Journal of Medical Research and Health Sciences
Received 24 Nov | Revised 27 Dec 2023 | Accepted 25 Jan 2024 | Published Online 05 Feb 2024

DOI: https://doi.org/10.52845/JMRHS/2024-7-2-1

JMRHS 7 (2), 3004–3012 (2024)

ISSN (O) 2589-9031 | (P) 2589-9023

Original Article **Open Access Journal**

Relationship Between the Exposure of Malaria in an Endemic Zone and its Association with Cancer Incidence.

Mondragon Leonel (BSc)[1], Richard Silvina (PhD)[2], Martinez Marignac Veronica (PhD)[3]

[1]School of Medicine, Faculty of Health and Life Sciences, Adventist University of River Plate, Libertador San Martin, Argentina.

[2]Department of Genetics and Molecular Biology, Insitituto Multidisciplinario de Biologia Celular, La Plata, Argentina

[3]Interdisciplinary Laboratory of Biology and Molecular Genetics, CICYTTP, and National Council of Scientific and Technical Research, Diamante, Argentina.

Correspondig Author: Martinez Marignac Veronica (PhD)

Abstract

An inverse association between malaria infection and risk of cancer has been established worldwide, however nutritional, economical incomes, social parameters bias and cancer risk increased by year related to life style and other factors have not been studied in an endemic malaria region such as those in South America. The present analysis examines the association by malaria and cancer and neoplasm incidence, restricting analyses to studies performed by the Institute for Health Metrics and Evaluation (IHME) where data for South America for endemic countries (Suriname, Guyana, Ecuador, Peru, Venezuela, Colombia, Brazil, Bolivia) and non malaria endemic countries were available (Argentina, Paraguay). Uruguay and Chile were included as outliers per more than 10 years with no reported cases of Malaria. The authors reviewed available databases through 30 years, examining both sexes, people of 25 year of age and olders, and analyzed the association between malaria, year of incidence, nutrition and risk of having different types of cancers and neoplasm as they were defined by Global Health Data Exchange (GHDx) and IHME. An inverse association between malaria total cancer and a strong negative correlation with neoplasm was found in both sexes. This study confirms previous studies reporting an inverse association between malaria and cancer and provides quantitative estimates of the inverse association in South American countries. We suggest that two malaria non-endemic countries (Chile and Uruguay) have an elevated risk level of cancer incidence. We discuss possible mechanism of malaria infection as an antagonist to cancer or neoplasm development.

Keywords: malaria, cancer, cross immune response, endemic countries, South America.

Relationship Between the Exposure of Malaria in an Endemic Zone and its Association with Cancer Incidence.

Introduction

Malaria is the most prevalent parasitic infectious disease currently in the world. According to World Health Organization by every year are more than 220 million cases of malaria in 90 countries [1]. The World Health Organization (WHO) estimates that 558,000 people died because of malaria in 2019; the Institute of Health Metrics and Evaluation (IHME) puts this estimate at 643,000 and children under 5 years are the most affected, accounting in 2019 for 67% of all malaria deaths worldwide [2]. This disease is caused by the protozoan parasite from the *Plasmodium* species. There are five species of the parasite that infects humans and includes *P. falciparum, P. vivax, P. malariae, P. ovale* and P. knowlesi [3]. Nevertheless, the majority of the malaria infection is caused by *P. falciparum* (>90%).

On another hand, cancer is responsible for approximately 9.6 million deaths in 2018 and 10 millons makes it the second leading cause of death in the worldwide, which causes 1 in 6 deaths globally according to WHO sources [3] and by 2020 there were reported globally more than 18 millons cases [4]. They state that 70% of cancer mortalities happen in low- and middle-income countries and around one third of deaths are related to leading nutritional and lifestyles: low fruit and vegetable intake, high body mass index, tobacco and alcohol use [5]. Oncogenic infections, such as Helicobacter pylori, human papillomavirus (HPV), hepatitis B virus, hepatitis C virus, and Epstein-Barr virus accounted for approximately 13% of cancers diagnosed in 2018 globally, and caused 25-45% of cancer cases in low- and middle-income countries since 2012 [6-7]. It also predicted that the global burden of cancer will rise to nearly 22 million cases and 13 million deaths by 2030, with the major burden on low/middle-income countries [4]. In Brazil, where there are endemic regions of malaria, 592,371 new cancer cases in both sexes of all ages were reported in 2019 alone [8]. The estimations from 2018 to 2019 for around 600,000 new cases which would have emerged in Brazil, were confirmed and that the most common type were prostate cancer in men and breast cancer in women [9].

