The growing evidence behind the connection between infections and cancer (Part 2)

AONM webinar 6th September 2022

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This follows on from Part 1 last month

https://aonm.org/view-past-webinars/

DR. ARMIN SCHWARZBACH

PDF OF SLIDE PRESENTATION

THE GROWING EVIDENCE BETWEEN INFECTIONS AND CANCER (PART 1)

- Breast cancer
- Monoclonal Gammopathy
- Prostate cancer
- Blood cancers
- Glioblastoma

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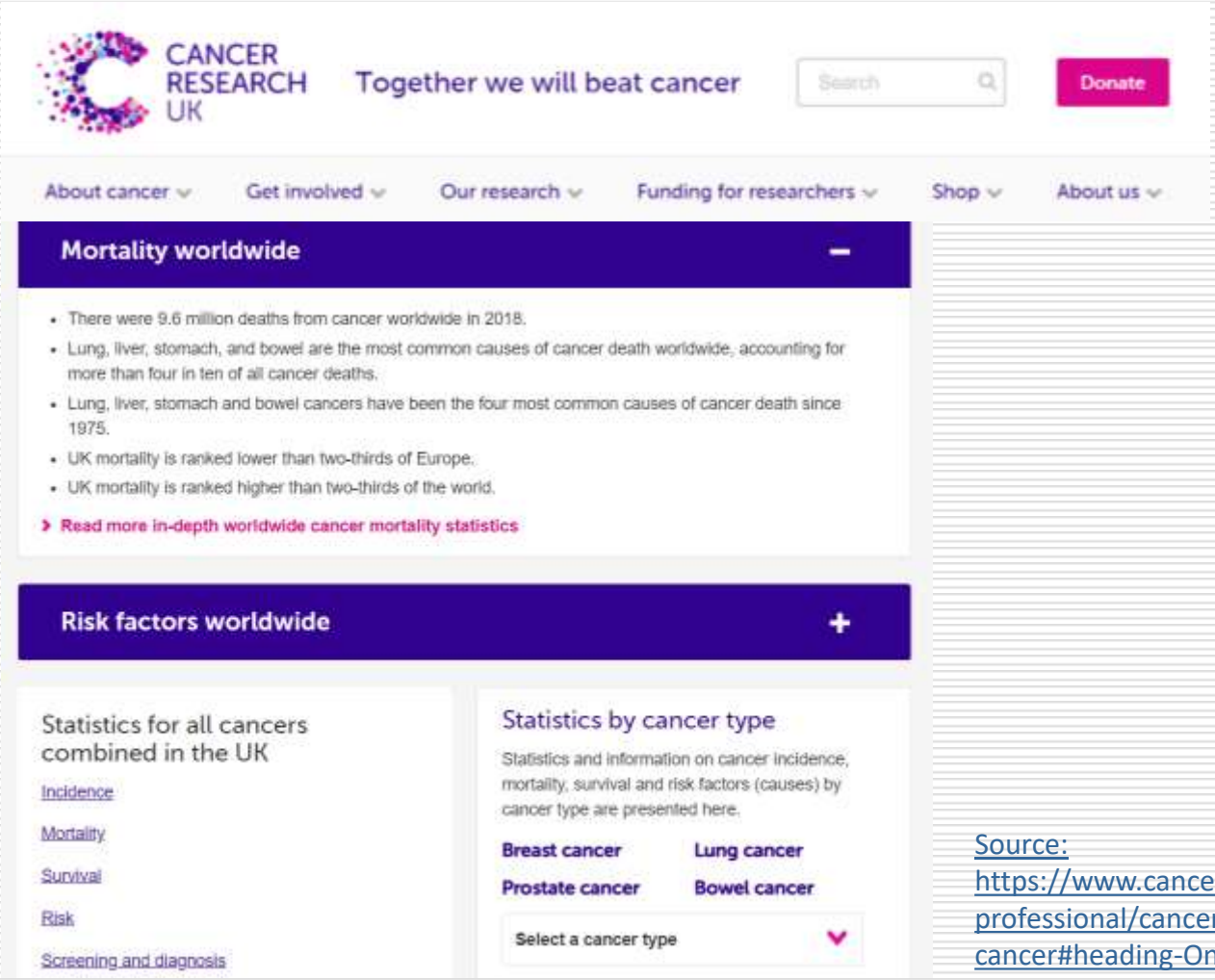
Lung, liver, stomach and bowel the most common causes of cancer death worldwide



Source: https://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer#heading-One

What cancers have infections been associated with?

Part 2:

- Lung
- Colorectal
- Gastric
- Oesophageal
- Cervical
- Liver

What cancers have infections been associated with?

Part 2:

- **Lung**
- Colorectal
- Gastric
- Oesophageal
- Cervical
- Liver

Lung cancer is the leading cause of cancer death worldwide

Journal List > Pathogens > v.11(2); 2022 Feb > PMC8878590

pathogens MDPI

Pathogens. 2022 Feb; 11(2): 132.
Published online 2022 Jan 21. doi: 10.3390/pathogens11020132

PMCID: PMC8878590
PMID: 35216076

Epstein–Barr Virus Infection in Lung Cancer: Insights and Perspectives

Julio C. Osorio,[1] Rancés Blanco,[2] Alejandro H. Corvalán,[3] Juan P. Muñoz,[4] Gloria M. Calaf,[4,5] and Francisco Aguayo[6,*]

Jochen Bodem, Academic Editor

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Associated Data

• Data Availability Statement

Abstract

Go to: •

Lung cancer (LC) is the leading cause of cancer death worldwide. Tobacco smoke is the most frequent risk factor etiologically associated with LC, although exposures to other environmental factors such as arsenic, radon or asbestos are also involved. Additionally, the involvement of some viral infections such as high-risk human papillomaviruses (HR-HPVs), Merkel cell polyomavirus (MCPyV), Jaagsiekte Sheep Retrovirus (JSRV), John Cunningham Virus (JCV), and Epstein–Barr virus (EBV) has been suggested in LC, though an etiological relationship has not yet been established. EBV is a ubiquitous gamma herpesvirus causing persistent infections and some lymphoid and epithelial tumors. Since EBV is heterogeneously detected in LCs from different parts of the world, in this review we address the epidemiological and experimental evidence of a potential role of EBV. Considering this evidence, we propose mechanisms potentially involved in EBV-associated lung carcinogenesis. Additional studies are warranted to dissect the role of EBV in this very frequent malignancy.

"Tobacco smoke ….. environmental factors such as arsenic, radon or asbestos …. Additionally, **the involvement of some viral infections such as high-risk human papillomaviruses** (HR-HPVs), Merkel cell polyomavirus (MCPyV), Jaagsiekte Sheep Retrovirus (JSRV), John Cunningham Virus (JCV), and **Epstein–Barr virus (EBV)**"

Source: Osorio JC, Blanco R, Corvalán AH, Muñoz JP, Calaf GM, Aguayo F. Epstein-Barr Virus Infection in Lung Cancer: Insights and Perspectives. Pathogens. 2022 Jan 21;11(2):132.

