RESEARCH ARTICLE

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# Social Determinants of Health Associated with Cholangiocarcinoma Risk in High-Risk Areas of Thailand: A Case-Control Study

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## Abstract

**Objective:** This case-control study sought to explore the social determinants of health (SDH) associated with cholangiocarcinoma (CCA) risk in high-incidence regions of Thailand. **Methods:** The research was conducted in two phases. Phase 1 assessed the prevalence, context, and conditions among at-risk populations for CCA in Yasothon, located in Northeast Thailand. This phase utilized a survey-based research design, employing verbal screening methods to categorize individuals into risk groups (at-risk vs. not at-risk). Phase 2 aimed to identify the SDH associated with CCA risk through a case-control study. Of 496 recruited participants, 238 cases of subjects were at risk of CCA, and 258 controls were not at risk of CCA. Data were collected using structured questionnaires. Multiple logistic regression was employed to analyze the factors associated with CCA risk. **Results:** The study revealed that 48.00% of participants were at risk for CCA, with 32.06% having a history of liver fluke eggs detected in their feces. Despite this, only 45.40% of participants engaged in adequate preventive behaviors. 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. Multivariate analysis indicated that overall SDH was a significant risk factor for CCA (AOR=1.63; 95% CI: 1.09-2.46), while perceived disease severity (AOR=0.57; 95% CI: 0.39-0.83) and safe working conditions (AOR=0.61; 95% CI: 0.42-0.90) were protective factors. **Conclusion:** Improving CCA prevention behaviors should focus on enhancing perceived severity and addressing the relevant SDH.

**Keywords:** Cholangiocarcinoma- *Opisthorchis viverrini*- social determinants of health- high-risk areas- case-control study

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## Introduction

Cholangiocarcinoma (CCA) represents a significant public health challenge in developing countries, particularly within the Greater Mekong Sub-region [1-3], which is among the poorest regions in Asia [4]. In response, the Ministry of Public Health of Thailand implemented the Decade Strategic Plan to Eliminate *Opisthorchis viverrini* (OV) and CCA (2016-2025) in commemoration of His Majesty King Bhumibol Adulyadej The Great, and as royal merit to Her Majesty Queen Sirikit The Queen Mother [5]. Between 2016 and 2021, the campaign targeted sub-districts in Yasothon Province, with an increasing number of areas covered over the years, ultimately including all sub-districts (78 sub-districts, 1 Yasothon Municipality). The OV infection rates during this period were 43.53%, 5.91%, 5.59%, 5.13%, 5.65%, and 4.29%, respectively. Concurrently, the CCA mortality rates in Yasothon from 2017 to 2021 were 37.5, 34.50, 32.23, 29.46, and 15.32 per 100,000 population, respectively. The persistence of OV and CCA in Yasothon is attributed to its geography and the cultural practice of consuming freshwater fish, particularly undercooked, which requires behavioral modification [6]. The districts with the highest CCA mortality rates over the past five years include Sai Mun, Pa Tiu, Kham Khuean Kaeo, Loeng Nok Tha, and Maha Chanachai, with average rates of 65.83%, 44.23%, 30.09%, 26.09%, and 20.07%, respectively [7].

Several studies have investigated the social determinants of health (SDH) associated with OV. For example, a cross-sectional study found that gender, education level, income, and residential context influenced

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OV infection risk [8]. Another study highlighted the role of health literacy in the behavioral prevention of OV, suggesting that comprehensive knowledge and self-management skills are crucial for preventing CCA [9]. Additionally, the rural culture of sharing food, especially raw fish, among households has been identified as a significant risk factor for OV infection [10, 11]. These findings emphasize the interplay between social ecology, cultural practices, and health outcomes in the Greater Mekong Sub-region [12-14]. The influence of SDH on health equity, including factors such as income, education, unemployment, social protection, and access to healthcare, is well-documented [15-18]. Given these considerations, this study aims to examine the association between SDH and CCA occurrence. The findings are expected to inform strategies to promote hygienic consumption practices to reduce CCA risk.

## Materials and Methods

*Study design*

The study was conducted in two phases: (1) a survey-based research design to estimate the prevalence, context, and situations of at-risk groups; and (2) a case-control study to investigate the SDH associated with CCA risk among the population of Yasothon Province, one of the northeastern provinces of Thailand, which has a high incidence of CCA. Importantly, the population in these areas maintains a rural culture of sharing food, which has been identified as a risk factor for OV infection [10, 11].

