Parasite-microbe-host interactions and cancer risk
Nolwenn Dheilly, Paul Ewald, Paul Brindley, Raina Fichorova, Frédéric Thomas

To cite this version:
Nolwenn Dheilly, Paul Ewald, Paul Brindley, Raina Fichorova, Frédéric Thomas. Parasite-microbe-host interactions and cancer risk. PLoS Pathogens, Public Library of Science, 2019, 15 (8), pp.e1007912. 10.1371/journal.ppat.1007912. hal-02502731

HAL Id: hal-02502731
https://hal.umontpellier.fr/hal-02502731
Submitted on 9 Mar 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution 4.0 International License
PEARLS

Parasite-microbe-host interactions and cancer risk

Nolwenn M. Dheilly1*, Paul W. Ewald2, Paul J. Brindley3, Raina N. Fichorova4, Frédéric Thomas5

1 School of Marine and Atmospheric Sciences, Stony Brook University, Stony Brook, New York, United States of America, 2 Department of Biology, University of Louisville, Louisville, Kentucky, United States of America, 3 Department of Microbiology, Immunology and Tropical Medicine and Research Center for Neglected Diseases of Poverty, School of Medicine and Health Sciences, George Washington University, Washington DC, United States of America, 4 Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, United States of America, 5 CREEC (UMR CNRS/IRD/UM1/UM2 5290), BP, France

* nolwenn.dheilly@stonybrook.edu

Can natural selection act on parasites to compromise barriers to cancer?

Characterizing the factors that disrupt the cellular barriers to cancer (e.g., cell-cycle arrest, apoptosis, repression of telomerase, cell adhesion, and asymmetric cell division) and are essential to oncogenesis is necessary to identify targets for therapeutic interventions [1]. Exacerbating causes can contribute to cancer by compromising host restraints on cancer rather than breaking barriers; examples of such exacerbating causes are factors that drive angiogenesis, or increased proliferation during pro-inflammatory responses [1]. All viruses that are recognized by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens, namely human papillomaviruses (HPV), Hepatitis B and C viruses (HBV and HCV), Human Herpes Virus type 8 (HHV-8), and Human T-cell lymphotropic virus type 1 (HTLV-1) [2], break barriers to cancer and therefore generate essential causes of their associated cancers [1]. These may be the result of natural selection. For example, from an evolutionary point of view, it is probably advantageous to a virus that its host cell resists cell death, evades the immune system, and proliferates. Other intracellular organisms (bacteria and unicellular eukaryotes) could similarly benefit from altering the cellular mechanisms that prevent oncogenesis. Indeed, the ability of intracellular bacteria and protozoan parasites to block apoptosis is now broadly recognized [3,4]. Increasing evidence implicates bacteria (certain strains of Escherichia coli, Fusobacterium nucleatum, Salmonella Typhi, Chlamydia trachomatis, and a range of Mycoplasma) and protists (Cryptosporidium parvum, Trichomonas vaginalis, Trypanosoma cruzi, Toxoplasma gondii) in cancer development [2, 5–26].

For extracellular parasites, and in particular helminths, the evolutionary path that could lead them to break the cellular barriers to cancer is more difficult. At present, three multicellular parasites, the trematodes Schistosoma haematobium, Opisthorchis viverrini, and Clonorchis sinensis are recognized as Group 1 carcinogens by IARC, contributing 0.4% to human cancer [2]. However, increased risk of cancer is associated with increasing numbers of other parasites, e.g., species of Echinococcus, Strongyloides, Fasciola, Heterakis, Platynosomum, and Trichuris [27] and is likely broadly underestimated due to the asymptomatic/subclinical nature of some of these infections, wide occurrence among healthcare underserved communities, and long latency between initial infection or exposure and clinical manifestation of cancer. The latest advances in microbiology suggest a new paradigm—multi-microbial factors could explain why
and how some parasites breach host barriers to cancer. Herein, we review the literature indicating that microbes can contribute in an essential sense to oncogenesis through their interaction with the host and with parasites.

**High prevalence of microbes with oncogenic potential in asymptomatic populations**

The composition of the microbiome is thought to result from complex co-evolutionary mechanisms among hosts and microbes. Antagonistic pleiotropy refers to genes that are beneficial early in life, and improve fitness, but become detrimental later in life [28]. Recent studies suggest that microbes and microbial communities can have similar effects: microbiome composition induces a life-history trade-off between life span and reproduction in flies [29]. Thus, natural selection will favor establishment of microbes that are either beneficial to the host or present a low cost of infection early in life, even if these microbes promote oncogenesis later in life. Indeed, the human microbiome includes known and often highly prevalent oncogenic microbes, such as Epstein Barr Virus (EBV), that infect 90% of the human population [30], and many members of the gut microbiota are associated with cancer [6]. Only a small fraction of the population carrying oncogenic microbes develops cancer, suggesting that cofactors that exacerbate the susceptibility to cancer are necessary. Other microbes that are not identified as oncogenic may show high prevalence and present as asymptomatic infection, but may enact essential causes of cancer. Microbial communities previously regarded as commensal may have diverse roles in oncogenesis during the long asymptomatic/subclinical period preceding clinical diagnosis of cancer.