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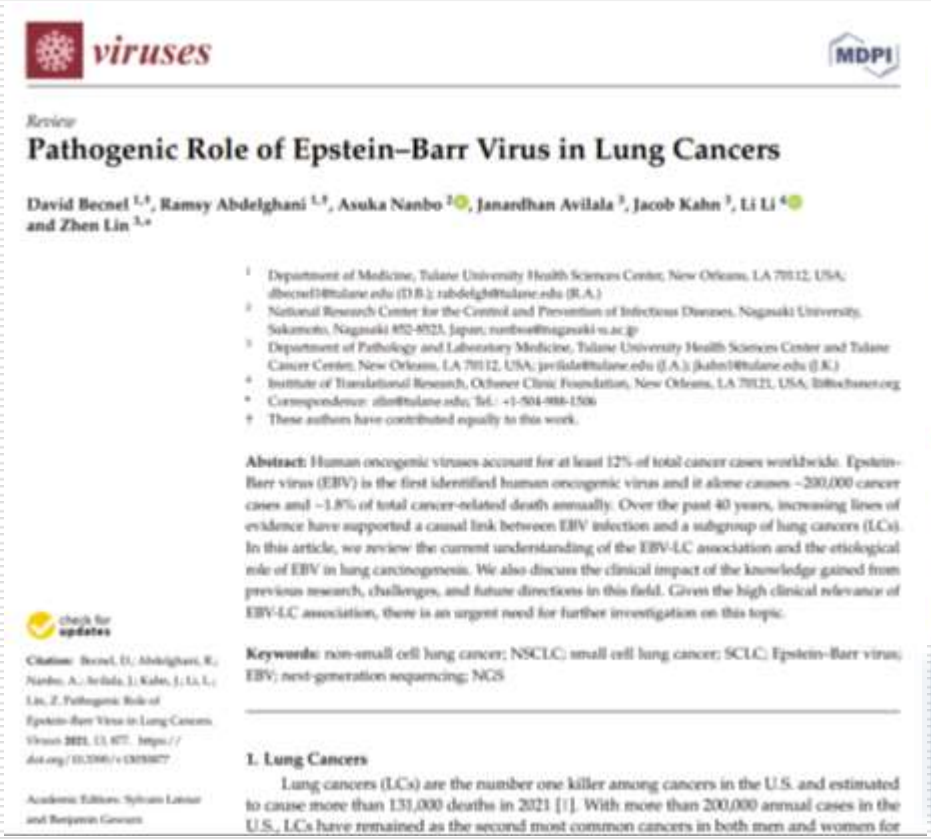
Viral oncogenes in EBV can activate various tumour-associated pathways



viruses

MDPI

Review

Pathogenic Role of Epstein–Barr Virus in Lung Cancers

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† These authors have contributed equally to this work.

Abstract: Human oncogenic viruses account for at least 12% of total cancer cases worldwide. Epstein-Barr virus (EBV) is the first identified human oncogenic virus and it alone causes ~200,000 cancer cases and ~1.8% of total cancer-related death annually. Over the past 40 years, increasing lines of evidence have supported a causal link between EBV infection and a subgroup of lung cancers (LCs). In this article, we review the current understanding of the EBV-LC association and the etiological role of EBV in lung carcinogenesis. We also discuss the clinical impact of the knowledge gained from previous research, challenges, and future directions in this field. Given the high clinical relevance of EBV-LC association, there is an urgent need for further investigation on this topic.

Keywords: non-small cell lung cancer; NSCLC; small cell lung cancer; SCLC; Epstein-Barr virus; EBV; next-generation sequencing; NGS

1. Lung Cancers

Lung cancers (LCs) are the number one killer among cancers in the U.S. and estimated to cause more than 131,000 deaths in 2021 [1]. With more than 200,000 annual cases in the U.S., LCs have remained as the second most common cancers in both men and women for

Table 1. EBV gene expression in different types of latency.

Latency Types	EBV Genes	Examples of EBV Associated Cancers
0	EBER1, EBER2, RPMS1, viral miRNAs	Memory B cells in EBV(+) individuals
I	EBER1, EBER2, RPMS1, viral miRNAs, and EBNA1	Burkitt's lymphoma
II	EBER1, EBER2, RPMS1, viral miRNAs, EBNA1, LMP1, LMP2A, and LMP2B	Nasopharyngeal carcinoma Lung cancer
III	EBER1, EBER2, RPMS1, viral miRNAs, EBNA1, EBNA2, EBNA3A, EBNA3B, EBNA3C, EBNA-LP, LMP1, LMP2A, and LMP2B	AIDS-associated lymphoma

Accumulating evidence has shown that both viral latency and lytic cycle are required for EBV pathogenesis. There are approximately 100 open reading frames encoded by the EBV genome. Among them, some latent genes such as EBV-encoded nuclear antigen 1 (EBNA1) [21], EBV-encoded nuclear antigen 2 (EBNA2), EBV-encoded nuclear antigen 3C (EBNA3C), and latent membrane protein 1 (LMP1) have been shown to mediate viral oncogenesis in cell and/or animal models. These viral oncogene products can activate various tumor-associated pathways such as Notch and nuclear factor-kB (NF-kB) signalings. In addition to well-characterized viral protein-coding genes, EBV has been shown to utilize viral non-coding RNAs (ncRNAs) such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), small non-coding EBV-encoded RNAs (EBERs), as well as recently identified circular RNA (circRNA) to facilitate its life cycle and oncogenesis [22–30].

"Both viral latency and the lytic cycle are required for EBV pathogenesis"

Source: Kheir F, Zhao M, Strong MJ, Yu Y, Nanbo A, Flemington EK, Morris GF, Reiss K, Li L, Lin Z. Detection of Epstein-Barr Virus Infection in Non-Small Cell Lung Cancer. Cancers (Basel). 2019 May 31;11(6):759.; Becnel D, Abdelghani R, Nanbo A, Avilala J, Kahn J, Li L, Lin Z. Pathogenic Role of Epstein-Barr Virus in Lung Cancers. Viruses. 2021 May 11;13(5):877.

Chlamydia pneumoniae is significantly related to the risk of lung carcinoma

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Home / Vol 8, No 8 (December 2019) / Association between Chlamydia pneumoniae infection and lung cancer: a meta-analysis

Original Article

Association between *Chlamydia pneumoniae* infection and lung cancer: a meta-analysis

Chunxi Wang, Naxin Zhang, Liang Gao

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Research Center, Tianjin Institute of Hepatobiliary Disease, The Third Central Hospital of Tianjin, Tianjin 300170, China

Contributions: (I) Conception and design: All authors; (II) Administrative support: N Zhang; (III) Provision of study materials or pati
Zhang; (IV) Collection and assembly of data: C Wang, N Zhang; (V) Data analysis and interpretation: All authors; (VI) Manuscript
authors; (VII) Final approval of manuscript: All authors.

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Engineering Technology Research Center, Tianjin Institute of Hepatobiliary Disease, The Third Central Hospital of Tianjin, No. 83, Jintang R
Hedong District, Tianjin 300170, China. Email: zhangnaxin801@163.com.

Background: The aim of this study is to explore the correlation between *Chlamydia pneumoniae* (*C. pneumoniae*) infection and lung carcinoma.

Methods: Databases of PubMed, Embase, Embase, Ovid, Wanfang and China National Knowledge Infrastructure (CNKI) database were investigated for eligible literatures from their establishments to February, 2019. Included studies were selected according to specific eligibility criteria. Statistical analysis was performed by RevMan 5.3 software.

"Results showed that **C. pneumoniae infection was significantly related to the risk of lung carcinoma**, with a 3.19-fold increased risk compared to a negative titre (95% CI, 1.96–5.19) for IgA and 2.02 times (95% CI, 1.29–3.16) for IgG"

Source: Wang C, Zhang N, Gao L. Association between *Chlamydia pneumoniae* infection and lung cancer: a meta-analysis. Transl Cancer Res. 2019 Dec;8(8):2813-2819.

