Review Article

DOES HUMAN MALARIA HAVE ANY LINK WITH CANCER AND CARDIOVASCULAR DISEASES?

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ABSTRACT

Background: Malaria is an age-old mosquito-borne disease still causing significant mortality and morbidity every year, majorly in the developing world. Apprehensions have been raised in certain quarters that there can be associations between cancer and human malaria. Malaria has also been linked with several cardiovascular diseases.

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Methods: A narrative review was conducted by using electronic databases–PubMed, Google scholar, medXiriv, Wiley Online Library- using terms for research articles up to the year 2022. All the findings are based on published information and they are listed in the references section.

Result: As per clinical reports, malaria infection may contribute to the development of ischemic cardiomyopathy, myocardial edema, and hypertension. Hitherto, the association between malaria and Burkitt's lymphoma is well-analyzed. It has been suggested that malaria may induce cancer by immune suppression of hosts leading to genetic modifications, loss of apoptosis, and uncontrolled proliferation of tumour cells, though the inverse relationship between these two diseases is also evident in experimental setups.

Conclusion: Malaria parasites can impact physiological and cell cycle regulations, which eventually may involve them in the disease dynamics of cardiovascular diseases and cancer. At this juncture, the authors are hesitant to arrive at any conclusion regarding the links of human malaria with cancer and cardiovascular diseases. But possibilities of such interlinks are not to be neglected. Further molecular epidemiological studies inclusive of molecular interactions, genetic modifications, cell cycle modifications, disease ecology, and host physiological conditions encompassing patients of these diseases from different geographical regions of the world are required to prove this causative association.

Keywords: Human malaria, Cancer, Cardiovascular disease, Interrelation

INTRODUCTION

Malaria has been a leading cause of severe public health mortality and morbidity occurring primarily in the tropical and subtropical belts of the world.[1] There is an estimation of 241 million malaria cases worldwide according to the

World Malaria Reports 2020,[2] with the African region of WHO accounting for more than 95% of global malaria cases.[2] There are five different *Plasmodium* sp., known to cause human malaria viz. *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*, but the burden of *P. falciparum* and *P. vivax* induced malaria is widespread in nearly all countries endemic to this disease.[2-4] According to the latest reports from WHO, case fatality rate (CFR) between 0.01% and 0.40% has been implicated for the reported number of *P. falciparum* cases, while CFR for *P. vivax* malaria is 0.01-0.06%.[2] Children below the age of 5 years display an increased susceptibility and vulnerability to severe malaria and account for 67% of global malaria-induced mortality, and 80% in the African region.[5,6]

Endemic Burkitt's lymphoma (eBL), a form of cancer, is a common tumour in the children of the African tropical region.[7] The geographical distribution of eBL has been linked with the occurrence of *P. falciparum* malaria.[7,8] Apprehensions have been raised in certain quarters that there can be associations between cancer and malaria at the molecular and immunological level.[9,10] In addition, *P. falciparum* also causes cytoadherence of the parasitized RBCs in the walls of the capillaries of the brain and heart.[11,12] Malaria has also been linked with cardiovascular diseases by several researchers.[11-13] Despite attempts at curbing the occurrence and incidence of malaria, this deadly disease is a recurring concern for all age groups. In this review, we attempt to explore and summarize the association and possible interactions of human malaria with cancer and cardiovascular diseases. An understanding of the interrelatedness between these globally distributed diseases may guide the development of novel approaches regarding therapeutic measures and prevention strategies against malaria, cancer, and cardiovascular diseases.

Methodology: PubMed, Google Scholar, and several other journals were searched for studies concerning Malaria, Cancer, and Cardiovascular diseases. All the findings are based on published information and they are listed in the references section. Data of case incidences and deaths were collected from www. who. int (Accessed on 27th April 2022).

CANCER METASTASIS AND MALARIA: AN UNUSUAL ASSOCIATION

Historically, cancer and malaria have emerged as two separate lethal diseases causing large-scale mortality. The possibility of a potential link between the two

has triggered an intense investigation by researchers. Both cancer and malaria have unique physiologies. Cancer is a result of genetic and epigenetic modifications that have accumulated over time and lead to the cessation of apoptosis and subsequent uncontrolled proliferation of cells.[10] The geographical occurrence of endemic Burkitt's lymphoma (eBL) closely corresponded to regions endemic to malaria.[7,8] Apprehensions have been raised in certain quarters regarding the synergistic effects of several components associated with malaria that contributes to the development of eBL.[7,8,14] An altered level of Vitamin A metabolism got reported in Burkitt's lymphoma. Retinoic acid, a derivative of vitamin A induces the expression of activation-induced cytidine deaminase (AID) by the germinal center (GC) B cells in BL. *P. falciparum* infected patients showed an increased number of GC B cells and deregulated expression synthesis of AID.[7] The AID contributes to c-myc oncogene translocation in GC B cells latently infected with Epstein-Barr virus (EBV), which gets commonly manifested in eBL cases. Apart from that *P. falciparum* infection results in high levels of B cells in transition at GC, which increases the number of B cells infected by EBV.[7,8,14] Together, these factors may increase the occurrence of eBL in individuals infected with malaria.[7]