Current Epidemiological Evidence Regarding Malaria and Cancer

In the past and nowadays, malaria has a controversial association with cancer [10-12] from been positively associated with the decrease of different viral infections, which are describe as a high carcinogen and which aggravates the output and symptomatology of cancer [11-12]. Furthemore, recently in a retrospective meta-analyses research including 1955 to 2008, it was indicated that endemic or epidemic malaria may decrease mortality for some solid cancers, including colon cancer both in men and women, lung and stomach cancer in men, and breast cancer in women [13]. The data was collected regarding global malarial incidence from 218 countries, age-standardized mortality rates and the 29 types of cancers in 194 countries. Their analysis also indicated that the increased levels of economic development and increased life span typically decrease malaria incidence and on the contrary increased cancer mortality [13]. In addition, at a preclinical trial in a murine model, the malaria parasite infection inhibited Lewis Lung Cancer (LLC) growth and metastasis, by inhibiting angiogenesis and prolonged the survival of tumor-bearing mice [14]. The preclinical study concluded that through the induction of innate and adaptive immunity, malaria infection significantly suppresses LLC growth and reduces metastases [15]. It was also found that malaria attenuated sporozoites and used to immunize against malaria markedly by increasing the percent of CD8+ T cells also induced antitumor activity against Lewis Lung Cancer (LLC) through the induction of host innate and adaptive immune response and a same mechanism was reported in mice infected by triple negative breast cancer cell lines [15-17].

Furthemore, Li Quin et al [13] showed that the year 1981 was a turning point in countries with endemic malaria incidence because malaria incidence increased while the all-cause cancer mortality significantly decreased. Therefore, we hypothesized that in countries with low levels of malaria or controlled endemic malaria, an inverse

relationship between malaria incidence and cancer mortality would be observed merely through a simple retrospective epidemiological analysis. The main objective of the study was to provide new epidemiological data regarding the relationship between cancer and malaria infection in South America and some of its malaria endemic countries. Of course we can not disregard studies that underline chloroquine treatment of patient with malaria as it was reported that chloroquine or hydroxyl-chloroquine could be repurposing for cancer and other viral infection [18].

Brazil was the country of reference for this research since it´s the South American country with most malaria incidence as reported in the 1990´s. It is geopolitically divided into five regions (North, Northeast, South, Southeast and Mid-west) and each is composed of multiples States. We were interested in the cancer incidence of this nation from 1990 to 2019 and other 9 South American countries, we analyzed if there´s an inverse relationship with the incidence with malaria from the same years [19-22]. We have long suspected that people living in endemic regions with malaria had a less incidence of cancer. Likewise, we hypothesize that if malaria incidence would decrease, the cancer rate would increase as the protecting factor is decreasing independent of nutritional or economical factors also included in the analysis.

Methods

We performed a retrospective epidemiological study carried out based on data collected from studies regarding malaria and cancer incidence in Brazil, and other South American countries during a span of 30 years. The study is based on records from male and female patients, from 25 year of age and olders, who had been diagnosed with different solid types of cancers and independent records of malaria infected persons reported from 1990 to 2019. We did not considered **prevalence, as it** reflects the number of existing cases of a disease at the selected period of time and add up chronic cancer patients, and as malaria is an acute infection we only considered incidence that reflects the number of new cases of disease at a time point and can be reported as a risk or as an **incidence** rate. We consider prevalence reflect differently both disease such as an acute malaria infection and other chronic such as cancer new cases in the selected period of time. In summary, we used incidence as GDB (the number of new cases of a given cause during a given period in a specified population). In the results tools it is expressed as the number of new cases in a year divided by the mid-year population size.

All of the subjects personal information was not access and only public records were used from Global Burden of Disease Collaborative Network, Global Burden of Disease Study 2019 (GBD 2019) and obtained using online Global Health Data Exchange- GDHx platform. GDHx as described it is a comprehensive catalog of surveys, censuses, vital statistics, and other health-related data by the IHME and it is an independent global health research center at the University of Washington.

The Global Burden of Disease **-GBD Results Tool**: Institute for Health Metrics and Evaluation database was used for data organization and download in cvs file type. The GBD allowed to collect incidence, prevalence, and disease (cancer or neoplasm, malaria) by age (over 25 yo), sex, years, and location for 354 diseases and injuries, and 3484 sequelae (ie, the disabling consequences of these diseases and injuries). For some graphics we used the charts of Our World in Data Organization.