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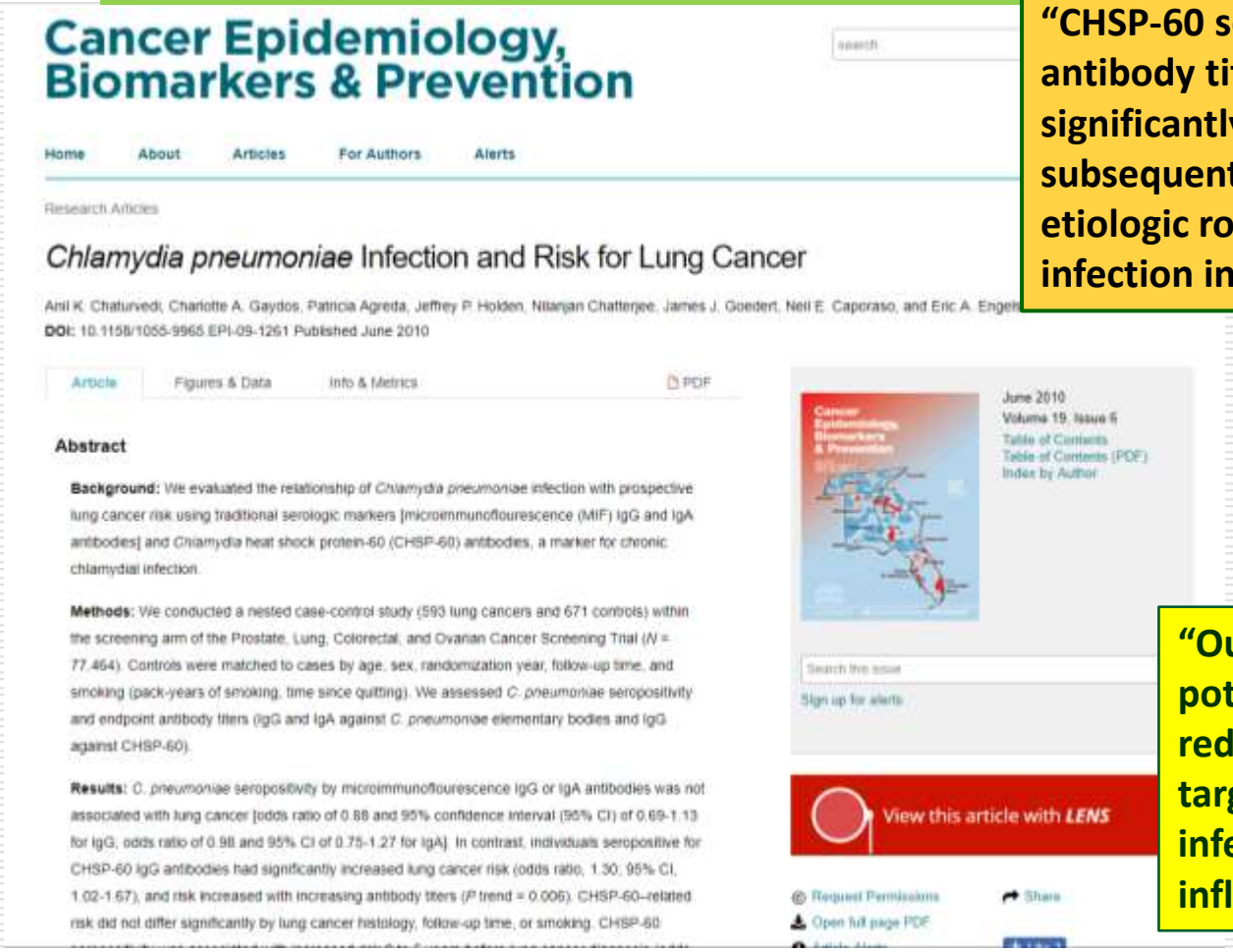
Chlamydia pneumoniae: "Elevated antibody titers associated with significantly increased risk"



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Chlamydia pneumoniae Infection and Risk for Lung Cancer

Anil K. Chaturvedi, Charlotte A. Gaydos, Patricia Agreda, Jeffrey P. Holden, Nilanjan Chatterjee, James J. Goedert, Neil E. Caporaso, and Eric A. Engels

DOI: 10.1158/1055-9965.EPI-09-1261 Published June 2010

Article Figures & Data Info & Metrics PDF

Abstract

Background: We evaluated the relationship of *Chlamydia pneumoniae* infection with prospective lung cancer risk using traditional serologic markers [microimmunofluorescence (MIF) IgG and IgA antibodies] and *Chlamydia* heat shock protein-60 (CHSP-60) antibodies, a marker for chronic chlamydial infection.

Methods: We conducted a nested case-control study (593 lung cancers and 671 controls) within the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (*N* = 77,464). Controls were matched to cases by age, sex, randomization year, follow-up time, and smoking (pack-years of smoking, time since quitting). We assessed *C. pneumoniae* seropositivity and endpoint antibody titers (IgG and IgA against *C. pneumoniae* elementary bodies and IgG against CHSP-60).

Results: *C. pneumoniae* seropositivity by microimmunofluorescence IgG or IgA antibodies was not associated with lung cancer [odds ratio of 0.88 and 95% confidence interval (95% CI) of 0.69-1.13 for IgG; odds ratio of 0.98 and 95% CI of 0.75-1.27 for IgA]. In contrast, individuals seropositive for CHSP-60 IgG antibodies had significantly increased lung cancer risk (odds ratio, 1.30; 95% CI, 1.02-1.67), and risk increased with increasing antibody titers (*P* trend = 0.006). CHSP-60–related risk did not differ significantly by lung cancer histology, follow-up time, or smoking. CHSP-60

June 2010
Volume 19, Issue 6
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"CHSP-60 seropositivity and elevated antibody titers were associated with significantly increased risk for subsequent lung cancer, supporting an etiologic role for C. pneumoniae infection in lung carcinogenesis."

"Our results highlight the potential for lung cancer risk reduction through treatments targeted toward C. pneumoniae infections and chronic pulmonary inflammation."

Source: https://aacrjournals.org/cebp/article/19/6/1498/68420/Chlamydia-pneumoniae-Infection-and-Risk-for-Lung

Thirteen studies with 2,553 lung carcinoma cases and 2,460 controls

Infectious Agents and Cancer

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Review | Open Access | Published: 22 March 2022

Chlamydia pneumoniae infections and development of lung cancer: systematic review

Nadeesha Madushani Premachandra & J. A. A. Sampath Jayaweera

Infectious Agents and Cancer **17**, Article number: 11 (2022) | Cite this article

1108 Accesses | **1** Altmetric | Metrics

Abstract

Background

Chlamydia pneumoniae is an obligate intracellular pathogen and is a common cause of human respiratory diseases, including pneumonia. It has been already known to have a causal relationship with some chronic diseases such as chronic obstructive pulmonary disease, asthma, and atherosclerotic cardiovascular diseases. In this review, we aim to find out the association between *C. pneumoniae* infection and lung cancer.

Methods

This is a systematic review on *C. pneumoniae* infection and the development of lung cancer

"One mechanism is through mediators of inflammation. Inflammation gives rise to reactive oxygen species that may cause damage to DNA. Inflammation causes cell injury, resulting in consequent cell repair, increasing the rate of cell division … higher cell turnover will increase the risk of a mutation, conferring a selective advantage to cells, leading to cancer."

Source: Premachandra NM, Jayaweera JAAS. Chlamydia pneumoniae infections and development of lung cancer: systematic review. Infect Agent Cancer. 2022 Mar 22;17(1):11.

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Mycoplasma infection in lung cancer was 52.6% in this study

World Journal of Gastroenterology

World J Gastroenterol 2001 Apr 15; 7(2): 266-269
Published online 2001 Apr 15. doi: 10.3748/wjg.v7.i2.266
PMCID: PMC4723534

Mycoplasma infections and different human carcinomas

Su Huang, Ji-You Li, Jian Wu, Lin Meng, and Cheng-Chao Shou

Abstract

Go to

AIM: To explore relationships between human carcinomas and mycoplasma infection.

METHODS: Monoclonal antibody PD4, which specifically recognizes a distinct protein from mycoplasma hyorhinis, was used to detect mycoplasma infection in different paraffin embedded carcinoma tissues with immunohistochemistry. PCR was applied to amplify the mycoplasma DNA from the positive samples for confirming immunohistochemistry.