Additionally, when the Programmed Cell Death Protein 1 (PD-1) on the surface of activated T cells binds to their ligand Programmed Cell Death Protein-Ligand 1 (PD-L1) induced by inflammatory cytokines, they promote tumour progression by neutralization, T cell dysfunction, and exhaustion.[15-17] Consistent with the idea of PD-1 being a negative modulator of T-cell, its numbers have reportedly shown a sharp increase in patients with falciparum malaria. Moreover, T –cell exhaustion in children having *P. falciparum* malaria has been reported by Butler *et al*., 2011.[18] The numbers of these PD-1 receptors were also seen to increase with the patient's age and their repeated exposure to malaria.[19-21] The incidence of malaria augments the incidence of cancer by suppressing the immune response.

An association between *P. vivax* malaria and cancer has also been demonstrated by a few groups of researchers.[9,10] Duffy Antigen Receptor for Chemokines (DARC) is a protein used by *P. vivax* to invade the host RBC.[22] The DARC has been found to be an inhibitor of tumour angiogenesis in breast cancer.[23] Apart from that, the interaction of DARC and CD82 protein is tumour suppressive.[24]

Table: Proteins involved in tumour progression that are actively expressed in falciparum malaria cases

Protein product/Enzyme	Role in cancer	Relation to malaria	References
Activation-induced cytidine deaminase (AID)	• c-myc oncogene translocation • GC B cell proliferation that are latently infected by EBV	AID levels increase during the infection of *P. falciparum*	Thorley-Lawson *et al.*, 2016;[14] Torgbor *et al.*, 2014;[7] Ellis *et al.*, 2021[8]
PD-1/PD-L1	• Pro-tumourigenic effect, • Immune evasion via T cell exhaustion promotes immune tolerance	Parasite-induced upregulation of PD-1 in T cells decreases immune response due to T cell exhaustion making the infected individual more susceptible to different types of cancer.	Alsaab *et al.*, 2017;[15] Sun *et al.*, 2015;[16] Moebius *et al.*, 2020;[19] Kamphorst *et al.*, 2013[20]
Duffy Antigen Receptor for Chemokines (DARC)	• Tumour suppressive effect when attached to CD82 protein • Inhibits tumour angiogenesis in breast cancer	DARC helps the *P. vivax* to invade the RBC	Nordor *et al.*, 2018;[9] Mannaa, 2018;[10] Michon *et al.*, 2001[22] Wang *et al.*, 2006; [23] Bandyopadhyay *et al.*, 2006[24]

ASSOCIATION BETWEEN CARDIOVASCULAR COMPLICATIONS AND MALARIA

The clinical cases of myocardial infarction resulting from impaired cardiac circulation systems got linked with severe malaria by several researchers.[11,25,26] Plasmodium *sp.* can typically make RBC less deformable with the destabilization of hemoglobin and other RBC proteins.[11,13] *P. falciparum* is well known to cause cytoadherence of RBC in the capillary walls, which with the loss of deformability, eventually results in blockage of capillaries, especially in the brain and heart.[11] Further, RBCs parasitized by *P. falciparum* and the subsequent obstruction by them

in capillaries are fundamental complications leading to ischaemic cardiomyopathy.[27,28]

Studies reiterated a suppressed myocardial function through a negative inotropic effect owing to a pro-inflammatory cytokine such as the tumour necrosis factor (TNF-α).[29] The glycosylphosphatidylinositol (GPI) anchor of Plasmodium falciparum is considered an endotoxin and impacts the apoptosis of cardiac myocytes.[29-31] Adding to that, myocarditis is a fatal complication and seems to be arising as a manifestation of a *P. vivax* infection.[32] The inadvertent link between the periodic malarial episodes in congruence with cardiovascular complications demands further investigation in this direction.