**Parasites can modulate the oncogenicity of host-associated microbes**

Coinfection by multiple parasites is common in the wild. If we consider that any host-associated microbe can move along the parasitism-mutualism spectrum in a context-dependent manner, coinfection is the norm. Viruses, bacteria, archaean, and eukaryotic parasites have cohabited the same host lineages for hundreds of millions of years and can either directly interact when they inhabit the same host tissue or indirectly interact via modulation of the host immune system. These interactions can influence tumor development and progression.

A widely appreciated example is the role of *Plasmodium falciparum* as an indirect risk factor for Burkitt lymphoma, a monoclonal B cells cancer for which EBV infection is generally considered essential [31]. Recent studies have clarified the mechanisms by which *P. falciparum* contributes to oncogenesis. The immunosuppression associated with *P. falciparum* malaria leads to an increase in EBV-infected B cells in the germinal center, which dysregulates activation-induced cytidine deaminase expression, leading to DNA damages, including *c-myc* translocation that should lead to cell apoptosis, but EBV rescues the infected cell by inhibiting apoptosis, effectively leading to Burkitt lymphoma [32–34].

Similarly, infection with *Strongyloides stercoralis*, a common parasitic nematode, shortens the delay between HTLV-1 infection and the occurrence of T-cell leukemia [35, 36]. *S. stercoralis* benefits HTLV-1 with a higher proviral load in individuals infected by the roundworm, due to the proliferative expansion of HTLV-1–infected cells [37]. By promoting cell proliferation, *S. stercoralis* is an exacerbating cause of cancer. Infection with HTLV-1 results in a suppressed immune response against helminths and in the reduced efficacy of antiparasitic drugs, which lead to higher prevalence of *S. stercoralis* infection in HTLV-1–infected individuals [38].
Evidence is accumulating that members of the gut, oral, and vaginal microbiomes could initiate or influence the progression of oncogenesis by different processes, including the induction of a chronic inflammatory state or immune response, altering stem cell dynamics, the biosynthesis of toxic and genotoxic metabolites, and affecting host metabolism [6, 39, 40]. Many parasites significantly alter their host microbiome composition [41]. Outcomes would therefore depend on the individual’s microbiome composition at the time of infection, which would render the association between parasite infection and cancer difficult to resolve.

A positive association between the highly prevalent sexually transmitted protozoan parasite *T. vaginalis* and cervical neoplasia in women and prostate cancer in men has been reported [13–18, 42]. *T. vaginalis* infection significantly affects the vaginal microbiome with a shift from a lactobacillus-dominated microbiome to a community of bacteria responsible for the widely spread syndrome of bacterial vaginosis [43]. Metabolites released by the parasite, e.g., indole, support the survival of intracellular sexually transmitted bacteria such as *C. trachomatis*, which has been independently associated with cancer [44]. Given the positive association between bacterial vaginosis and cervical precancerous lesions [45], studies are needed to clarify the role of the microbiota as a cofactor, or essential factor, for *T. vaginalis*–associated cancer.

*S. haematobium* is the causative agent of urogenital schistosomiasis (UGS). This trematode parasite is endemic in 76 countries in Africa and the Middle East, but it can also be found in Europe [46, 47]. UGS is a major risk factor for squamous cell carcinoma of the urinary bladder [48, 49]. Early studies have found that UGS promotes bacterial coinfection and is associated with a high concentration of N-nitroso compounds in the urine, suggesting that infection favors nitrate-reducing bacteria that produce the cancer-inducing nitrosamines [50–52]. More recent studies of the microbiome of noninfected and infected patients also revealed marked differences [53, 54]. In addition, schistosomes can directly interact with bacteria, and *Salmonella* is known to routinely attach to a range of species of schistosomes [55]. HPV, EBV, and BK polyomavirus (BKV) have been found in a minority of bladder cancers by some investigators, although not by others [56]. Given the potential for some of these viruses and bacteria to cause cancer, studies are needed to test their roles as causative agents for urinary bladder cancer associated with UGS.