RESULTS: Fifty of 90 cases (56%) of gastric carcinoma were positive for mycoplasma hyorhinis. In other gastric diseases, the mycoplasma infection ratio was 28% (18/49) in chronic superficial gastritis, 30% (14/46) in gastric ulcer and 37% (18/49) in intestinal metaplasia. The difference is significant with gastric cancer ($\chi^2 = 12.06$, $P < 0.05$). In colon carcinoma, the mycoplasma infection ratio was 55.1% (32/58),but it was 20.9% (10/49) in adenomatous polyp ($\chi^2 = 13.46$, $P < 0.005$). Gastric and colon cancers with high differentiation had a higher mycoplasma infection ratio than those with low differentiation ($P < 0.05$).

Table 1 Mycoplasma infection in different grades of gastric carcinoma.

Grades of differentiation	Total number of cases	Infection of mycoplasma: Negative cases (-)	Positive cases (+)	Positive cases (++)	Total positive cases	Ratio of positive (%)
I-II	23	3	12	8	20	87
II-III	18	7	9	2	11	61
III	49	30	14	5	17	39
Total	90	40	35	14	50	56

Table 3 Mycoplasma infection in different grades of colon carcinoma.

Grades of differentiation	Total number of cases	Infection of mycoplasma: Negative cases (-)	Positive cases (+)	Positive cases (++)	Total positive cases	Ratio of positive (%)
I-II	42	15	15	12	27	64
II-III	8	5	2	1	3	37
III	8	6	2	0	2	30
Total	58	26	19	13	32	55 (mean)

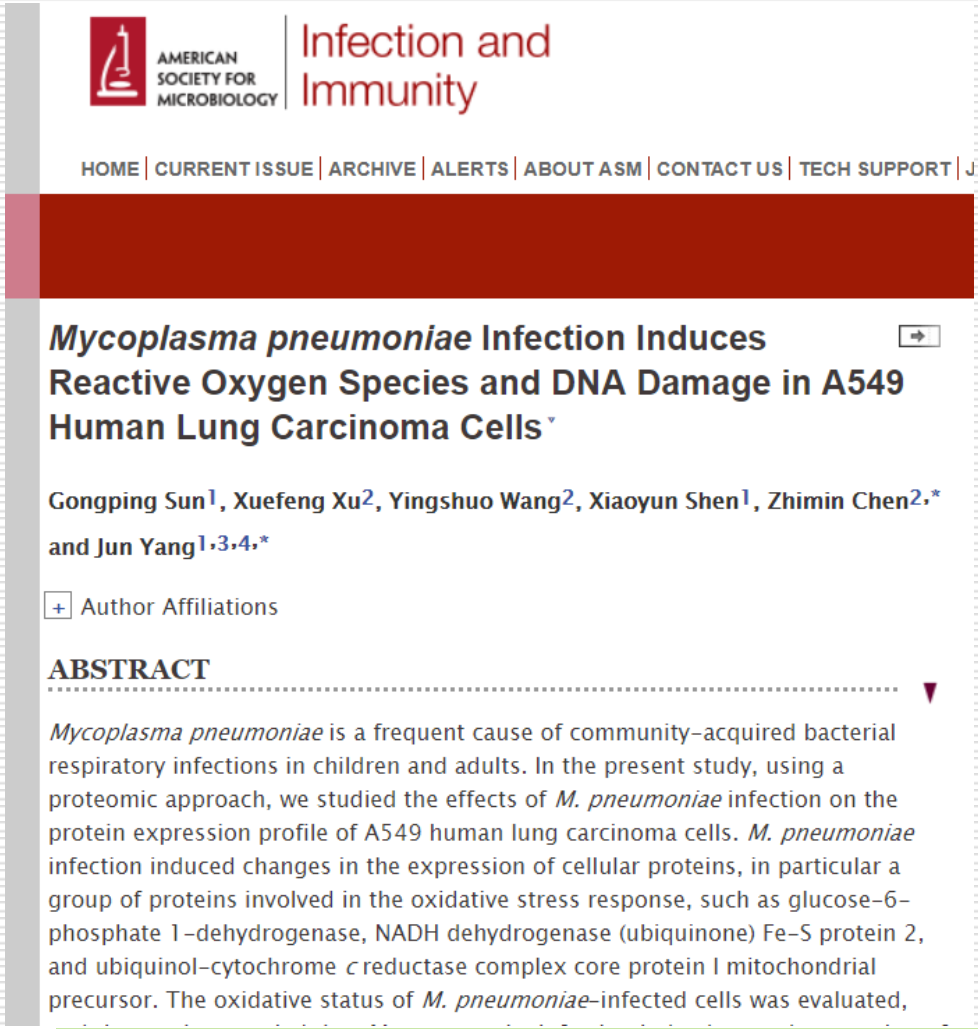
Table 4 Mycoplasma infection in other carcinoma tissues.

Types of carcinoma	Total number of cases	Infection of mycoplasma: Negative cases (-)	Positive cases (+)	Positive cases (++)	Total positive cases	Ratio of positive (%)
Esophagus	53	26	21	6	27	50.9
Lung	59	28	23	8	31	52.6
Breast	63	38	17	8	25	39.7
Glioma	91	53	27	11	38	41.0
Total	266	145	88	33	121	45.5

"There was high correlation between mycoplasma infection and different cancers, which suggests the possibility of an association between the two."

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4723534/

Mycoplasma pneumoniae infection induces reactive oxygen species and DNA damage, especially to the mitochondria



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***Mycoplasma pneumoniae* Infection Induces Reactive Oxygen Species and DNA Damage in A549 Human Lung Carcinoma Cells**

Gongping Sun[1], Xuefeng Xu[2], Yingshuo Wang[2], Xiaoyun Shen[1], Zhimin Chen[2,*] and Jun Yang[1,3,4,*]

+ Author Affiliations

ABSTRACT

Mycoplasma pneumoniae is a frequent cause of community-acquired bacterial respiratory infections in children and adults. In the present study, using a proteomic approach, we studied the effects of *M. pneumoniae* infection on the protein expression profile of A549 human lung carcinoma cells. *M. pneumoniae* infection induced changes in the expression of cellular proteins, in particular a group of proteins involved in the oxidative stress response, such as glucose-6-phosphate 1-dehydrogenase, NADH dehydrogenase (ubiquinone) Fe-S protein 2, and ubiquinol-cytochrome *c* reductase complex core protein I mitochondrial precursor. The oxidative status of *M. pneumoniae*-infected cells was evaluated,

"M. pneumoniae infection induced changes in the expression of cellular proteins, in particular a group of proteins involved in the oxidative stress response, such as glucose-6-phosphate 1-dehydrogenase, NADH dehydrogenase (ubiquinone) Fe-S protein 2, and ubiquinol-cytochrome c reductase complex core protein I mitochondrial precursor ... It was further shown that M. pneumoniae infection also induced DNA double-strand breaks, as demonstrated by the formation of H2AX foci. On the other hand, an ROS scavenger, N-acetylcysteine, could inhibit the ROS generation .."

Connections between lung cancer and SARS-CoV-2 now being investigated: vulnerability already detected

Source: Rolfo C et al. Lung Cancer and Severe Acute Respiratory Syndrome Coronavirus 2 Infection: Identifying Important Knowledge Gaps for Investigation. J Thorac Oncol. 2022 Feb;17(2):214-227.