*Study area determination*

Yasothon Province, located in Northeast Thailand (coordinates: 15.79°N 104.15°E), approximately 575 kilometers from Bangkok, was selected as the study area. A multi-stage sampling method was employed. 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 (Figure 1).

*Population and sample*

The population included 182,653 people aged 40 years and over who resided in Yasothon Province as of August 20, 2022 [7]. Two study designs were utilized:

1) 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.

2) Case-control study: From the 496 participants, 238 cases at risk for CCA and 258 controls not at risk for CCA were identified. 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. (2) Being able to read and write Thai, and (3) Voluntarily participating in the research project. Exclusion criteria were refusal to participate or a confirmed CCA diagnosis.

*Research tools, quality validation, and outcome measures*

*The study utilized tools organized into two phases*

*Phase 1*

A verbal screening form, designed by the researchers, was employed. This form was divided into two sections: the first focused on gathering personal information from the respondents, and the second included four questions adapted from a public health screening form developed by the Kham Khuean Kaeo District Health Service Network, Yasothon Province [19]. The questions addressed the following: (1) Do you have a history of OV egg examination in your feces? (2) Does anyone in your family have a history of illness or death due to CCA? (3) Have you undergone an abdominal ultrasound that revealed any abnormalities? and (4) Do you consume alcoholic beverages? The response options were binary: Yes=1 and No=0 (Figure 2). The content validity of this form was evaluated by five experts, achieving an Index of Item-Objective Congruence (IOC) of 0.97.

*Phase 2*

A questionnaire was developed, comprising five sections:

1) General Information: Contained 12 questions about the respondents.

2) Knowledge of CCA: Included 20 questions with yes/no answers, scored Yes=1, No=0.

3) Health Beliefs about CCA: Consisted of 16 questions rated on a 5-point Likert scale: Strongly Agree=5, Agree=4, Not Sure=3, Disagree=2, Strongly Disagree=1. The responses were interpreted into five levels [20]: very high (4.20-5.00), high (3.40-4.19), moderate (2.60-3.39),

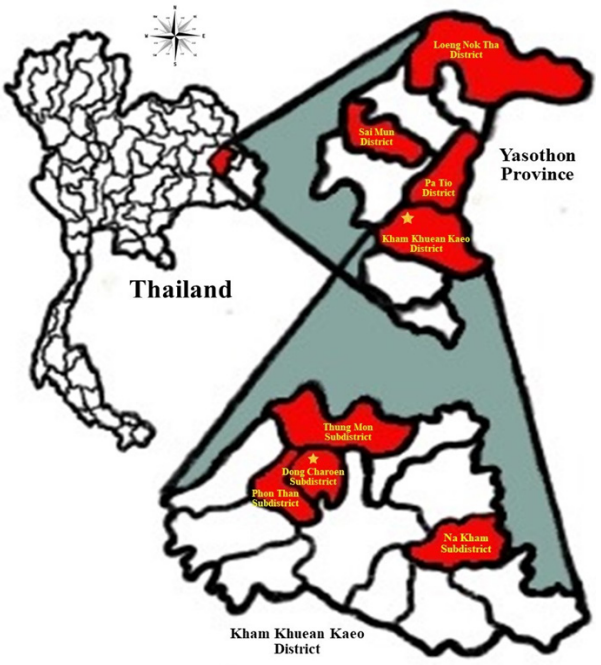


Figure 1. Study Site Selection Steps.