DISCUSSION

The modification of cellular properties by the infection of external pathogens such as *Plasmodium* sp. leading to unexpected links with other diseases has been studied by several researchers extensively.[9,10,29,30] Most of the modifications are related to the expression of different proteins in the cytoskeleton which are evolutionary shaped to facilitate the invasion of the parasite to host cells. One such modification is the binding of *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), a surface antigen protein on the expressed 'knobs' on the surface of parasitized RBCs.[10,33,34,35] The antigen variant, variant surface antigen 2-chondroitin sulfate A (VAR2CSA), is a member of the PfEMP1 protein family that binds to chondroitin sulfate A (CSA), a protein found exclusively in the placenta.[10,36,37] The similar CS modification has been found in several cancer cells, helping in proliferation and growth.[9] This association has been proposed to be beneficial in using the VAR2CSA as an agent for tumour-specific drug delivery.[10] Another protein mediated by the *Plasmodium* sp. for its invasion is the p53 protein. Lower levels of p53 are ideal for the invasion of *Plasmodium* sp. into host cells.[38] Experimentally, it has been demonstrated that rodent malaria parasites *Plasmodium yoelii* perturb regulation of cell proliferation, cell survival, and autophagy, possibly by decreasing the levels of p53 for their survival.[38] Hitherto, no such associations between human malaria parasites and p53 have been reported. But owing to the evolving nature of human malaria parasites, such possibilities may not get neglected. The liver stage of the parasite is of particular significance regarding this aspect as p53 is the cell cycle regulator and tumour suppressor protein in liver cells

crucial for apoptosis of damaged or mutated cells.[39] However, further research in this direction is required to verify these assumptions. An inverse connection exists between Duffy Antigen for Chemokines (DARC) expressed on the surface of RBCs, which gets utilized by the *P. vivax* to gain entry into the host cell while simultaneously inhibiting the proliferation of cancerous cells.[8,9] The functionality of DARC lies in its ability to sequester mobile chemokines and thereby abate tumour metastasis.[9,23,24] From an evolutionary perspective the avoidance of *P. vivax* malaria requires down regulation of the DARC proteins on the cell surface, which may, in turn, reduce the protection against tumour proliferation.[9] However, an inverse relationship between cancer and malaria is also reported. In experimental setups, in mice models, plasmodium-induced proteins were found to suppress the tumour angiogenesis.[8]

With the blockage of capillaries from parasitized RBCs, it is of no surprise that malaria would be associated with cardiovascular complications such as ischaemic cardiomyopathy.[27,28,31] Consequently, with the increase in peripheral vascular resistance in malaria-affected patients, the cardiac output (CO) is automatically reduced.[29] Spitz *et al*. (1946) revealed how interstitial myocardial edema was identified in patients exposed to malaria.[26,40] A greater prevalence of hypertension in people persistently exposed to malaria has led many researchers to suspect an association between malaria and cardiovascular diseases.[13,41-43] A suppressed myocardial function is also due in part to the parasite toxin and mediators of the host immune system.[5] Considering the inter-relatedness that human malaria shares with cancer and cardiovascular diseases, the possibility of these diseases acting as comorbidities of malaria in the future may not be neglected. From the evolutionary perspective, genetic modifications for better adaptation and evasion of the host immune system by human malaria parasites can further result in unexpected outcomes. During the literature search, we noticed that there is scanty research regarding the association of *P.vivax* malaria with other diseases inspite of several possible links. Therefore, further inclusive studies on such unusual associations of different human malaria parasites with other maladies should be done, to further explore and assess potential threats regarding the diseases and development of therapeutic measures.

CONCLUSION

Malaria is an age-old mosquito-borne disease still causing significant mortality and morbidity every year, majorly in the developing world. Cardiovascular diseases have been the leading cause of global death in humans for more than two decades. Cancer also accounts for millions of mortality globally. Possible unusual links between human malaria with cancer and cardiovascular diseases at the molecular and immunological levels got reported and hypothesized by several authors. Due to the invasion of RBC and other host cells, malaria parasites can impact physiological and cell cycle regulations, which eventually may involve them in the disease dynamics of cardiovascular diseases and cancer, respectively. As per clinical reports, malaria infection may contribute to the development of ischemic cardiomyopathy, myocardial edema, and hypertension.

Hitherto, the association between Burkitt's lymphoma is the most well-analyzed aspect among the possible interlinks between cancer and malaria. It has been suggested, malaria may induce cancer by immune suppression of hosts leading to genetic modifications, loss of apoptosis, and uncontrolled proliferation of tumour cells, though the inverse relationship between these two diseases is also evident in experimental setups.

At this juncture, the authors are hesitant to arrive at any conclusion regarding the links of human malaria with cancer and cardiovascular diseases. Yet the possibilities of such interlinks are not to be neglected. Further molecular epidemiological studies inclusive of molecular interactions, genetic modifications, cell cycle modifications, disease ecology, and host physiological conditions encompassing patients of these diseases from different geographical regions of the world are required to prove this causative association.

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