**Parasites can transmit pro-inflammatory or oncogenic microbes**

There are numerous compelling examples of parasites that carry microbes that participate in the infectious process, notably the well-documented Wolbachia-filarial nematodes system [57, 58]. There is even evidence that parasites have received genes from prokaryotic symbionts via horizontal gene transfers, including numerous Wolbachia genes in symbiont-free filarial nematodes [59], the thymidine kinase of *C. parvum* [60], and the N-acetylneuraminate lyase of *T. vaginalis* [61], further demonstrating the selective advantage that microbial symbionts confer to their parasitic hosts. Microbial symbionts of parasites can be transmitted to the host and be responsible for inflammatory-associated pathogenesis [62, 63]. In addition, the release of Wolbachia from filarial nematodes and of *Trichomonaviruses* (TVV) from *T. vaginalis* upon parasite death have significant adverse effects that impair treatment efficiency [62, 63]. Similarly, relapse of *Salmonella* infection can occur in the absence of antischistosomal treatment, probably because of the antibiotic resistance of *Salmonella* attached to the blood fluke [64, 65]. Could the ability of parasite-associated microbes to infect host cells, and their role in inflammation, be responsible for oncogenesis, in lieu of their parasitic host?

Infection with the liver fluke *O. viverrini* is recognized as a definitive cause of cancer, as infection often leads to cholangiocarcinoma (bile duct cancer). The factors that lead to cancer development have not yet been clearly identified [66]. One intriguing hypothesis is the
potential for *O. viverrini* to serve as a vector of the oncogenic bacterium *Helicobacter pylori* and other bacteria into the biliary tree, triggering the malignant transformation of cholangiocytes [67]. Indeed, *H. pylori* was found within the gut of *O. viverrini* [68], and coinfection is associated with higher expression of pro-inflammatory cytokines and more severe hepatobiliary morbidity, suggesting that the bacteria contributes to opisthorchiasis-associated cholangiocarcinoma [69, 70]. Sequencing of prokaryotic 16S genes from *O. viverrini* revealed the presence of diverse bacteria, including *Bordetella*, *Brochothrix*, *Burkholderia*, *Leminorella*, *Pseudomonas*, *Serratia*, and *Sphingomonas* [71]. The role of other microbes, such as viruses, in the disease cannot be excluded given the ability of *O. viverrini* to convey bacteria to the biliary tract.

It is now well recognized that *T. vaginalis* hosts a complex core microbiome composed of double-stranded RNA (dsRNA) endobiont viruses of the genus TVV and eubacterial *Mycoplasma* species that substantially increase *T. vaginalis* pathogenicity by up-regulating pro-inflammatory responses [72]. Transmission of *M. hominis*, a member of the *T. vaginalis* microbiome, is associated with malignant transformation and genome instability that promote prostate cancer development in men and skew the adaptive immune response towards a T-helper 17 cell phenotype, thus creating a favorable environment for tumor development [19, 72–75]. TVV can trigger endosomal TLR3/TRIF-dependent pathways, which means that it can penetrate human cells and could also cause oncogenic damage [62]. Both TVV and *Mycoplasma* can resist clearance by the host and antimicrobial therapy, which explains adverse effects of metronidazole treatment [62, 72]. Should the bacterial or viral symbionts of *T. vaginalis* induce cancer associated with trichomoniasis, novel therapy could be developed to block malignant transformation in both men and women.

For most parasites, the presence of microbes residing in or directly associated with parasites has not been investigated, and when microbes have been observed, their contribution to oncogenesis has not been assessed. For example, and focusing on parasites listed above that have been linked to cancer prevalence, virus-like particles have been observed in *T. cruzi* [76], a dsRNA virus has been found in *Cryptosporidium* and virus load correlates with parasite fecundity [8, 77], *Heterakis gallinarum* is a vector of the pathogenic bacterium *Histomonas meleagridis* [78, 79], *Trichuris muris* hosts a complex bacterial microbiome [80], *Schistosoma mansoni* might be a vector of HCV [81], and genome sequencing of *Fasciola hepatica* revealed the presence of the endobacterium, *Neorickettsia* [82]. In view of these examples, the general lack of information highlights the value of a comprehensive characterization of the viral and bacterial communities associated with parasites [83], and of epidemiological studies that assess the presence of parasites, the prevalence of known microbes, and the transmission to the host, to identify prospective microbial cofactors of oncogenesis.

**Conclusions**

Interindividual variations in microbial communities associated with the host or with the parasite at the time of infection could explain apparently contradictory results in parasite association with cancer among studies due to variations in microbe prevalence among populations. Variations in microbial communities could also explain why some patients, but not others, develop cancer. The task of identifying the contribution of parasites and microbes to cancer can appear overwhelming, but causal inference is feasible with a combination of experimental and epidemiological studies (Fig 1). Following the systematic characterization of microbes associated with parasites, as proposed by the Parasite Microbiome Project [83], and by leveraging the findings from other projects such as the Human Microbiome project [84, 85], epidemiological and clinical studies of cancer could investigate the potential for coinfection by different parasites and microbes, and investigate their interacting effects. Testing for the role
of microbes in cancer attributed to parasites has the potential to propel the field forward by revealing cofactors that contribute to the development of precancerous lesions and to the transition from benign to malignant cancer. The presence of newly identified microbes in archived cancer tissues should also be tested to assess their potential role. The payoff for identifying microbial factors that contribute to oncogenesis would be self-evident and compelling with respect to new leads for clinical intervention and prevention. In particular, if a virus plays a causal role or exacerbates cancer progression, vaccine development would be justified, as demonstrated by the protection against both infection and infection-associated cancers delivered by the acclaimed HBV and HPV vaccines [86, 87].