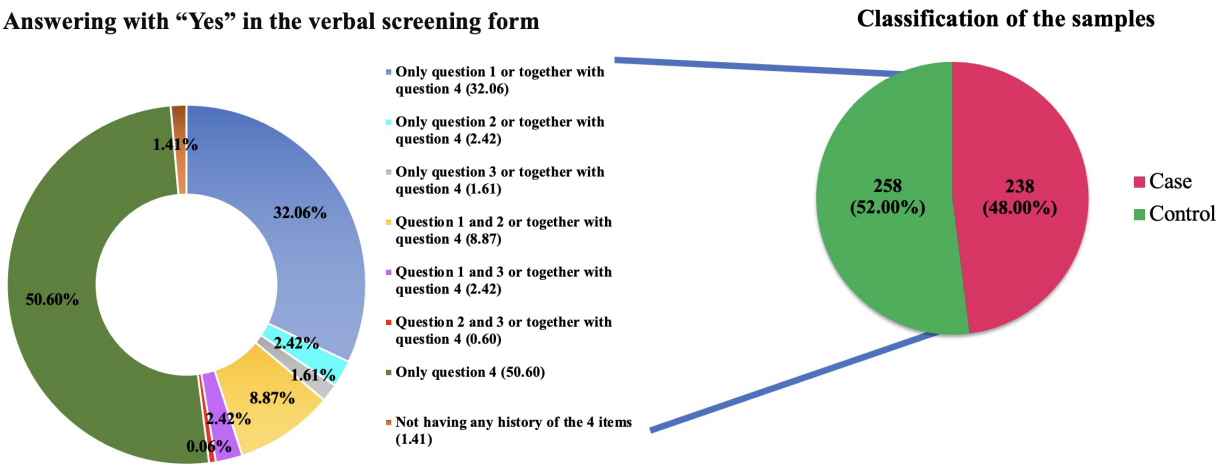


Figure 2. Classification of the Samples.

low (1.80-2.59), and very low (1.00-1.79).

4) CCA Prevention Behaviors: Contained 10 questions with responses on a 4-point ordinal scale: Always=4, Often=3, Sometimes=2, Never=1. The interpretation of scores was divided into four levels [20]: very high (3.26-4.00), high (2.51-3.25), low (1.76-2.50), and very low (1.00-1.75).

5) SDH Related to CCA: Comprised 26 questions across six SDH items, rated on a 5-point Likert scale: Strongly Agree=5, Agree=4, Not Sure=3, Disagree=2, Strongly Disagree=1. The score interpretation followed the same five-level system as in the health beliefs section.

Five experts reviewed the questionnaire for content validity, resulting in an IOC of 0.95. The questionnaire was then pilot-tested on 30 individuals with similar characteristics to the study population in Sri Wilai Subdistrict, Selaphum District, Roi Et Province. The knowledge section was analyzed using the Kuder-Richardson Formula 20 (KR-20), yielding a reliability coefficient of 0.75. The Cronbach's alpha coefficients for the health beliefs, and SDH sections were 0.79, and 0.90, respectively.

*Data collection*

The data collection process was carried out in three steps:

1) Researchers prepared the research tools and coordinated with the organizations in the study areas to obtain permission to conduct the study.

2) The research team held a planning meeting to organize the data collection process in the experimental and control areas.

3) A formal request for cooperation was submitted to the village headmen of all seven villages in Dong Charoen Subdistrict, Kham Khuean Kaeo District, Yasothon Province. This included clarifying the research objectives, applying for ethical approval, obtaining permission for data collection, and seeking the village headmen's support in conducting the research and gathering participant data. Subsequently, data was collected using a general information questionnaire from both the cases and controls. The accuracy of the collected data was then verified before analysis using a statistical software package.

*Statistical analysis*

All statistical analyses were conducted using SPSS Software, version 26.0 (IBM Corp., Chicago, IL, USA). Descriptive statistics, including frequency, percentage, mean, and standard deviation (SD), were utilized to evaluate demographic, economic, and social characteristics. The associations between risk factors and the likelihood of developing CCA were determined by estimating odds ratios (OR) with 95% confidence intervals (CIs) through logistic regression. 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. A p-value of less than 0.05 was deemed statistically significant.

## Results

Of 238 cases and 258 controls, most participants were female, comprising 63.03% of the cases and 59.69% of the controls. The average age was 58.19 ± 11.52 years for cases and 57.89 ± 11.95 years for controls. Regarding marital status, 56.30% of cases and 62.79% of controls were married. 59.24% of cases and 62.40% of controls reported educational attainment at the secondary level. Most participants were engaged in agriculture as their primary occupation, with 97.90% of cases and 97.29% of controls involved in this sector. The average monthly family income was 3,202.52 ± 2,511.56 Baht for cases and 3,319.76 ± 2,873.38 Baht for controls. 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. Both cases and controls received treatment with Praziquantel whenever public health personnel detected OV eggs (90.34% for both groups), and none of the participants purchased the medication independently. Additionally, all participants were screened for CCA (100.0%). Both groups received information and education

about CCA from public health officials (Table 1).