Tailored testing protocol for the possibility of infection-associated lung cancer

» Lung cancer:

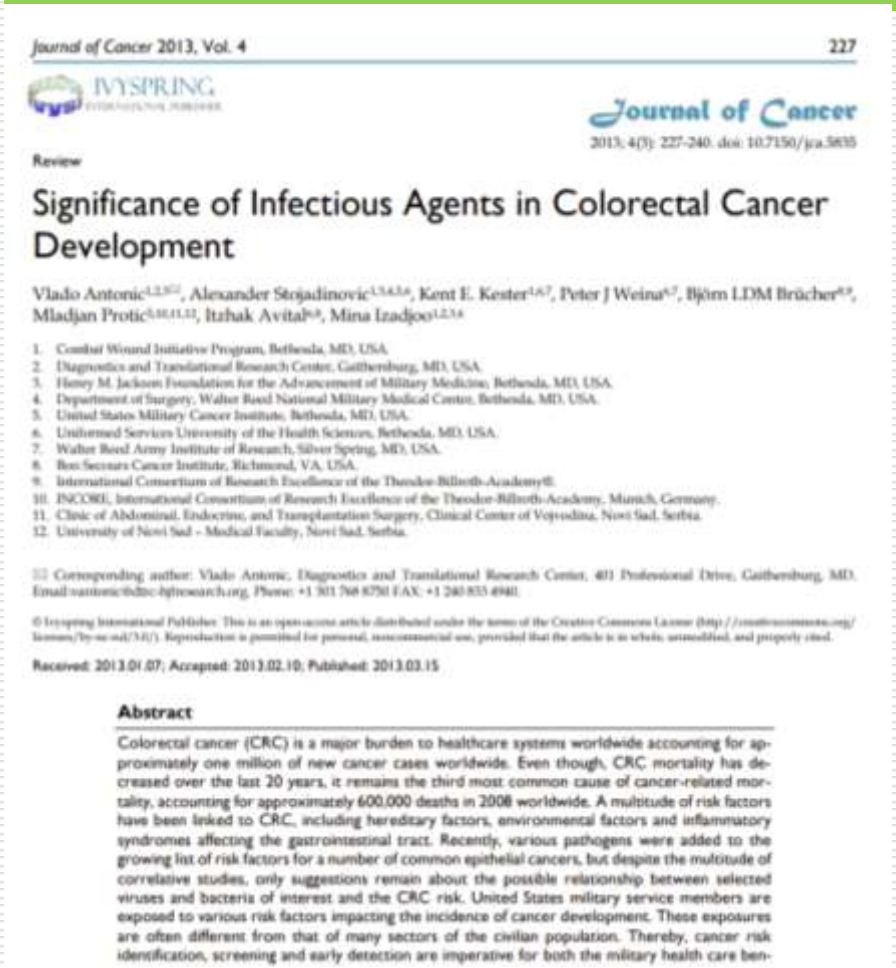
1. Chlamydia pneumoniae EliSpot + IgG/IgA antibodies
2. Mycoplasma pneumoniae EliSpot + IgG/IgA antibodies
3. EBV EliSpot

What cancers have infections been associated with?

Part 2:

- Lung
- **Colorectal**
- Gastric
- Oesophageal
- Cervical
- Liver

A number of bacteria implicated in the development of colorectal cancer



Journal of Cancer 2013, Vol. 4 227

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Journal of Cancer

2013; 4(3): 227-240. doi: 10.7150/jca.5835

Review

Significance of Infectious Agents in Colorectal Cancer Development

Vlado Antonic[1,2,3✉], Alexander Stojadinovic[1,3,4,5,6], Kent E. Kester[1,6,7], Peter J Weina[6,7], Björn LDM Brücher[8,9], Mladjan Protic[5,10,11,12], Itzhak Avital[8,9], Mina Izadjoo[1,2,3,6]

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Received: 2013.01.07; Accepted: 2013.02.10; Published: 2013.03.15

Abstract

Colorectal cancer (CRC) is a major burden to healthcare systems worldwide accounting for approximately one million of new cancer cases worldwide. Even though, CRC mortality has decreased over the last 20 years, it remains the third most common cause of cancer-related mortality, accounting for approximately 600,000 deaths in 2008 worldwide. A multitude of risk factors have been linked to CRC, including hereditary factors, environmental factors and inflammatory syndromes affecting the gastrointestinal tract. Recently, various pathogens were added to the growing list of risk factors for a number of common epithelial cancers, but despite the multitude of correlative studies, only suggestions remain about the possible relationship between selected viruses and bacteria of interest and the CRC risk. United States military service members are exposed to various risk factors impacting the incidence of cancer development. These exposures are often different from that of many sectors of the civilian population. Thereby, cancer risk identification, screening and early detection are imperative for both the military health care ben-

"Several **bacteria** have been identified and implicated in the development of CRC. These include: *Streptococcus bovis*, *Helicobacter pylori*, *E. coli*, *Klebsiella pneumoniae*, and more recently, *Fusobacterium*."

Source: Antonic V, Stojadinovic A, Kester KE, Weina PJ, Brücher BL, Protic M, Avital I, Izadjoo M. Significance of infectious agents in colorectal cancer development. J Cancer. 2013;4(3):227-40.

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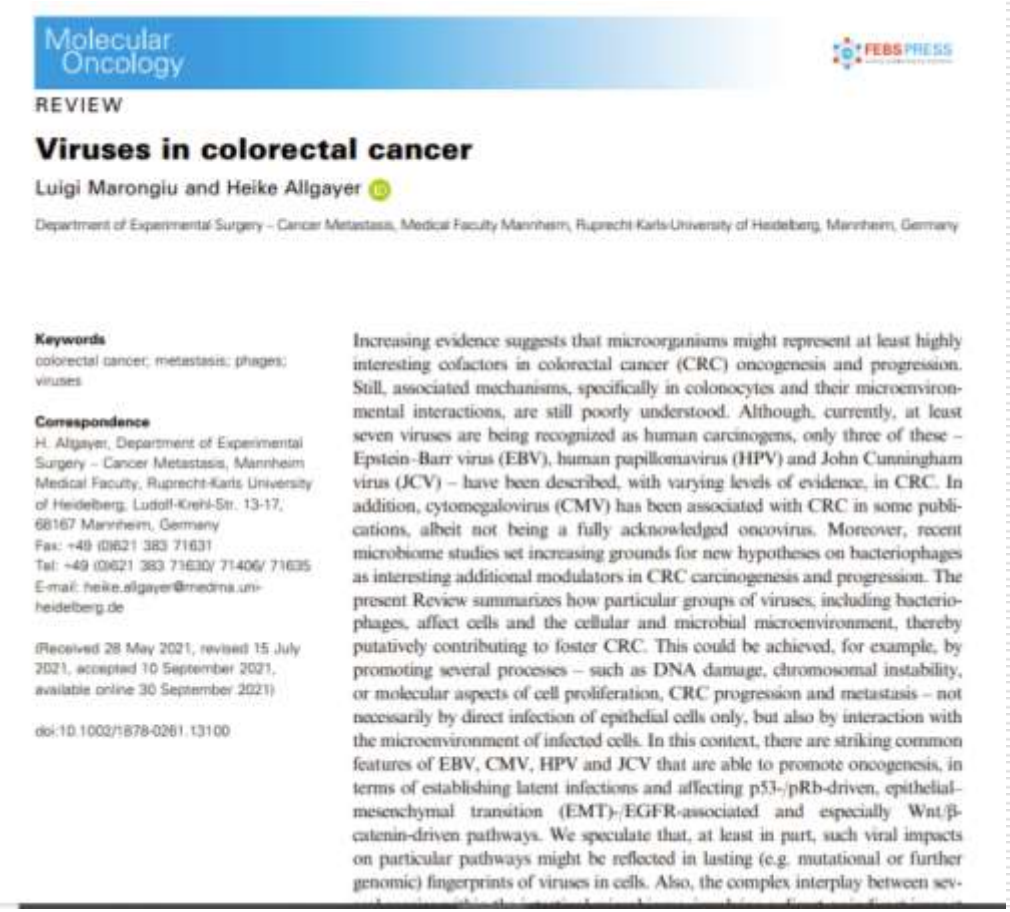
… as well as several viruses: EBV, HPV, CMV and JCV



Molecular Oncology

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REVIEW

Viruses in colorectal cancer

Luigi Marongiu and Heike Allgayer

Department of Experimental Surgery – Cancer Metastasis, Medical Faculty Mannheim, Ruprecht-Karls-University of Heidelberg, Mannheim, Germany