References

1. Wald PW, Swain Ewald HA. Toward a general evolutionary theory of oncogenesis. *Evol Appl*, 2013; 6 (1): 70–81. https://doi.org/10.1111/eva.12023 PMID: 23396676
2. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. The Lancet Oncology. 2012; 13(6):607–15. https://doi.org/10.1016/S1470-2045(12)70137-7 PMID: 2257588

3. Gao L-Y, Kwaik YA. The modulation of host cell apoptosis by intracellular bacterial pathogens. Trends in Microbiology. 2000; 8(7):306–13. https://doi.org/10.1016/S0966-842X(00)01784-4 PMID: 1087865

4. Carmen JC, Sinai AP. Suicide prevention: disruption of apoptotic pathways by protozoan parasites. Molecular Microbiology. 2007; 64(4):904–16. https://doi.org/10.1111/j.1365-2958.2007.05714.x PMID: 17501916

5. Whitmore SE, Lamont RJ. Oral Bacteria and Cancer. PLoS Pathog. 2014; 10(3):e1003933. https://doi.org/10.1371/journal.ppat.1003933 PMID: 24676390

6. Fulbright LE, Ellermann M, Arthur JC. The microbiome and the hallmarks of cancer. PLoS Pathog. 2017; 13(9):e1006480. https://doi.org/10.1371/journal.ppat.1006480 PMID: 28934351

7. Huang S, Li JY, Wu J, Meng L, Shou CC. Mycoplasma infections and different human carcinomas. World J Gastroenterol. 2001; 7(2):266–9. Epub 04/15. https://doi.org/10.3748/wjg.v7.i2.266 PMID: 11819772.

8. Jenkins MC, Higgins J, Abrahante JE, Kniel KE, O’Brien C, Trout J, et al. Fecundity of Cryptosporidium parvum is correlated with intracellular levels of the viral symbiont CPV. Int J Parasitol. 2008; 38 (8):1051–5. https://doi.org/10.1016/j.ijpara.2007.11.005.

9. Shebl FM, Engels EA, Goedert JJ. Opportunistic intestinal infections and risk of colorectal cancer among people with AIDS. AIDS res hum retrovi r. 2012; 28(9):994–9. https://doi.org/10.1089/AID.2011.0185 PMID: 22149090.

10. Osman M, Benamrouz S, Guyot K, Baydoun M, Frealle E, Chabe M, et al. High association of Cryptosporidium spp. infection with colon adenocarcinoma in Lebanese patients. PLoS ONE. 2017; 12(12):e0189422. e. https://doi.org/10.1371/journal.pone.0189422 PMID: 29261714.

11. Certad G, Benamrouz S, Guyot K, Mouray A, Chassat T, Flament N, et al. Fulminant cryptosporidiosis after near-drowning: a human Cryptosporidium parvum strain implicated in invasive gastrointestinal adenocarcinoma and cholangiocarcinoma in an experimental model. App enviro microbiol. 2012; 78 (6):1746–51. https://doi.org/10.1128/AEM.06457-11 PMID: 22247151.

12. Certad G, Ngouanesavanh T, Guyot K, Gantois N, Chassat T, Mouray A, et al. Cryptosporidium parvum, a potential cause of colic adenocarcinoma. Infect agents cancer. 2007; 2:22–. https://doi.org/10.1186/1750-9378-2-22 PMID: 18031572.

13. Viiki M. Gynaecological Infections as Risk Determinants of Subsequent Cervical Neoplasia AU—Viikki, Merja. Acta Oncologica. 2000; 39(1):71–5. https://doi.org/10.1080/028418600431003 PMID: 10752657

14. Li C-D, Zhang W-Y, Wu M-H, Zhang S-W, Zhou B-L, Zhu L, et al. [Analysis of high risk factors associated with cervical intraepithelial neoplasia in married women aged 25–54 years in Beijing between 2007–2008] . Zhonghua Fu Chan Ke Za Zhi. 2010; 45(10):757–61. PMID: 21176557.

15. Yap EH, Ho TH, Chan YC, Thong TW, Ng GC, Ho LC, et al. Serum antibodies to Trichomonas vaginalis in invasive cervical cancer patients. Genit med. 1995; 71(6):402–4. https://doi.org/10.1136/sti.71.6.402 PMID: 8566984.