The SDH scores were stratified into low and high levels according to the mean score within each domain. The case and control groups exhibited high poverty levels, with mean scores of 15.90 ± 1.59 and 15.80 ± 1.60, respectively. Other SDH factors, including health inequality, food security, social exclusion, housing, working conditions, and overall SDH, were consistently low across both groups. The mean scores for these factors were as follows: 11.51 ± 2.02, 15.32 ± 2.52, 13.14 ± 2.00, 8.61 ± 1.89, 7.37 ± 1.64, and 71.75 ± 4.50 for cases, and 11.64 ± 1.97, 15.00 ± 2.49, 13.00 ± 1.88, 8.33 ± 1.80, 7.71 ± 2.08, and 71.50 ± 4.71 for controls, respectively. The overall SDH scores related to CCA were 71.75 ± 4.50 for cases and 71.50 ± 4.71 for controls. While most factors did not significantly differ between the case and control groups, there was a statistically significant difference in the overall SDH score between the two groups (p = 0.022) (Table 2).

In analyzing the factors associated with CCA risk, simple logistic regression followed by a multiple logistic regression model revealed that overall SDH was significantly associated with an increased risk of CCA (Adjusted OR=1.63, 95% CI=1.09-2.46, p=0.019). Protective factors significantly associated with a reduced risk of CCA included perceived disease severity (Adjusted OR=0.57, 95% CI=0.39-0.83, p=0.004) and safe working conditions (Adjusted OR=0.61, 95% CI=0.42-0.90, p=0.012) (Table 3).

## Discussion

Among the 496 participants screened for CCA risk, 238 (48.00%) were found to be at risk. A history of OV egg examination in feces was present in 32.06% of cases, and 2.42% had family members with a history of illness or death from CCA. Some cases exhibited overlapping risk factors, such as having a history of OV egg examination in feces and a family history of CCA (8.87%) or having a history of OV egg examination in feces and abdominal ultrasound abnormalities (2.42%). The prevalence of OV eggs found in the feces of cases was consistent with other studies in high-risk areas of Thailand, with 37.8% of CCA cases in a case-control study [13, 21, 22] and 45.7% in a cohort study [23].

In this study, CCA prevention behavior was found to be low among most cases (50.60%). This is attributed to the participant's residence in the Chi River basin area, where fish consumption from the Chi River, such as white carp, is a risk factor for OV. The most frequently practiced preventive behavior was cooking freshwater fish with scales, such as carp, before eating (53.2%). This aligns with a study on factors associated with CCA risk in Greater Mekong Sub-region countries [24], where most participants exhibited low- CCA prevention behavior (65.25%).

Additionally, 49.8% of cases did not regularly consume raw or undercooked pickled fish, and 47.2% did not mix fish in raw fermented fish with boiled fermented fish for dishes like papaya salad or chili sauce, indicating

Table 1. General Information Classified by Case and Control Group.

| General information | Case (n=238) | | Control (n=258) | | p-value |
|---|---|---|---|---|---|
| | Number | % | Number | % | |
| Gender | | | | | 0.446 |
| Male | 88 | 36.97 | 104 | 40.31 | |
| Female | 150 | 63.03 | 154 | 59.69 | |
| Age (years) | | | | | 0.779 |
| 40-49 | 71 | 29.83 | 80 | 31.01 | |
| 50-59 | 43 | 18.07 | 38 | 14.73 | |
| ≥60 | 124 | 52.10 | 140 | 54.26 | |
| $\bar{x}$ ± SD | 58.19±11.52 | | 57.89±11.95 | | |
| Marital status | | | | | 0.141 |
| Married | 134 | 56.30 | 162 | 62.79 | |
| Widowed/divorced | 104 | 43.70 | 96 | 37.21 | |
| Educational level | | | | | 0.384 |
| Primary school | 92 | 38.66 | 90 | 34.89 | |
| Secondary school | 141 | 59.24 | 161 | 62.40 | |
| Bachelor's degree and above | 5 | 2.10 | 7 | 2.71 | |
| Occupation | | | | | 0.658 |
| Agriculture | 233 | 97.90 | 251 | 97.29 | |
| Non-agriculture | 5 | 2.10 | 7 | 2.71 | |
| Average monthly family income (Baht) | | | | | 0.382 |
| ≥3,000 | 187 | 78.57 | 193 | 74.81 | |
| <3,000 | 51 | 21.43 | 65 | 25.19 | |
| $\bar{x}$ ± SD | 3,202.52±2,511.56 | | 3,319.76±2,873.38 | | |