Statistical analysis: A descriptive analysis was carried out on the sample of women and men, ages from 25 and over years. Use as control data of testicular, and prostate cancer for association with male and ovarian, breast and uterus for female. In this research, we considered data related to cancer and malaria and performed an ANOVA analysis as well as Pearson's, Spearman's coefficient analysis. The significance level was 0.05.

The relative risk (RR) or risk ratio is the ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group. Together with risk difference and odds ratio, relative risk measures the association between the exposure and the outcome, we used as exposed endemic regions and Chile and Uruguay as non exposed samples.

To obtain this we use different countries endemic and not to evaluate the relative risk of develop any type of cancer in that population.

Results

Malaria in Brazil and in the South Americas.

We focused on population and health databases information regarding cancer and malaria incidence in order to gather data, interpret them and analyze if it matches our hypothesis. In South America, the total incidence in Brazil kept dropping over the following years, is for this reason that Brazil is an example of the control of malaria disease in the Americas.

Since Brazil is the focus of our research, we evaluated the incidence of malaria from different years. In a span of 30 years, the incidence of malaria has declined drastically in Brazil and the other 9 countries studied. Back in 1990, the incidence in Brazil, which the majority of the cases are in the Amazons basin, were at 31 cases per 1,000 in population approximately, but decreased gradually to a couple new cases per 1,000 in population in 2017. It dropped approximately 90% of the incidence during this period. In Ecuador, there was an incidence reduction of approximately 82% from 1990 to 1995, and then increased 5 times fold from 1996 to 2000 [21-23]. Ecuador has experienced ~99% reduction in malaria clinical cases since the turn of the millennium and is now pointing towards an elimination phase, with 917 cases in the year 2016 [22]. Venezuela also had a malaria incidence reduction from 1990 until early 2005. Then, maintain a steady rate until 2011 when the incidence increased a little less than 3 times fold. Colombia also had a significant reduction of new cases over the years, as well as Paraguay and Argentina had very low incidence nearly non-existing during this period, so far the last two countries, Chile and Uruguay were considered for this study as no endemic regions for Malaria [20-23].

Cancer in Brazil and the South Americas

In Brazil, cancer is the second most common cause of death, after cardiac and cerebrovascular diseases. About 395,000 new cases came in 2014, where 205,000 were men and 190,000 were women. In men the most types of cancer incidence are prostate, lung, colon and rectum while in women are breast, colon, rectum, cervix, lung and thyroid cancer [19, 23]. According to Globocan and WHO, Brazil's population in 2018 was 210,867,959. There were 1,307,120 prevalent cases for up to 5 years, 559,371 new cases and 243,588 deaths due to cancer. Out of the new cases, we found that 278,607 were males and 280,764 women.

In men from all ages, 84,992 (30.5%) were prostate cancer, 24,737 (8.9%) were colorectum cancer, 19,169 (6.9%) were lung cancer, 12,340 (4.4%) were stomach cancer, 9,127 (3.3%) were bladder cancer and 128,242 (46%) were other types of cancers. In women from all ages, 85,620 (30.5%) were breast cancer, 27,046 (9.6%) were colorectum cancer, 16,901 (6%) were thyroid cancer, 16,298 (5.8%) were cervix uterine cancer, 15,342 (5.5%) were lung cancer and 119,557 (42.6%) were other types of cancers [20-21].

Since 1990, the incidence of cancer in Brazil´s total population has had a constant growth, while the malaria incidence in Brazil demonstrated a steady decrease over the same years. Brazil had around 255 new cases per 100,000 in population in 1990 and progressively increased to about 305 new cases per 1000,000 population in the year 2017 [20]. It seems to have this common pattern for every country involved; the relationship between malaria and cancer has had a direct inverse outcome. For example, in Ecuador we see in this same tendency that from the year 2001 the cancer incidence rate began to increase from approximately 160 new cases per 100,000 in population to 200 new cases, while malaria began to decrease its incidence the previous year constantly until 2017 [21-22]. In Venezuela, from the year 2012, we can evaluate that the cancer incidence began to drop, but in the previous year, malaria incidence began to increase. As it happened with Ecuador, Venezuela and Brazil, when there´s a shift in the incidence in one disease, there´s an inverse outcome of the other.

Cancer in South American countries:

Our cohort of 10 malaria endemics countries from South America, from 1990-2019, of adult of both sexes older than 25 yo, results in a negative

correlation of malaria and neoplasm incidence, by the Pearson's correlation coefficient of R= -0.2 with a P value of 0.000492.