16. Sutcliffe S, Giovannucci E, Alderete JF, Chang T-H, Gaydos CA, Zenilman JM, et al. Plasma Antibodies against Trichomonas vaginalis and Subsequent Risk of Prostate Cancer. Cancer Epidem iol Biomark Preven. 2006; 15(5):939. https://doi.org/10.1158/1055-9965.EPI-05-0781 PMID: 16702374

17. Sutcliffe S, Alderete JF, Till C, Goodman PJ, Hsing AW, Zenilman JM, et al. Trichomonosis and subsequent risk of prostate cancer in the Prostate Cancer Prevention Trial. Inter J Cancer. 2009; 124 (9):2082–7. https://doi.org/10.1002/ijc.24144 PMID: 19117055.

18. Mittregger D, Aberle SW, Makristathis A, Walochnik J, Brozek W, Marberger M, et al. High detection rate of Trichomonas vaginalis in benign hyperplastic prostatic tissue. Medic Microbiol Immunol. 2012; 201(1):13–116.

19. Twu O, Desi D, Vu A, Mercer F, Stevens GC, de Miguel N, et al. Trichomonas vaginalis homolog of macrophage migration inhibitory factor induces prostate cell growth, invasiveness, and inflammatory responses. Proc Nat Acad Sci. 2014; 111(22):8179. https://doi.org/10.1073/pnas.1321884111 PMID: 24843155

20. Sacerdote de Lustig E, Puricelli L, Bal E, Lansetti J. Association of Chagas disease and cancer. Medicina. 1980; 40(1):43–6. PMID: 6776385

21. Murta E, Oliveira G, Prado Fde O, De Souza M, BM TM, Adad S. Association of uterine leiomyoma and Chagas' disease. Am J Trop Med Hyg. 2002; 66(3):321–4. https://doi.org/10.4269/ajtmh.2002.66.321 PMID: 12139229

22. Oliveira E, Lette M, Ostermayer A, Almeida A, Moreira H. Chagasic megacolon associated with colon cancer. Am J Trop Med Hyg. 1997; 56(6):586–98.
23. Manoel-Caetano FdS Borim AA, Caetano A, Cury P, amp x, et al. Cytogenetic alterations in chagasic achalasia compared to esophageal carcinoma. Cancer Gen Cytogen. 2004; 149(1):17–22. https://doi.org/10.1016/S0165-4608(03)00274-7

24. Zhang X, Li Q, Hu P, Cheng H, Huang G. Two case reports of pituitary adenoma associated with Toxoplasmosa gondii infection. J clin pathol. 2002; 55(12):965–6. https://doi.org/10.1136/jcp.55.12.965 PMID: 12461069.

25. Khurana S, Dubey M, Malla N. Association of Parasitic Infections and Cancers. Ind J Medic Microbiol. 2005; 23(2):74–9. https://doi.org/10.4103/0255-0857.16044

26. Baumgartner M. Theileria annulata promotes Src kinase-dependent host cell polarization by manipulating actin dynamics in podosomes and lamellipodia. Cell Microbiol. 2011; 13(4):538–53. https://doi.org/10.1111/j.1462-5822.2010.01553.x PMID: 21091599

27. Machicado C, Marcos LA. Carcinogenesis associated with parasites other than Schistosoma, Opisthorchis and Clonorchis: A systematic review. Inter J Cancer. 2016; 138(12):2915–21. https://doi.org/10.1002/ijc.30028 PMID: 26840624

28. Williams GC. Pleiotropy, Natural Selection, and the Evolution of Senescence. Evolutio n. 1957; 11(4):398–411.

29. Gould AL, Zhang V, Lamberti L, Jones EW, Obadia B, Korasidis N, et al. Microbiome interactions shape host fitness. Proc Nat Acad Sci. 2018; 115(51):E11951–E60. https://doi.org/10.1073/pnas.1809349115 PMID: 30510004

30. Tzellos S, Farrell PJ. Epstein-Barr Virus Sequence Variation—Biology and Disease. Pathogens. 2012; 1(2):156. https://doi.org/10.3390/pathogens1020156 PMID: 23818857

31. Molyneux EM, Rochford R, Griffth R, Newton R, Jackson G, Menon G, et al. Burkitt’s lymphoma. The Lancet. 2012; 379(9822):1234–44. https://doi.org/10.1016/S0140-6736(11)61177-X

32. Thorley-Lawson D, Deitsch KW, Duca KA, Torgbor C. The Link between Plasmodi um falciparum Malaria and Endemic Burkitt’s Lymphoma-New Insight into a 50-Year-Old Enigma. PLoS Pathog. 2016; 12(1):e1005331–e. https://doi.org/10.1371/journal.ppat.1005331 PMID: 26794909.

33. Robbiani DF, Deroiriaux S, Feldhahn N, Oliveira TY, Callen E, Wang Q, et al. Plasmidfection Promotes Genomic Instability and AID-Dependent B Cell Lymphoma. Cell. 2015; 162(4):727–37. https://doi.org/10.1016/j.cell.2015.07.019 PMID: 26276629.