Table 2. Levels of Social Determinants of Health associated with Cholangiocarcinoma.

| Social determinants of health (SDH) | Case | | Control | | p-value |
|---|---|---|---|---|---|
| | Number | % | Number | % | |
| Poverty | | | | | 0.539 |
| Low (< 15.90 points) | 95 | 46.34 | 110 | 53.66 | |
| High (≥15.90 points) | 143 | 49.14 | 148 | 50.86 | |
| $\bar{x}$±SD | 15.90±1.59 | | 15.80±1.60 | | |
| Health inequality | | | | | 0.677 |
| Low (<11.51 points) | 140 | 48.78 | 147 | 51.22 | |
| High (≥11.51 points) | 98 | 46.89 | 111 | 53.11 | |
| $\bar{x}$±SD | 11.51±2.02 | | 11.64±1.97 | | |
| Food security | | | | | 0.117 |
| Low (<15.32 points) | 132 | 45.05 | 161 | 54.95 | |
| High (≥15.32 points) | 106 | 52.22 | 97 | 47.78 | |
| $\bar{x}$±SD | 15.32±2.52 | | 15.00±2.49 | | |
| Social exclusion | | | | | 0.75 |
| Low (<13.15 points) | 135 | 47.37 | 150 | 52.63 | |
| High (≥13.15 points) | 103 | 48.82 | 108 | 51.18 | |
| $\bar{x}$±SD | 13.14±2.00 | | 13.00±1.88 | | |
| Housing | | | | | 0.36 |
| Low (<8.61 points) | 124 | 46.10 | 145 | 53.90 | |
| High (≥8.61 points) | 114 | 50.22 | 113 | 49.78 | |
| $\bar{x}$±SD | 8.61±1.89 | | 8.33±1.80 | | |
| Working conditions | | | | | 0.071 |
| Low (<7.37 points) | 141 | 51.65 | 132 | 48.35 | |
| High (≥7.37 points) | 97 | 43.50 | 126 | 56.50 | |
| $\bar{x}$±SD | 7.37±1.64 | | 7.71±2.08 | | |
| Overall SDH | | | | | 0.022 |
| Low (<71.75 points) | 113 | 43.13 | 149 | 56.87 | |
| High (≥71.75 points) | 125 | 53.42 | 109 | 46.58 | |
| $\bar{x}$±SD | 71.75±4.50 | | 71.50±4.71 | | |

inadequate OV and CCA prevention behavior. This finding is consistent with a study of OV infection among adolescents in urban Laos [25], which reported an OV infection rate of 39.0%. The high infection rate is likely due to the participant's proximity to the Mekong Basin and their practice of catching fish for consumption. Further, other risk factors were examined in a hospital-based case-control study, which found that 51.2% of rural people in Ubon Ratchathani, Thailand, habitually consumed raw fish, primarily for its taste [26]. The access to risk screening services aligns with findings from a study on OV infection among ASEAN populations working in Thailand [27], which showed that personal, environmental, and cultural factors influenced OV infection in the target community. While public health services provide screening and treatment to support policy, there is a need for more continuous awareness-raising.

Regarding factors associated with CCA risk, perceived severity, working conditions, and overall SDH were significantly related to CCA risk at the 0.05 level. Compared to low perceived severity (adjusted OR=0.57), high perceived severity was identified as a protective factor against CCA development among those at risk in Yasothon Province, Thailand. This is attributed to the local population's awareness of CCA severity and the risks associated with consuming raw fish, raw fermented fish, raw pickled fish, and raw fermented pork sausage, leading to better preventive behavior among those with high perceived severity. Cultural practices related to rural lifestyles are profoundly entrenched and account for about 76.9% of the reasons for continued raw fish consumption [28]. SDH can impact the survival of hepatocellular carcinoma and CCA, mainly through social deprivation [29], highlighting the significant effect of SDH on population health.