Keywords
colorectal cancer; metastasis; phages; viruses

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doi:10.1002/1878-0261.13100

Increasing evidence suggests that microorganisms might represent at least highly interesting cofactors in colorectal cancer (CRC) oncogenesis and progression. Still, associated mechanisms, specifically in colonocytes and their microenvironmental interactions, are still poorly understood. Although, currently, at least seven viruses are being recognized as human carcinogens, only three of these – Epstein–Barr virus (EBV), human papillomavirus (HPV) and John Cunningham virus (JCV) – have been described, with varying levels of evidence, in CRC. In addition, cytomegalovirus (CMV) has been associated with CRC in some publications, albeit not being a fully acknowledged oncovirus. Moreover, recent microbiome studies set increasing grounds for new hypotheses on bacteriophages as interesting additional modulators in CRC carcinogenesis and progression. The present Review summarizes how particular groups of viruses, including bacteriophages, affect cells and the cellular and microbial microenvironment, thereby putatively contributing to foster CRC. This could be achieved, for example, by promoting several processes – such as DNA damage, chromosomal instability, or molecular aspects of cell proliferation, CRC progression and metastasis – not necessarily by direct infection of epithelial cells only, but also by interaction with the microenvironment of infected cells. In this context, there are striking common features of EBV, CMV, HPV and JCV that are able to promote oncogenesis, in terms of establishing latent infections and affecting p53-/pRb-driven, epithelial–mesenchymal transition (EMT)-/EGFR-associated and especially Wnt/β-catenin-driven pathways. We speculate that, at least in part, such viral impacts on particular pathways might be reflected in lasting (e.g. mutational or further genomic) fingerprints of viruses in cells. Also, the complex interplay between sev-

"EBV and HPV, together with cytomegalovirus (CMV or human herpesvirus type 5) and John Cunningham virus (JCV), have been consistently reported to be prevalent in CRC."

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8978519/pdf/MOL2-16-1423.pdf

Cytomegalovirus detected in 42.3% of colorectal tumor specimens in this 2012 study

J Clin Virol. 2012 Jul;54(3):240-4. doi: 10.1016/j.jcv.2012.04.007. Epub 2012 May 15.

Human cytomegalovirus preferentially infects the neoplastic epithelium of colorectal cancer: a quantitative and histological analysis

Hsin-Pai Chen [1], Jeng-Kai Jiang, Cheng-Yu Chen, Teh-Ying Chou, Yen-Chung Chen, Ya-Ting Chang, Shiou-Fu Lin, Chia-Hao Chan, Chih-Yung Yang, Chi-Hung Lin, Jen-Kou Lin, Wen-Long Cho, Yu-Jiun Chan

Affiliations + expand

PMID: 22595308 DOI: 10.1016/j.jcv.2012.04.007

Abstract

Background: It has long been suggested that human cytomegalovirus (HCMV) might be involved in human oncogenesis. However, whether HCMV was associated with colorectal cancer (CRC) was still controversial.

Objective: To clarify whether HCMV specifically infects the tumorous tissue of CRC.

Study design: Paired tumor and adjacent non-neoplastic CRC specimens were collected from 163 patients. HCMV DNA was detected and quantified through PCR and quantitative real-time PCR. Virus location was determined by in situ hybridization (ISH) of formalin-fixed paraffin-embedded tissue sections with an HCMV-specific probe.

Results: By PCR, HCMV DNA was detected in 42.3% (69/163) of the tumor specimens, while only 5.6% (14/163) samples of adjacent non-neoplastic tissue were positive for HCMV ($p<0.0001$). Quantitative real-time PCR in 54 sample pairs revealed significantly higher viral copies in the tumor specimens than the adjacent non-neoplastic tissue specimens ($p<0.001$). By ISH, the nucleic acids of HCMV were detected in the cytoplasm of neoplastic epithelium. No hybridization was detected in the inflammatory infiltrates, submucosa, or other stromal tissues.

Conclusions: HCMV preferentially infects the tumor epithelium of CRC. How the virus subsists in and interacts with the microenvironment of tumor epithelium of CRC should be studied.

163 specimens: "HCMV DNA was detected in 42.3% (69/163) of the tumor specimens"

Source: Chen HP, Jiang JK, Chen CY, Chou TY, Chen YC, Chang YT, et al. Human cytomegalovirus preferentially infects the neoplastic epithelium of colorectal cancer: a quantitative and histological analysis. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2012;54(3):240-4.

Tailored testing protocol for the possibility of infection-associated colorectal cancer

» Colorectal cancer:

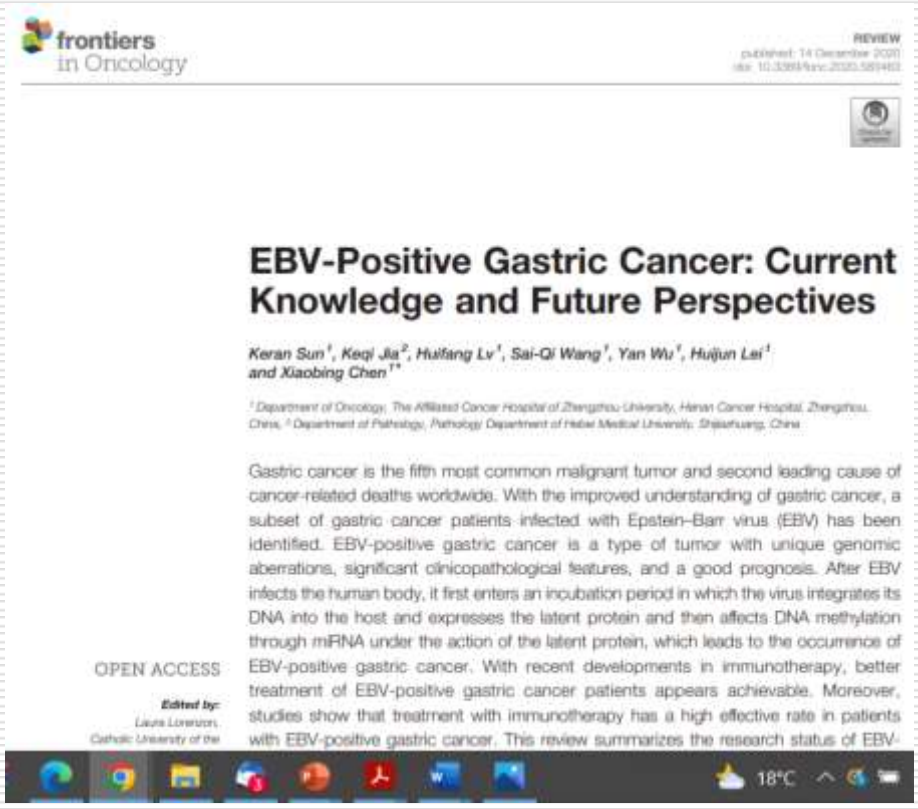
1. H. pylori IgG/IgA
2. EBV EliSpot
3. CMV EliSpot

What cancers have infections been associated with?

Part 2:

- Lung
- Colorectal
- **Gastric**
- Oesophageal
- Cervical
- Liver

Gastric cancer and H pylori/Epstein Barr Virus



frontiers in Oncology

REVIEW

EBV-Positive Gastric Cancer: Current Knowledge and Future Perspectives

Keran Sun[1], Keqi Jia[2], Huifang Lv[1], Sai-Qi Wang[1], Yan Wu[1], Hujun Lei[1] and Xiaobing Chen[1]*

[1] Department of Oncology, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China, [2] Department of Pathology, Pathology Department of Hebei Medical University, Shijiazhuang, China

Gastric cancer is the fifth most common malignant tumor and second leading cause of cancer-related deaths worldwide. With the improved understanding of gastric cancer, a subset of gastric cancer patients infected with Epstein–Barr virus (EBV) has been identified. EBV-positive gastric cancer is a type of tumor with unique genomic aberrations, significant clinicopathological features, and a good prognosis. After EBV infects the human body, it first enters an incubation period in which the virus integrates its DNA into the host and expresses the latent protein and then affects DNA methylation through miRNA under the action of the latent protein, which leads to the occurrence of EBV-positive gastric cancer. With recent developments in immunotherapy, better treatment of EBV-positive gastric cancer patients appears achievable. Moreover, studies show that treatment with immunotherapy has a high effective rate in patients with EBV-positive gastric cancer. This review summarizes the research status of EBV-

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Edited by: Laura Lorenzon, Catholic University of the

18°C

"In the past decades, Helicobacter pylori and Epstein Barr virus infections have been identified and confirmed to be causal factors of gastric cancer."

