

Balancing Biomedical and Ecological Views in the Study of Liver Fluke

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Abstract

Opisthorchis viverrini, *Clonorchis sinensis*, and *Opisthorchis felinus* are considered to be of significant global public health importance, with an estimated 700 million people at risk of infection and 10, 35, and 1.6 million infected, respectively, in their contiguous geographic ranges spanning Central to East and Southeast Asia. In the literature, *O. viverrini* (Ov) is portrayed as causing hepatobiliary illness, sometimes referred to clinically as 'Opisthosis', particularly cholangiocarcinoma (CCA), presuming a causative chain including raw fish eating, followed by infection with this liver fluke, leading to cancer.

Keywords: Ecology • Cholangiocarcinoma • Fluke

Introduction

The relationship between Asian liver flukes and cholangiocarcinoma (CCA) from two opposing study perspectives: those that aligned with the biomedical model that has been widely used to date. An examination of the assumptions that underpin the majority of this research, which is required for evidence-based health research, demonstrates how a broader research frame that incorporates 'ecologic' perspectives provides alternatives to the dominant scientific interpretations and public narrative. To overcome the region's slow success in reducing liver fluke infection prevalence and CCA incidence, a more balanced and integrated research method combining aspects of the biomedical model and ecological models of health is proposed.

Literature Review

Despite the focus of disease management efforts in the Northeast, Ov infection prevalence and CCA incidence remain higher in the Northeast than in any of Thailand's other three geographic regions: Northern, Central, and Southern Thailand. The majority of the study and evidence for the "Ov-CCA relationship" comes from studies in Northeast Thailand, where Ov's role in the formation of malignant biliary tumours with a poor prognosis and a high mortality rate has been widely examined. Three sources of evidence are commonly cited in support of the Ov-CCA causal relationship: (i) the geographic coincidence of high infection prevalence and CCA incidence in Northeast Thailand; (ii) pathophysiology research demonstrating Ov's ability to induce cancer in artificially infected lab animals (hamsters); and (iii) the International Agency for Cancer Research (IARC) classification of Ov as a Group 1 carcinogen (primarily based on these animal model results). In this scientific community, a narrative compatible with the Ov-CCA model prevails, as indicated not only in clinical research and parasitology publications, but also in presentations, formal and informal debates, and conferences and symposia relevant to the topic. This dominant Ov-CCA narrative has not only

influenced Thai government health education policies and campaigns for decades, but it is also promoted in the popular press both locally and globally. A recent BBC item says that "raw fish has been discovered to be behind a high incidence of liver cancer in the area," as an example of the latter. Another recent "sensationalised" journalistic account, "This Thai Meal Gives You Liver Cancer," comes to the same conclusion [1].

Discussion

As a beginning point for justifying (and conveying) research and disease prevention agendas, simplicity is key. Historically, the aforementioned model and narrative may have fulfilled both of these functions successfully, particularly in Thailand generally. Nonetheless, despite an outstanding body of laboratory research on the pathology of liver fluke infection, new data has emerged since the last IARC assessment, bolstering the case for a more nuanced allegation of Ov and *Clonorchis sinensis* carcinogenicity. Regardless of such allegations, IARC results concern the carcinogenicity of a specific substance. The importance of such social, ecological, and environmental data and analysis in study on helminthes and Ov and associated disease is well documented in the papers described above. For example, there are a number of potential hurdles to successful control in Isaan that could be overcome through "field or community-based" research. Similarly, the failure to do studies guided by ecology and evolutionary biology, which is required to understand transmission patterns and virulence, results in Ov infection and related disorders, including CCA. This and other recent ecologically oriented studies call into question the widely held belief that Ov is universally pathogenic, that eating raw fish dishes is unsanitary and necessarily contributes to poor health, and that villagers must be "educated" about the "high risk" behaviour of eating traditional, uncooked fish dishes.

When one analyses the frame's essential influence on research, the importance of considering it becomes evident. The frame influences how research questions are posed, and hence the sort of evidence available; as well as how aetiology, causality, and evidence are debated, described in written documents, and researched. To the best of our knowledge, "logic models" demonstrating presumed (logical) linkages between independent variables (intervention components) and presumed dependent variables (target behaviours, social, ecological systems, health status measures, etc.) have not been developed prior to and throughout existing intervention programmes. The absence of logic models, an approach created within the social sciences, prevents academics and public health workers from properly assessing treatments.

Another simplifying assumption of the dominant model and narrative is that liver flukes and related disease adhere to the germ theory and Koch's idealised version of his Postulates: infection equates with pathogen reproduction in the

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human host, and consequently disease. Of course, Koch was well aware that, in the case of cholera, the causal agent, *Vibrio cholerae*, could be found in both sick and healthy people, rendering his first premise incorrect. These early apparent imitations of the theory, openly acknowledged by Koch himself, are now corroborated by modern analyses of host-pathogen interactions in which complexity in pathogenic pathways and synergies across levels of biological organisation (i.e. genes, cells, organs, individuals, their direct habitats, etc.) are leading to non-trivial patterns of susceptibility/virulence that the model cannot explain [2,3].

We have previously presented in detail the evidence for an immune-modulation involvement in this Ov-human host connection. This not only explains why the vast majority of infected persons are asymptomatic, but it also has implications for assessing the risks versus benefits of deworming drug toxicity, which is discussed further below. Furthermore, it raises the issue of the epidemiological consequences of deworming on autoimmune and metabolic diseases in the Isaan population, indicating how the problem frame has implications in terms of ethical considerations of interventions [4], particularly in light of the region's broader context of environmental, livelihood, and epidemiological transitions. The multifactorial nature of liver cancer is supported by well-established pathophysiological studies that reveal carcinogenesis is promoted by inflammation and oxidative stress, both of which are influenced by a variety of biological, chemical, and physical variables. Alcohol usage, a well-known contributor to liver pathophysiology and cancer, is said to have increased severalfold. The northeast has the highest rates of use and abuse, which can be explained by the region's lower socioeconomic position and poverty.

Two other factors that have been linked to an increased risk of cancer through disrupting anti-inflammatory processes or acting as inflammatory agents must be mentioned. First, though it is not widely acknowledged in medical, parasitological, or even public health literature dealing with the Ov-CCA association, poverty has significant implications for chronic disease risk via chronic psychosocial stress, which, in addition to predisposing a population to alcohol abuse and other risky behaviours, is known to contribute to physiological pathology, including allostatic load, a known factor in many chronic diseases [5]. A final sort of model, dubbed the "lay health model," is held by Isaan-Lao peasants, who are the intended recipients of most liver fluke teaching initiatives in Isaan. Despite health "education" initiatives that meet the above psychosocial notion of health and include ecologic factors, a field study recently demonstrated that Isaan-Lao villagers maintain a perspective of the OvCCA relationship with regard to their health that is significantly unique from the prevalent biomedical model.

Conclusion

To present, research and management strategies addressing Ov infection in connection to cholangiocarcinoma have been almost entirely informed by the 'biomedical model,' which considers infection and illness to be similar and places a priority on pathology. Although some parts of ecology have occasionally tempered the epistemological dominance of the biological model in some parasitological studies engaged in transmission, this biomedical problem frame has also been extended to parasitological inquiries. The majority of CCA patients are also infected with Ov. Clearly, from the clinician's point of view, Ov is the causative agent, especially given Ov's status as an IARC-certified carcinogen. Given this, and the generally dismal prognosis of CCA patients, the prevalent practise of consuming raw or undercooked fish preparations is cause for concern.

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