34. Torgbor C, Awuah P, Deitsch K, Kalantari P, Duca KA, Thorley-Lawson DA. A Multifactori al Role for P. falciparum Malaria in Endemic Burkitt’s Lymphoma Pathogenes is. PLoS Pathog. 2014; 10(5):e1004170. https://doi.org/10.1371/journal.ppat.1004170 PMID: 24874410.

35. Plumelle Y, Gonin C, Edouard A, Bucher B, Thomas L, Brevion A, et al. Effect of Strongyloides stercoralis infection and eosinophilia on age at onset and prognosis of adult T-cell leukemia. Am J Clin Pathol. 1997; 107(1):81–7. https://doi.org/10.1093/ajcp/107.1.81 PMID: 8980372

36. Montes M, Sawhney C, Barros N. Strongyloides stercoralis: there but not seen. Curr opin infect dis. 2010; 23(5):500–4. https://doi.org/10.1097/QCO.0b013e32833df718 PMID: 20733481.

37. Gabet A-S, Mortreux F, Talarmin A, Plumelle Y, Leclercq I, Leroy A, et al. High circulating proviral load with oligoclonal expansion of HTLV-1 bearing T cells in HTLV-1 carriers with strongyloidiasis. Oncogene. 2000; 19:4954. https://doi.org/10.1038/sj.onc.1203870 PMID: 11042682.

38. Montes M, Sawhney C, Barros N. Strongyloides stercoralis: there but not seen. Curr opin infect dis. 2010; 23(5):500–4. https://doi.org/10.1097/QCO.0b013e32833df718 PMID: 20733481.

39. Gabet A-S, Mortreux F, Talarmin A, Plumelle Y, Leclercq I, Leroy A, et al. High circulating proviral load with oligoclonal expansion of HTLV-1 bearing T cells in HTLV-1 carriers with strongyloidiasis. Oncogene. 2000; 19:4954. https://doi.org/10.1038/sj.onc.1203870 PMID: 11042682.

40. Carvalho EM, Da Fonseca Porto A. Epidem iological and clinical interaction between HTLV-1 and Strongyloides stercoralis. Par Immunol. 2004; 26(11–12):487–97. https://doi.org/10.1111/j.1411-9838.2004.00726.x PMID: 15771548

41. Champer M, Wong A, Champer J, Brito I, Messer P, Hou J, et al. The role of the vaginal microbiome in gynaecological cancer. BJOG: Inter J Obstet Gynaecol. 2018; 125(3):309–15. https://doi.org/10.1111/1471-0528.14631 PMID: 28278350

42. Garrett WS. Cancer and the microbiota. Science (New York, NY). 2015; 348(6230):80–6. https://doi.org/10.1126/science.aaa4972 PMID: 25838377.

43. Leung JM, Graham AL, Knowles SCL. Parasite-Microbiota Interactions With the Vertebrate Gut: Synthesis Through an Ecologica l Lens. Front microbiol. 2018; 9:843–. https://doi.org/10.3389/fmicb.2018.00843 PMID: 29867790.

44. Twu O, Desi D, Vu A, Mercer F, Stevens GC, de Miguel N, et al. &lt;em&gt;Trichomonas vaginalis&amp;lt;/em&gt; homolog of macrophage migration inhibitory factor induces prostate cell growth, invasiveness, and inflammatory responses. Proceedings of the National Academy of Sciences. 2014; 111(22):8179. https://doi.org/10.1073/pnas.1321884111 PMID: 24843155

45. Onderdonk AB, Delaney ML, Fichorova RN. The Human Microbiome during Bacterial Vaginosis. Clin microbiol rev. 2016; 29(2):233–8. Epub 02/10. https://doi.org/10.1128/CMR.00075-15 PMID: 26864580.
44. Aiyar A, Quayle AJ, Buckner LR, Sherchand SP, Chang TL, Zea AH, et al. Influence of the tryptophan-indole-IFNγ axis on human genital Chlamydia trachomatis infection: role of vaginal co-infections. Front cell infect microbiol. 2014; 4:72–. https://doi.org/10.3389/fcimb.2014.00072 PMID: 24918090

45. Sodhani P, Gupta S, Gupta R, Mehrotra R. Bacterial Vaginosis and Cervical intraepithelial Neoplasia: Is there an Association or is Co-Existence Incidental? Asia Pac J cancer prevent APJCP. 18(5):1289–92. https://doi.org/10.22034/APJCP.2018.5.1289 PMID: 28610416.

46. Berry A, Moné H, Iriart X, Mouahid G, Aboo O, Boissier J, et al. Schistosomiasis haematobium, Corsica, France. Emerg infect dis. 2014; 20(9):1595–7. https://doi.org/10.3201/eid2009.140928 PMID: 25153697.

47. Engels D, Chitsulo L, Montresor A, Savioli L. The global epidemiological situation of schistosomiasis and new approaches to control and research. Acta tropica. 2002; 82(2):139–46. PMID: 12020886.