The incidence of Total cancer by the definition of GDH of 10 countries from South America, from 1990-2019, in adults of both sexes older than 25 yo, exhibited a negative correlation with malaria by the Pearson's correlation coefficient with R= -0.32 (P value <0.005).

Chile and Uruguay were considered no malaria endemic countries due to the lack of epidemiological data for malaria in the last three decades. Nevertheless, we evaluated the correlation between the year of report against neoplasm and total cancer in these 2 countries. In Chile, we found no significant increase or correlation for neoplasm and the year of report, while for total cancer we found a significant positive correlation R=0.93 (P value <0.001). For Uruguay, we evidenced a strong positive correlation between neoplasm or total cancer increase incidence and the year of report (R=0.8491 and R=0.78, respectively; p Values <0.001).

The correlation between malaria incidence in 10 countries and year of report was negative with a R=-0.30 P >0.001. Keeping in mind the negative correlation per year we suggest that this could be due to the improvement of health and social system of each country as well as the access to preventive treatment (e.g chloroquine; and hydrochloroquine); while for neoplasm and total cancer the correlation by year of report in the other endemic countries was not significant correlated and the model would not explain a relationship between these parameters.

On the other hand, we observed a significant decrease in Malaria incidence in all endemic countries with some peaks for Venezuela, Ecuador and Suriname (R=-0.3, R2=0.09, P value <0.001). However, the year of incidence of neoplasm and total cancer was significantly not correlated and the model does not explain a relationship (R2= 0.009 or 0.008, R=0.096 and R= 0.288, respectively; p Values <0.001).

Unfortunately, GHDH does not possess data or an index regarding improvement of social or health system, though it does have regarding nutrition. Therefore, we considered this nutritional data to perform a correlation analysis against malaria in endemic countries; we found no correlation, by Pearson's.

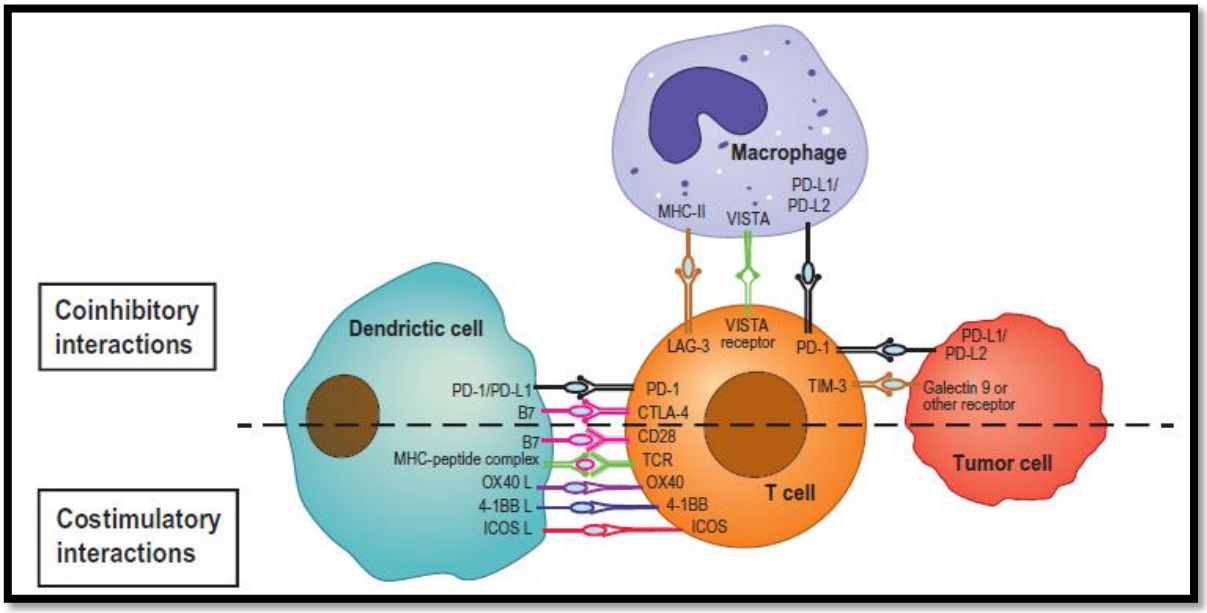

Figure 1. Costimulatory and co-inhibitory ligand–receptor interactions: A schematic overview of the costimulatory and co-inhibitory interactions between a T cell and dendritic cell; T cell and a macrophage and a T cell and a tumor cell in the tumor microenvironment. Dendritic cells phagocytes

malaria parasites and the TLR-9 interacts with malarias unmethylated CpG dinucleotides. This reaction expresses OX40-L (CD134-L) on its membrane surface and interacts with its corresponding OX40 (CD134) receptor on a T cell, which creates an antitumor effect [29-30].

