiocarcinoma Risk in High-Risk Areas of Thailand: A Case-Control Study" published in Asian Pacific Journal of Cancer Prevention Volume 25, issue number 11, pages: 4081-4088. doi: 10.31557/APJCP.2024.25.11.4081.

## References


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## *Reply to the letter to the editor:* Challenges in Methodology and Data Reporting: Reflections on a Cholangiocarcinoma Study

## Dear Editor

We would like to thank Dr. Pratap Kumar Jena and colleagues for their thoughtful comments on our published article. Their feedback provides an opportunity to clarify our methodology and address potential concerns. Below, we address the key points raised in their letter:

As outlined in our methodology, we employed a multi-stage sampling design to select study sites. In the first step, the top four districts with the highest cholangiocarcinoma (CCA) mortality rates were identified. These districts were selected as high-risk areas crucial for understanding the role of social determinants in CCA. The term "simple random sampling" may have been misinterpreted. Specifically, randomization occurred within the constraints of these high-risk areas to ensure relevance and efficiency. Our choice was guided by public health priorities and epidemiological relevance, ensuring robust and actionable results.

The inclusion criteria for cases required at least one of the following: 1) Opisthorchis viverrini (OV) eggs detected in feces, 2) a family history of CCA, 3) abnormalities detected via abdominal ultrasound, or 4) a combination of alcohol consumption and any of the first three criteria. The statement in the Results section that "OV eggs were detected in 100.00% of cases and 90.34% of controls" reflects outcomes of fecal examinations conducted during the study screening process rather than prerequisites for enrollment. This apparent contradiction arises from the context of risk status assessment at the time of study participation. All participants underwent fecal examinations as part of the study protocol. While OV positivity was a common factor among cases, controls (who had no prior history of CCA risk factors) were included if they met the non-risk criteria. Furthermore, a previous study in a high-risk OV area of Thailand reported that 53.1% of men and 50.9% of women were never drinkers [1], underscoring the feasibility of recruiting controls in this context.

The recruitment period of 14 days reflects the efficiency of our process rather than a limitation. After subject recruitment from the HosXP PCU database, we collaborated with community leaders to invite eligible participants to meetings, where verbal screening and data collection occurred simultaneously through structured questionnaires. This efficient, structured, interviewer-administered process ensured consistency in data collection and classification, enabling timely completion of the recruitment process, an advantage of cross-sectional or survey studies.

We appreciate the comment regarding the use of McNemar's Chi-square test. The terminology used in the Methods section was imprecise; we utilized a standard Chi-square test for bivariate analysis. While the multivariate analysis in Table 3 included variables statistically significant at $p < 0.05$, we acknowledge that

some contextually important but statistically insignificant variables were not presented in this article. This limitation will be addressed in future research to provide a more comprehensive interpretation.

We acknowledge the perceived inconsistencies between the abstract and results section describing participants' risk status and OV egg detection. Additionally, we recognize errors in some references and will ensure greater accuracy and rigor in future work.

Describing rates slightly below 50% (e.g., health inequality at 48.78%) as "lower" may misrepresent their significance. These rates reflect substantial prevalence and should not be underestimated. Moreover, terms such as "inadequate housing," "food security," and "social exclusion" are broad and require more precise definitions to enhance contextual relevance. We recognize this may have caused ambiguity for readers and will ensure thorough definitions and contextualization in subsequent studies to enhance clarity and interpretability.

We deeply value the constructive critique and the opportunity to clarify aspects of our work. We hope these clarifications reinforce the credibility and utility of our research in addressing critical public health challenges related to CCA.

## References

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