For working conditions, those at a higher level of SDH in terms of working conditions (adjusted OR=0.61) were considered to have a protective factor against CCA. This is because employees working in environments where cancer screening is provided at least once a year or where sanitary toilets and hygienic food are available exhibit better preventive behavior against cancer, including CCA, compared to those with lower levels of SDH in working conditions. This is consistent with studies showing that

Table 3. Analysis of the Factors associated with the Risk of Cholangiocarcinoma.

| Factors | Case Number (%) | Control Number (%) | Adjusted OR | 95% CI | p-value |
|---|---|---|---|---|---|
| Marital status | | | | | |
| Married | 134 (45.30) | 162 (54.70) | 1 | | |
| Widowed/divorced | 104 (52.00) | 96 (48.00) | 1.30 | 0.90-1.90 | 0.166 |
| Perceived risk | | | | | |
| Low (<15.66 points) | 118 (52.40) | 107 (47.60) | 1 | | |
| High (≥15.66 points) | 120 (44.30) | 151 (55.70) | 0.76 | 0.53-1.10 | 0.155 |
| Perceived severity | | | | | |
| Low (<12.88 points) | 170 (53.10) | 150 (46.90) | 1 | | |
| High (≥12.88 points) | 68 (38.60) | 108 (61.40) | 0.57 | 0.39-0.83 | 0.004* |
| Perceived benefits | | | | | |
| Low (<18.98 points) | 183 (50.40) | 180 (49.60) | 1 | | |
| High (≥18.98 points) | 55 (41.40) | 78 (58.60) | 0.70 | 0.46-1.01 | 0.086 |
| Prevention behavior | | | | | |
| Low (<16.25 points) | 124 (50.60) | 121 (49.40) | 1 | | |
| High (≥16.25 points) | 114 (45.40) | 137 (54.60) | 0.82 | 0.57-1.19 | 0.298 |
| Food security | | | | | |
| Low (<15.32 points) | 132 (45.10) | 161 (54.90) | 1 | | |
| High (≥15.32 points) | 106 (52.20) | 97 (47.80) | 1.11 | 0.75-1.66 | 0.586 |
| Working conditions | | | | | |
| Low (<7.37 points) | 141 (51.60) | 132 (48.40) | 1 | | |
| High (≥7.37 points) | 97 (43.50) | 126 (56.50) | 0.61 | 0.42-0.90 | 0.012* |
| Overall SDH | | | | | |
| Low (<7.75 points) | 113 (43.10) | 149 (56.90) | 1 | | |
| High (≥7.75 points) | 125 (53.40) | 109 (46.60) | 1.63 | 1.09-2.46 | 0.019* |

SDH affects workers' health disparities [30].

SDH was significantly associated with CCA risk, with an adjusted OR value of 1.63. SDH may also be linked to social marketing and health beliefs in preventing CCA in high-risk areas of Thailand [31]. The study concludes that perceived risk, perceived severity, perceived benefits, perceived barriers, and correct CCA prevention behaviors in the experimental group were significantly improved compared to the experiment and the comparison group.

*Limitations*

The case-control study encountered several challenges, particularly in participant selection. One notable limitation was recall bias, as participants may have had difficulty remembering past events. Additionally, selection bias was present during participant recruitment, as some individuals might have already been ill but had not yet received a formal CCA diagnosis.

In conclusion, in this study, overall SDH emerged as a significant risk factor for CCA, while perceived disease severity and safe working conditions were identified as protective factors. Employers should prioritize improvements in the working environment to mitigate CCA risk. Public health agencies must also develop and implement targeted initiatives to enhance awareness of disease severity and address SDH. These efforts are crucial to fostering more effective CCA prevention behaviors within the population. Expanding these findings to other regions with similar contexts could be highly beneficial. From a public health perspective, a comprehensive understanding of the risk factors associated with CCA across all dimensions is crucial for devising effective strategies to address the issue at its core.

## Author Contribution Statement

PK, NS, and CT conceived and designed the research. PK and NS were responsible for connecting and coordinating the fieldwork. PK collected the data. PK, NS, CT, and WC carried out the analyses. PK and NS reviewed drafts of the paper. All authors contributed to the writing and revisions of the manuscript and approved the final version.

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*Ethical approval*

This study was approved by the Human Research Ethics Committee of Yasothon Provincial Public Health Office based on the Declaration of Helsinki and the

ICH-GCP Guidelines (Ref. no. HE6658). Researchers explained the study objectives to participants at the beginning of the study. Each participant was approved to participate in the investigation by signing the consent form. Then, the participants were informed of the right to refuse participation in the study or withdraw at any time with no consequences.

*Availability of data (if apply to your research)*

Data will be available upon request.

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*Conflict of interest*

The authors declare no competing interests.

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