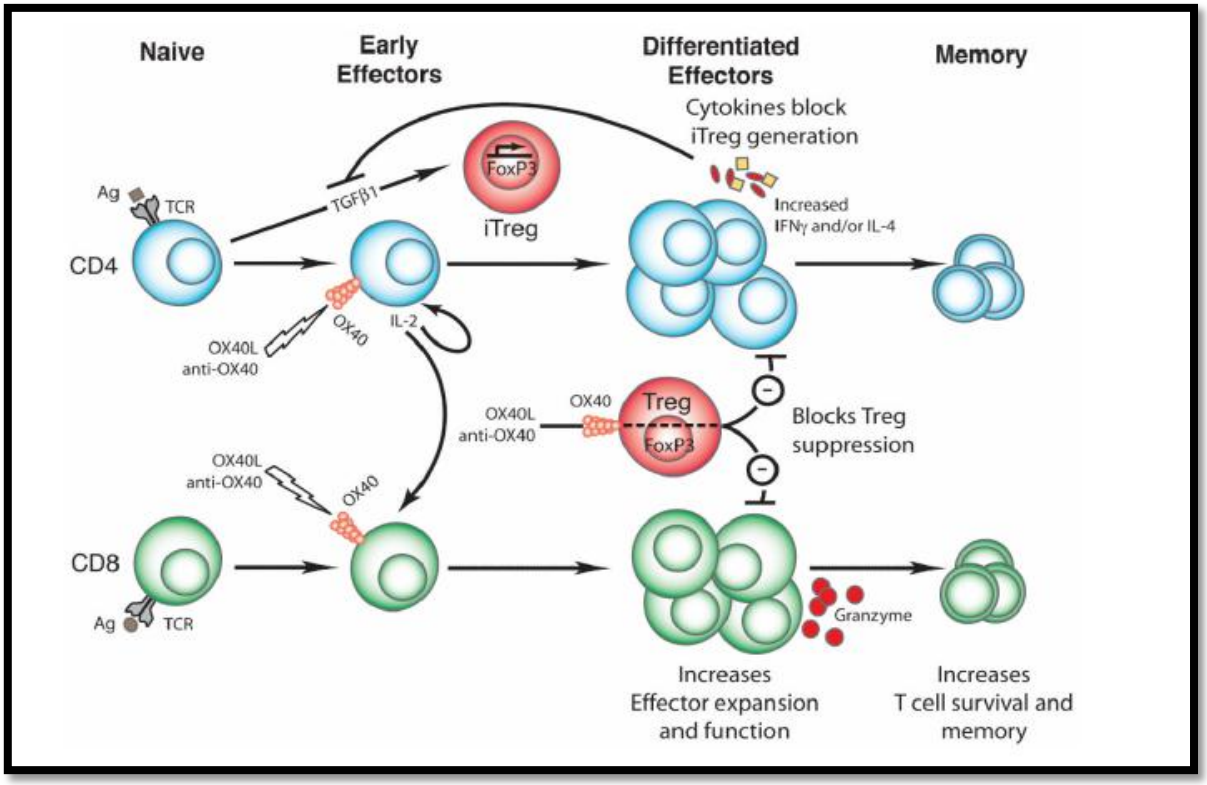

Figure 2. Effects of OX40 ligation on effector versus regulatory T cells. OX40 engagement by the OX40L or agonist OX40 reagents augments CD4 and CD8 T cell clonal expansion, differentiation, and survival. One of the major effects of OX40 ligation is increased IL-2 production and IL-2R expression, which together serve to enhance CD4 and CD8 T cell effector differentiation and the generation of long-lived memory cells. Alternatively, OX40 is also expressed on regulatory T cells (Treg) and OX40 ligation on Treg can potentially abrogate their suppressive activity. OX40 engagement can also affect the generation of induced Treg (iTreg) as OX40-stimulated effector CD4 T cells can prevent the generation of iTreg through the secretion of pro-inflammatory cytokines, such as IL-4, IL-6, and IFN-γ [29-30].