48. IARC. Biological agents Volume 100B A review of human carcinogens. IARC Monogr Eval Carcinog Risks Hum. 2012; 100(Pt B):1–441. PMID: 23189750

49. IARC. Schistosomes, Liver Flukes and Helicobacter Pylori. IARC working group on the evaluation of carcinogenic risks to humans. Lyon, 7–14 June 1994. IARC Monogr Eval Carcinog Risks Hum. 1994; 61:1–241. PMID: 7715068

50. Hicks RM, Walters CL, Elsebai I, Aasser AB, Merzabani ME, Gough TA. Demonstration of nitrosamines in human urine: preliminary observations on a possible etiology for bladder cancer in association with chronic urinary tract infections. Proc Roy Soc Med. 1977; 70(6):413–7. PMID: 8771115.

51. Hicks RM, Walters CL, Elsebai I, Aasser AB, Merzabani ME, Gough TA. Demonstration of nitrosamines in human urine: preliminary observations on a possible etiology for bladder cancer in association with chronic urinary tract infections. Proceedings of the Royal Society of Medicine. 1977; 70(6):413–7. PMID: 8771115.

52. Fenn K, Blaxter M. Are filarial nematode Wolbachia obligate symbionts? Trends Ecol Evol. 2004; 19(4):163–6. https://doi.org/10.1016/j.tree.2004.01.002 PMID: 16701248

53. McNealy SN, Foster JM, Mitreva M, Dunning Hotopp JC, Martin J, Fischer K, et al. Endosymbiont DNA in Endobacteria-Free Filarial Nematodes Indicates Ancient Horizontal Genetic Transfer. PLoS ONE. 2010; 5(6):e1005928. https://doi.org/10.1371/journal.pone.01005928 PMID: 20543958

54. Fichorova RN, Lee Y, Yamamoto HS, Takagi Y, Hayes GR, Goodman RP, et al. Endobiont viruses sensed by the human host, beyond conventional antiparasitic therapy. PLoS ONE. 2012; 7(11):e109315. https://doi.org/10.1371/journal.pone.0109315 PMID: 23144878

55. Taylor MJ, Cross HF, Ford L, Makunde WH, Prasad GBKS, Bilo K. Wolbachia bacteria in filarial immunity and disease. Parasite Immunology. 2001; 23(7):401–9. https://doi.org/10.1046/j.1365-3024.2001.00400.x PMID: 11472559

56. Gendrel D, Richard-Lenoble D, Kombila M, Engohan E, Nardou M, Moussavou A, et al. Schistosoma Intercalatum and Relapses of Salmonella Infection in Children. Am J Trop Med Hyg. 1984; 33(6):1166–9. https://doi.org/10.4269/ajtmh.1984.33.1166 PMID: 6439063
65. Barnhill AE, Novozhilova E, Day TA, Carlson SA. Schistosoma-associated Salmonella resist antibiotics via specific fimbrial attachments to the flatworm. Par Vect. 2011; 4(1):123. https://doi.org/10.1186/1756-3305-4-123 PMID: 21711539

66. van Tong H, Brindley PJ, Meyer CG, Velavan TP. Par Infect Carcinogen Hum Malign. EBioMedicine. 2016; 15:12–23. https://doi.org/10.1016/j.ebiom.2016.11.034 PMID: 27956028.

67. Chng KR, Chan SH, Ng AHQ, Li C, Jusakul A, Bertrand D, et al. Tissue microbiome profiling identifies an enrichment of specific enteric bacteria In Opisthorchis viverrini associated cholangiocarcinoma. EBioMedicine. 2016.

68. Deenopoe R, Chomvarin C, Pairojkul C, Chamgramol Y, Loukas A, Brindley PJ, et al. The carcinogenic liver fluke Opisthorchis viverrini is a reservoir for species of Helicobacter. APJCP. 2015; 16(5):1751–8. https://doi.org/10.7314/apjcp.2015.16.5.1751 PMID: 25773821.

69. Danngarot R, Pinlaor S, Itthitaitrakool U, Chaidee A, Chomvarin C, Sangka A, et al. Coinfection with Helicobacter pylori and Opisthorchis viverrini Enhances the Severity of Hepatobiliary Abnormalities in Hamsters. Infect Immun. 2017; 85(4):e00009–17. https://doi.org/10.1128/IAI.00009-17 PMID: 28138021.

70. Deenopoe R, Mairiang E, Mairiang P, Pairojkul C, Chamgramol Y, Rinaldi G, et al. Elevated prevalence of Helicobacter species and virulence factors in opisthorchiasis associated hepatobiliary disease. Sci Rep. 2017; 7:42744. https://doi.org/10.1038/srep42744 PMID: 28198451

71. Pileskatt JL, Deenopoe R, Mulvenna JP, Krause L, Sirpa B, Bethony JM, et al. Infection with the carcinogenic liver fluke Opisthorchis viverrini modifies intestinal and biliary microbiome. FASEB J. 2013; 27(11):4572–84. https://doi.org/10.1096/fj.13-232751 PMID: 23925654.