"EBV-positive gastric cancer often occurs in the proximal stomach (cardia and gastric body), where it forms lumps or ulcers that are accompanied by lymphocyte infiltration. Another noteworthy feature of EBV-positive gastric cancer is the ease of invasion into the submucosa, with a low rate of lymph node metastasis."

Source: *1. https://pubmed.ncbi.nlm.nih.gov/25186851/; 2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7769310/pdf/fonc-10-583463.pdf;* Selgrad M et al. (2008) The role of viral and bacterial pathogens in gastrointestinal cancer. J Cell Physiol 216, 378–388; Costa N, Gil da Costa R & Medeiros R (2018) A viral map of gastrointestinal cancers. Life Sci 199, 188–200.

EBV is the causal agent of a subset of gastric carcinomas

J Clin Pathol Mol Pathol 2000;53:255–261 255

Epstein-Barr virus and gastric carcinoma

K Takada

Abstract

The Epstein-Barr virus (EBV) is detected in the tissue of about 10% of gastric carcinoma cases throughout the world. In each case, 100% of carcinoma cells are infected with EBV. Analysis of EBV in carcinoma biopsies indicates that carcinoma is formed by the proliferation of a single EBV infected cell. These findings suggest that EBV plays an important role in the development of EBV positive gastric carcinomas. The EBV genes expressed are EBV determined nuclear antigen 1 (EBNA1), two small non-polyadenylated RNAs known as EBER1 and EBER2, and the transcripts from the BamHI-A region (BARF0); in addition, some cases also express a small amount of latent membrane protein 2A (LMP2A). Epithelial cells are refractory to EBV infection in vitro. This has hampered the study of the role of EBV in epithelial malignancies. The use of recombinant EBV carrying a selectable marker has enabled this difficulty to be overcome. EBV infected cell clones can be obtained from most carcinoma cell lines examined, and it was found that cell to cell contact was an efficient mode of EBV infection. Furthermore, it was possible to immortalise primary gastric epithelial cells by EBV infection. The cells expressed identical EBV genes to those typically seen in EBV positive gastric carcinoma, and showed accelerated malignant properties, including growth in soft agarose and tumorigenicity in severe combined immunodeficient (SCID) mice. These re-

carcinomas, and the worldwide occurrence of EBV positive gastric carcinoma is estimated at more than 50 000 cases/year.

Unlike B cells, epithelial cells have displayed a remarkable resistance to EBV infection in vitro. This has hampered the study of the role of EBV in the development of epithelial malignancies. Therefore, we have established a system for the infection of epithelial cells in vitro, which has allowed us to study the role of EBV in the development of epithelial malignancies. Here, I review the literature concerning the association of EBV and gastric carcinoma, and introduce our recent findings obtained using our system for the infection of epithelial cells.

Epidemiology

Most nasopharyngeal carcinomas are undifferentiated and accompanied by intense lymphoid infiltration (termed lymphoepithelioma). Carcinomas with a similar histological profile occur at a low incidence in organs such as the salivary glands, thymus, lungs, etc, mainly in Chinese and Inuits. These carcinomas are termed lymphoepithelioma-like carcinomas or carcinomas with lymphoid stroma, and most cases are EBV positive.[1] The association between EBV and gastric carcinoma was first reported in this particular type of gastric carcinoma.[2] EBV DNA was demonstrated in more than 80% of gastric carcinomas of the lymphoepithelioma type by PCR and ISH.[3–5] Subsequently, Shibata and Weiss demonstrated EBV infection in gastric adenocarcinomas of ordinary histology (fig 1).[6] They reported that EBV is present in almost all carcinoma cells in

"The Epstein-Barr virus (EBV) is **detected in the tissue of about 10% of gastric carcinoma cases throughout the world**. In each case, 100% of carcinoma cells are infected with EBV. Analysis of EBV in carcinoma biopsies indicates that carcinoma is formed by the proliferation of a single EBV infected cell."

Source: Tokunaga, M.; Land, C.E.; Uemura, Y.; Tokudome, T.; Tanaka, S.; Sato, E. Epstein-Barr virus in gastric carcinoma. Am. J. Pathol. 1993, 143, 1250–1254; Osorio JC, Blanco R, Corvalán AH, Muñoz JP, Calaf GM, Aguayo F. Epstein-Barr Virus Infection in Lung Cancer: Insights and Perspectives. Pathogens. 2022 Jan 21;11(2):132.

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Tailored testing protocol for the possibility of infection-associated gastric cancer

» Gastric cancer:

1. H. pylori IgG/IgA
2. EBV EliSpot

What cancers have infections been associated with?

Part 2:

- Lung
- Colorectal
- Gastric
- **Oesophageal (Barrett's Syndrome)**
- Cervical
- Liver

Mycoplasma infection in oesophageal cancer was 50.9% in this study

World Journal of Gastroenterology

World J Gastroenterol. 2001 Apr 15; 7(2): 266–269
Published online 2001 Apr 15. doi: 10.3748/wjg.v7.i2.266

Mycoplasma infections and different human carcinomas

Su Huang, Ji-You Li, Jian Wu, Lin Meng, and Cheng-Chao Shou

Abstract

AIM: To explore relationships between human carcinomas and mycoplasma infection.

METHODS: Monoclonal antibody PD4, which specifically recognizes a distinct protein mycoplasma hyorhinis, was used to detect mycoplasma infection in different paraffin em tissues with immunohistochemistry. PCR was applied to amplify the mycoplasma DNA samples for confirming immunohistochemistry.

RESULTS: Fifty of 90 cases (56%) of gastric carcinoma were positive for mycoplasma gastric diseases, the mycoplasma infection ratio was 28% (18/49) in chronic superficial (14/46) in gastric ulcer and 37% (18/49) in intestinal metaplasia. The difference is signif cancer ($\chi^2 = 12.06$, $P < 0.05$). In colon carcinoma, the mycoplasma infection ratio was 5 was 20.9% (10/49) in adenomarous polyp ($\chi^2 = 13.46$, $P < 0.005$). Gastric and colon ca differentiation had a higher mycoplasma infection ratio than those with low differentiatio

than that of low differentiation colon carcinoma tissues (Table 3, $P<0.05$).

In the 49 cases of adenomarous polyp, there were 10 cases with mycoplasma infection. The positive ratio was 20.4%. The difference between the infection ratio of colon carcinoma and that of adenomarous polyp was significant ($\chi^2 = 13.46$, $P<0.005$).

Table 3 Mycoplasma infection in different grades of colon carcinoma

Grades of differentiation	Total number of cases	Infection of mycoplasma: Negative cases (-)	Positive cases (+)	Positive cases (++)	Total positive cases	Ratio of positive (%)
I-II	42	15	15	12	27	64
II-III	8	5	2	1	3	37
III	8	6	2	0	2	30
Total	58	26	19	13	32	55 (mean)

Mycoplasma infection in other carcinoma tissues

Beside the gastriointestinal carcinomas, other cancer tissues from human esophagus, lung, breast and brain were also analyzed (Table 4).