Discussion

Malaria is an infectious disease caused by the female mosquito bite *Anopheles*, which carries the parasite in its saliva. Within the life cycle inside both hosts, mosquito-human, it differentiates into 10 morphological stages and more, which are a replica from one cell into 10,000 cells and varies in population from one to more than 106 organisms. In the human host, only a few morphological stages causes the clinical illness and most of the infected patients with malaria in the world produces little to no symptoms [24-26]. During this human life cycle, there is two types of asexual cycles, where the first one takes place as the infective structure sporozoite, which reaches the liver through the bloodstream. Once it reaches the liver, it enters the hepatocytes thanks to its anterior apical complex. When they are inside the liver cells, they asexually reproduce through a reproductive process known as schizogony, in which a parasite divides due to multiple fusion, generating millions of new parasitic structures called merozoites. When these structures mature, they rupture the hepatocytes. These merozoites later are capable of infecting red blood cells (RBC), which marks the beginning of the second asexual life cycle. Once in the bloodstream,

merozoites invade RBC in the same manner they infected hepatocytes and initiate its erythrocytic phase. In the RBC, the merozoites differentiates into a younger form called Ring, and later differentiate into a trophozoite, which gives origin to the erythrocytic schist [27-28]. Once they mature, these release 32 merozoites into the bloodstream. These new merozoites can invade new healthy RBC and begin again the schizogony. After the RBC invasion, some can be differentiating into male or female gametocytes. This form would be the sexual parasitic form that could infect the female mosquito after biting an infected host with Plasmodium. Later, the gametocytes continue their differentiation in the mosquito´s intestines until they mature and fertilize among the gametes, forming a new zygote until it completes its reproductive cycle generating thousands of sporozoites, which indeed are the host infective structures that gets infected with after bitten by the mosquito [27].

Human Immune Response Against Plasmodium

Host immune response initiates symptoms at the erythrocytic phase. Proteins and merozoites surface antigen are released from the infected erythrocytes, in which the host induces cytokine production. These cytokines, where TNF, IFN-y and IL-1 are present, inhibits the production of erythrocytes, elevates fever, stimulates the reactive nitrogen species (which causes tissue damage) and induces Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) [28]. Monocytes and polymorphonuclear leukocytes usually begin their response once the antimalarial antibodies opsonizes infected erythrocytes and facilitates phagocytosis by these leukocytes. This only happens after post primary infection and never in the first P. falciparum infection during the acute phase [27]. Studies has proven that Plasmodium genome has unmethylated CpG (cytosine-phosphate-guanine) regions. These are recognized by the TLR9 (Toll Like Receptors 9) present on the endosome membrane surface when they are internalized by the macrophage capacity leukocytes that recognizes them, like DC (dendritic cells) for example, which is an APC (antigen presenting cell). This genomic sequence is a weak TLR9 agonist, but the hemozoin, malaria pigmentation, rapidly access the endosome compartment and effectively activates TLR9 [28]. Hemozoin production happens during its intra erythrocytic asexual reproduction, when the Plasmodium consumes up to 80% of the host cell hemoglobin [25, 27]. Unmethylated CpG is a TLR9 ligand that is part of the innate immune system that when it recognizes and activates, the OX40 ligand (OX40-L) protein expresses upon the APC surface membrane; DC, macrophages or activated B cells. This ligand will bind unto the OX40 co-stimulatory molecule that belongs to the family of the TNF receptors expressed upon activated CD4+ and CD8+ [15, 29-30].

Does the population incidence of malaria play a role as a protection factor against cancer and neoplasms?

Similar Immune Response in Malaria Infection and Cancer:

It has been demonstrated that using an unmethylated CpG oligodeoxynucleotide (CpG ODN) as a TLR9 ligand activates and expresses OX40-L on APC, DC, macrophages and intratumoral CD4+ when injected into the tumor microenvironment (TME). These activated OX40, also known as CD134, stimulates effector T cell and inhibits regulatory T cells in order to break the mediate immune tolerance a tumor acquired [30]. In the same manner, the unmethylated CpG from the Plasmodium genome, having access to the APC endosome and its TLR9, activates and expresses OX40-L on the APC membrane surface. This creates co-stimulatory molecules with CD4+ and CD8+ OX40 receptors, which activated will create a response against cancerous tumors by activating effector T cells. There´s also co-inhibitory molecules that by inhibiting regulatory T cells, which takes the brakes off the immunity in order to fight cancer. OX40 has been shown to influence the generation, proliferation, and suppressive function of regulatory CD4 T cells [17, 31,32].