72. Fichorova R, Fraga J, Rappelli P, Fiori PL. Trichomonas vaginalis infection in symbiosis with Trichomonasvirus and Mycoplasma. Res Microbiol. 2017; 168(9):882–91. https://doi.org/10.1016/j.resmic.2017.03.005.

73. Namiki K, Goodison S, Porvasnik S, Allan RW, Iczkowski KA, Urbanek C, et al. Persistent Exposure to Mycoplasma Induces Malignant Transformation of Human Prostate Cells. PLoS ONE. 2009; 4(9):e6872. https://doi.org/10.1371/journal.pone.0006872 PMID: 19721714

74. Khan S, Zakariah M, Palaniappan S. Computational prediction of Mycoplasma hominis proteins targeting in nucleus of host cell and their implication in prostate cancer etiology. Tumor Biol. 2016; 37(8):10805–13.

75. Alves JJP, De Medeiros Fernandes TAA, De Araújo JMG, Cobucci RNO, Lanza DCF, Bezerra FL, et al. Th17 response in patients with cervical cancer. Oncol lett. 2018; 16(5):6215–27. Epub 09/21. https://doi.org/10.3892/ol.2018.9481 PMID: 30405758.

76. Fernández-Presas AM, Padilla-Noriega L, Becker I, Robert L, Jiménez JA, Solano S, et al. Enveloped and non-enveloped viral-like particles in Trypanosoma cruzi epimastigotes. Rev Inst Med Trop. 2017; 59(e):46–e. https://doi.org/10.1590/S1678-99462017590046 PMID: 28793017.

77. Nibert ML, Woods KM, Upton SJ, Ghabrial SA. Cryspovirus: a new genus of protozoan viruses in the family Partitiviridae. Arch Virol. 2009; 154(12):1959–65. https://doi.org/10.1007/s00705-009-0513-7 PMID: 19856142

78. Gibbs B. The occurrence of the protozoan parasite Histomonas meleagridis in the adults and eggs of the cecal worm Heterakis gallinarum. J Protozool. 1962; 9:288–93. PMID: 13898352

79. Springer WT, Johnson J, Reid WM. Transmission of histomoniasis with male Heterakis gallinarum (Nematoda). Parasitol. 2009; 59(2):401–5. Epub 04/06. https://doi.org/10.1017/S0031182000082378

80. White EC, Houlden A, Bancroft AJ, Hayes KS, Goldrick M, Grecis RK, et al. Manipulation of host and parasite microbiotas: Survival strategies during chronic nematode infection. Sci Adv. 2018; 4(3):eaap7399. https://doi.org/10.1126/sciadv.aap7399 PMID: 29546242

81. Abou-Zied A, El-Beltagy T, Tantawy H, Soliman R, Badr F. Studies on the genomic association between schistosomiasis and hepatitis C virus infection. Clin Cancer Invest J. 2015; 4(3):318–22. https://doi.org/10.4103/2278-0513.151937

82. McNulty SN, Tort JF, Rinaldi G, Fischer K, Rosa BA, Smirich P, et al. Genomes of Fasciola hepatica from the Americas Reveal Colonization with Neorickettsia Endobacteria Related to the Agents of Potomac Horse and Human Sennetsu Fevers. PLoS Genet. 2017; 13(1):e1006537–e. https://doi.org/10.1371/journal.pgen.1006537 PMID: 28060841.

83. Dheilly NM, Bolnick D, Bordenstein SR, Brindley PJ, Figueres C, Holmes EC, et al. Parasite Microbiome Project: Systematic investigation of microbiome dynamics within and across parasite-host interactions. mSystems. 2017; 2(4).

84. The Integrative Human Microbiome Project: Dynamic Analysis of Microbiome-Host Omics Profiles during Periods of Human Health and Disease. Cell Host & Microbe. 2014; 16(3):276–89. https://doi.org/10.1016/j.chom.2014.08.014 PMID: 25211071
85. Huttenhower C, Gevers D, Knight R, Abubucker S, Badger JH, Chinwalla AT, et al. Structure, function and diversity of the healthy human microbiome. Nature. 2012;486. https://doi.org/10.1038/nature11234 PMID: 22699609

86. Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter D, et al. Efficacy of human papilloma-virus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by onco-genic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. The Lancet. 2009; 374(9686):301–14. https://doi.org/10.1016/S0140-6736(09)61248-4

87. Chang M-H, You S-L, Chen C-J, Liu C-J, Lai M-W, Wu T-C, et al. Long-term Effects of Hepatitis B Immunization of Infants in Preventing Liver Cancer. Gastroenterology. 2016; 151(3):472–80.e1. https://doi.org/10.1053/j.gastro.2016.05.048 PMID: 27269245