In addition, it could play a role the treatment received by malaria infected patients, as it has been reported certain role of chloroquine or hydroxyl-chloroquine as also an antitumoral or other virus infection treatment [18] for its anti-autophagy and immunomodulatory actions. Unfortunately, the population data bases lack of

the treatment information for the infected patients, been this an important future focus of study as probably not malary but the administration of chloroquine in a certain period of time decrease tumor or neoplasm incidence [18].

Conclusion

We crossed population data about the incidence of malaria and cancer in Brazil and other 9 countries for almost three decades and it´s clear that there is a direct inverse relationship between them. As malaria incidence began to drop, cancer incidence began to increase in the same respective years. This is associated with the multinational meta-analyses study on worldwide malaria incidence and cancer mortality, which in 1981 there was an increased malaria incidence and all-cause cancer mortality decreased [11, 13], which suggest that as malaria infection takes on new cases per year, the cancer rate decreases. Likewise, with our study we were able to concur that the inverse is also correct, for as malaria incidence decreased over the course of almost three decades, cancer incidence increased over the same period of years as we already have proven. It would be interesting to evaluate all malaria endemic regions in the world and cross-examine their malaria incidence with their cancer incidence in order to concur with the findings on this research. Furthermore, we present here a hypothesis of why this inverse relationship between malaria and cancer could be explain on the immunomodulatory effect of the infection itself [15-17]. We suggest that by the chronic response of the immune system to the Plasmodium spp. infection the infected patient‘s immune system could interact with tumor cells eliminate neoplastic and tumoral development [25-30].

Acknowledgements

We are grateful to Joao Hugo Abdalla Santos MD and Samuel Pinheiro Pinto Junior MD for early contributions in this project. We want to thank Antonio Dávila MD for his great effort in this

project as a mentor and guide to the authors.

Conflict of interest statement

The authors have not declared any conflict of interests.

Funding

We thank to River Plate Adventist University, Science and Technology Secretary for financial fundings to the project, and CICYTTP-CONICET.

References

1. World Malaria Report 2019, Genova, WHO 2019. Licence CC BY NC SA 3.0-IGO.
2. Roser M. and Ritchie H. (2019) - "Malaria". *Published online at OurWorldInData.org.* Retrieved from: 'https://ourworldindata.org /malaria' [Online Resource]
3. Gowda et al., Parasite Recognition and Signaling Mechanisms in Innate Immune Responses to Malaria, Frontiers in Immunology, 2018, December 19. DOI: 10.3389/fimmu.2018.03006
4. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today. Lyon: International Agency for Research on Cancer; 2020(https://gco.iarc.fr/today,accessed March 2022).4.Globocan 2020, Cancer Today IARC, accessed March 2022.
5. McCormack VA, Boffetta P, lifestyles Today’s. Today's lifestyles, tomorrow's cancers: trends in lifestyle risk factors for cancer in low- and middle-income countries. *Ann Oncol* 2011;**22***:*2349–57.doi: 10.1093/annonc/mdq763
6. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetc analysis. Lancet Glob Health. 2016 Sep;4(9):e609-16. doi: 10.1016/S2214109X (16)30143-7.
7. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020 ;8(2):e180-e190.
8. The Global Cancer Observatory, International Agency for Research on Cancer, World Health Organization, May 2019; http://gco.iarc.fr/ today/data/factsheets/populations/76-brazil-fact-sheets.pdf
9. De Oliveira Santos, Marceli, Estimate 2018: Cancer Incidence in Brazil, Revista Brasileira de Cancerologia 2018; 64(1): 119-120.

10. Hans Elias,Carcinoma and malaria,Medical Hypotheses,Volume 12, Issue 1, 1983, Pages 53-54, ISSN 0306-9877, https://doi.org/10.1016/0306-9877(83)90032-4.(https://www.sciencedirect.com/science/article/pii/0306987783900324).
11. Bouvard et al., Carcinogenicity of Malaria and Some Polyomaviruses, www.thelancet.com/oncology, Vol 13, April 2012. DOI: 10.1016/S1470-2045(12)70125-0.
12. Whittle HC, Brown J, Marsh K, Greenwood BM, Seidelin P, Tighe H, et al. T-cell control of Epstein-Barr virus-infected B cells is lost during P. Falciparum malaria. Nature. 1984; 312(5993):449–50.
13. Li Quin et al., Worldwide Malaria Incidence and Cancer Mortality Are Inversely Associated, Infectious Agents and Cancer, Open Access (2017). https://doi.org/10.118 6/s13027-017-0117-x
14. Darani HY et al., Parasites and cancers: parasite antigens as possible targets for cancer immunotherapy. Future Oncology 2012; 8(12):1529–35. DOI: 10.2217/fon.12.155.
15. Pan J et al,. Plasmodium infection inhibits triple negative 4T1 breast cancer potentially through induction of CD8+ T cell-mediated antitumor responses in mice. Biomedicine & Pharmacotherapy 138 (2021) 111406- DOI link:https://doi.org/10.1016/j.biopha.2021.111406.
16. Chen L, He Z, Qin L, Li Q, Shi X, et al. (2011) Antitumor Effect of Malaria Parasite Infection in a Murine Lewis Lung Cancer Model through Induction of Innate and Adaptive Immunity. PLoS ONE 6(9): e24407. doi:10.1371/journal.pone.0024407
17. Xu-Feng Deng et al., Antitumor effect of intravenous immunization with malaria genetically attenuated sporozoites through induction of innate and adaptive immunity, Int J Clin Exp Pathol 2016;9(2):978-986.
18. Zhou W., Wang H., et al., Chloroquine against malaria, cancers and viral diseases. Drug Discovery Today, Vol.25:11, 2020, :2012-2022. ISSN 1359-6446, https://doi.org/10.1016/j.drudis.2020.09.010
19. Institute for Health Metrics and Evaluation. CL5plus, Cancer Incidence in Five Continents Time Trends, IACR, checked on January 2023.
20. Global Burden of Disease Cancer Collaboration. (2018).Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups, 1990 to 2016. *JAMA Oncol.* 2018; 4(11):1553-1568. doi:10.1001/jamaoncol.2018.2706.
21. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2018.Available from http://ghdx.healthdata.org/gbd-results-tool.
22. Sáenz, Fabián E et al. "Malaria epidemiology in low-endemicity areas of the northern coast of Ecuador: high prevalence of asymptomatic infections." *Malaria journal* vol. 16,1 300. 26 Jul. 2017, doi:10.1186/s12936-017-1947-0
23. Barbosa, Isabelle et al. "Cancer Mortality in Brazil: Temporal Trends and Predictions for the Year 2030." Medicine Journal Volume 94, Number 16, April 2015, doi: 10.1097/MD. 00000000000000746
24. Milner et al., Cold Spring Harb Perspect Med doi: 10.1101/cshperspect.a025569
25. Berrecil, M. 2014, Parasitología Médica, McGraw-Hill/Interamericana Editores, S.A. De C.V., México D.F., Edición 4, pp. 149.
26. Kumar, V., 2015, Patología Estructural y Funcional de Robbins y Cotran, Elsevier, S.L.U., Barcelona, España, Edición 9, pp. 391.
27. Celada et al., Assessment of Immune Phagocytosis of Plasmodium falciparum Infected Red Blood Cells by Human Monocytes and Polymorphonuclear Leukocytes. A Method for Visualizing Infected Red Blood Cells Ingested by Phagocytes, Journal of Immunology Methods, Vol. 63, October 14, 1983, pp. 263-271. DOI: 10.1016/0022-1759(83)90430-1
28. Faiboim et al. 2001, Introducción a la Inmunología Humana. Editorial Médica Panamericana, Buenos Aires. Edición 6, pp. 26.
29. *Rosenthal PJ, Meshnick SR (December 1996). "Hemoglobin catabolism and iron utilization*

by malaria parasites". Mol Biochem Parasitol. ***83*** *(2): 131–139. doi:10.1016/S0166-6851(96)02763-6. PMID 9027746.*

30. Zhou et al., OX40 signaling directly triggers the antitumor effects of NKT cells, The Journal of Clinical Investigation, Vol. 117, November 11, 2007, pp. 3169-3172.
31. Sagiv-Barfi et al., Eradication of Spontaneous Malignancy by Local Immunotherapy, Sci. Transl. Med. 10, eaan4488, 31 January, 2018, DOI: 10.1126/scitranslmed.aan4488.
32. Redmond, William L et al. "The role of OX40-mediated co-stimulation in T-cell activation and survival." Critical reviews in immunology vol. 29,3 (2009): 187-201. doi: 10.1615/critrevimmunol.v29.i3.10

How to Cite : Martinez Marignac, V., Mondragon, L. F., & Richard, S. (2024). Relationship Between the Exposure of Malaria in an Endemic Zone and its Association with Cancer Incidence.: • Correlation between malaria and cancer in South American. Jour Med Resh and Health Sci,7(2),3004–3012. https://doi.org/10.52845/JMRHS/2024-7-2-1