Table 4 Mycoplasma infection in other carcinoma tissues

Types of carcinoma	Total number of cases	Infection of mycoplasma: Negative cases (-)	Positive cases (+)	Positive cases (++)	Total positive cases	Ratio of positive (%)
Esophagus	53	26	21	6	27	50.9
Lung	59	28	23	8	31	52.5
Breast	63	38	17	8	25	39.7
Glioma	91	53	27	11	38	41.0
Total	266	145	88	33	121	45.5

Some immunoperoxidase stainings of different carcinoma are shown in Figure 1. The low differential gastric cancer (ring cell cancer) was negative reacted with PD4

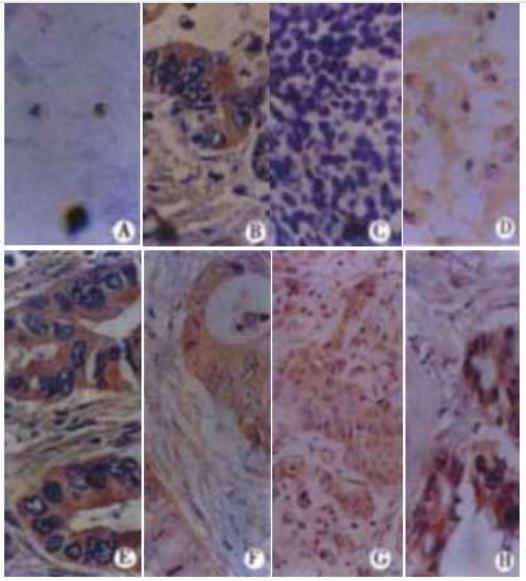
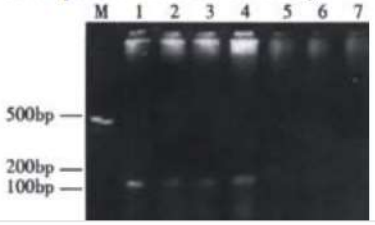


Figure 1 Immunoperoxidase stainings of different carcinoma tissues reacted with monoclonal antibody PD4 (× 400). Both A and B were gastric carcinomas. A (singnet-ring cell carcinoma) was negative, B (adenocarcinoma) was positive. C (glioma) indicated the negative reaction, D (glioma), E (lung cancer), F (esophagus cancer), G (breast cancer) and H (colon cancer) presented the positive reactions with antibody PD4.



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4723534/

Tailored testing protocol for the possibility of infection-associated oesophageal cancer

» Oesophageal cancer:

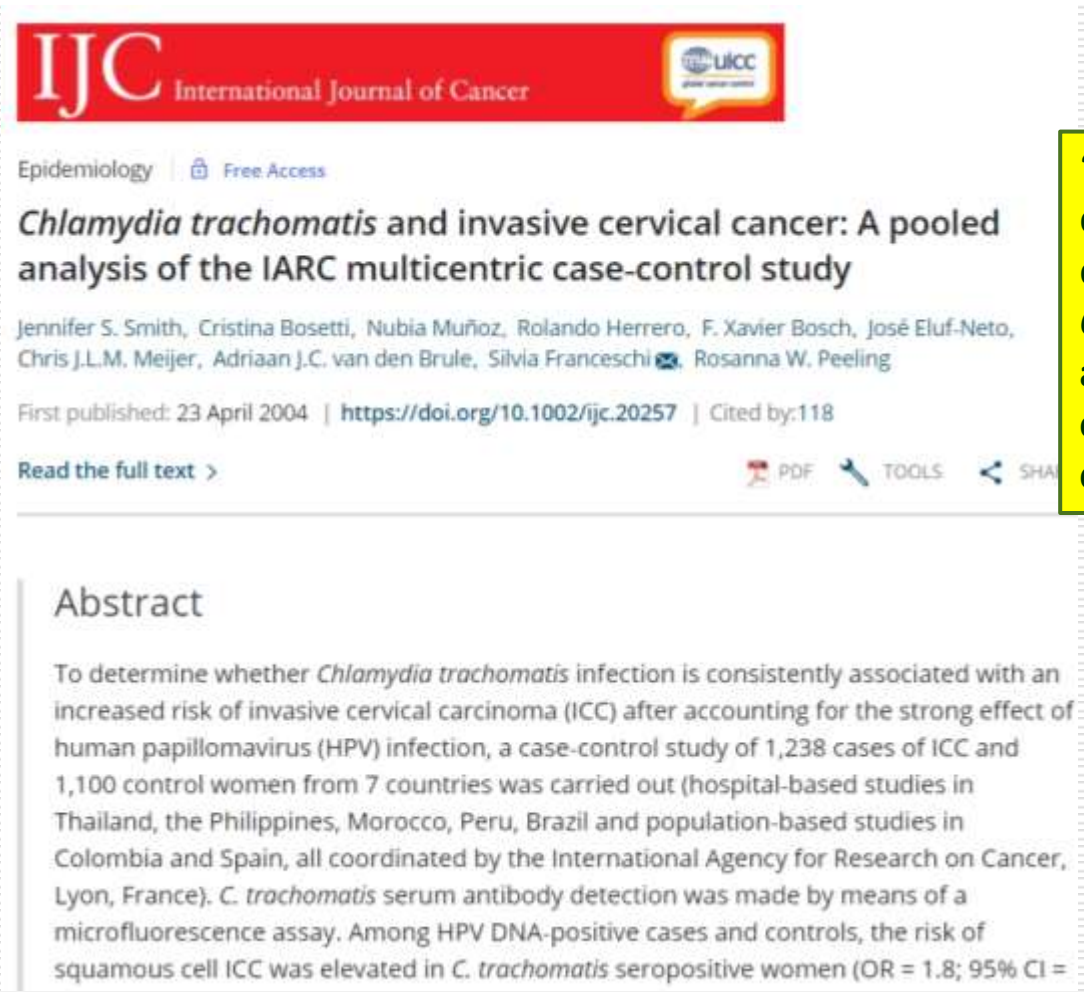
1. Mycoplasma pneumoniae Elispot and IgG/IgA antibodies
2. H. pylori IgG/IgA

What cancers have infections been associated with?

Part 2:

- Lung
- Colorectal
- Gastric
- Oesophageal
- **Cervical**
- Liver

Chlamydia trachomatis is associated with a greater risk of invasive cervical cancer



IJC International Journal of Cancer

Epidemiology | Free Access

Chlamydia trachomatis and invasive cervical cancer: A pooled analysis of the IARC multicentric case-control study

Jennifer S. Smith, Cristina Bosetti, Nubia Muñoz, Rolando Herrero, F. Xavier Bosch, José Eluf-Neto, Chris J.L.M. Meijer, Adriaan J.C. van den Brule, Silvia Franceschi, Rosanna W. Peeling

First published: 23 April 2004 | https://doi.org/10.1002/ijc.20257 | Cited by:118

Read the full text > PDF TOOLS SHA

Abstract

To determine whether *Chlamydia trachomatis* infection is consistently associated with an increased risk of invasive cervical carcinoma (ICC) after accounting for the strong effect of human papillomavirus (HPV) infection, a case-control study of 1,238 cases of ICC and 1,100 control women from 7 countries was carried out (hospital-based studies in Thailand, the Philippines, Morocco, Peru, Brazil and population-based studies in Colombia and Spain, all coordinated by the International Agency for Research on Cancer, Lyon, France). *C. trachomatis* serum antibody detection was made by means of a microfluorescence assay. Among HPV DNA-positive cases and controls, the risk of squamous cell ICC was elevated in *C. trachomatis* seropositive women (OR = 1.8; 95% CI =

"This study, based on data from 1,238 case and 1,100 control participants in 7 countries worldwide, shows that ***C. trachomatis*** **serum antibodies were associated with a 1.8-fold increased risk of squamous cell invasive cervical cancer**."

Source: https://onlinelibrary.wiley.com/doi/abs/10.1002/ijc.20257

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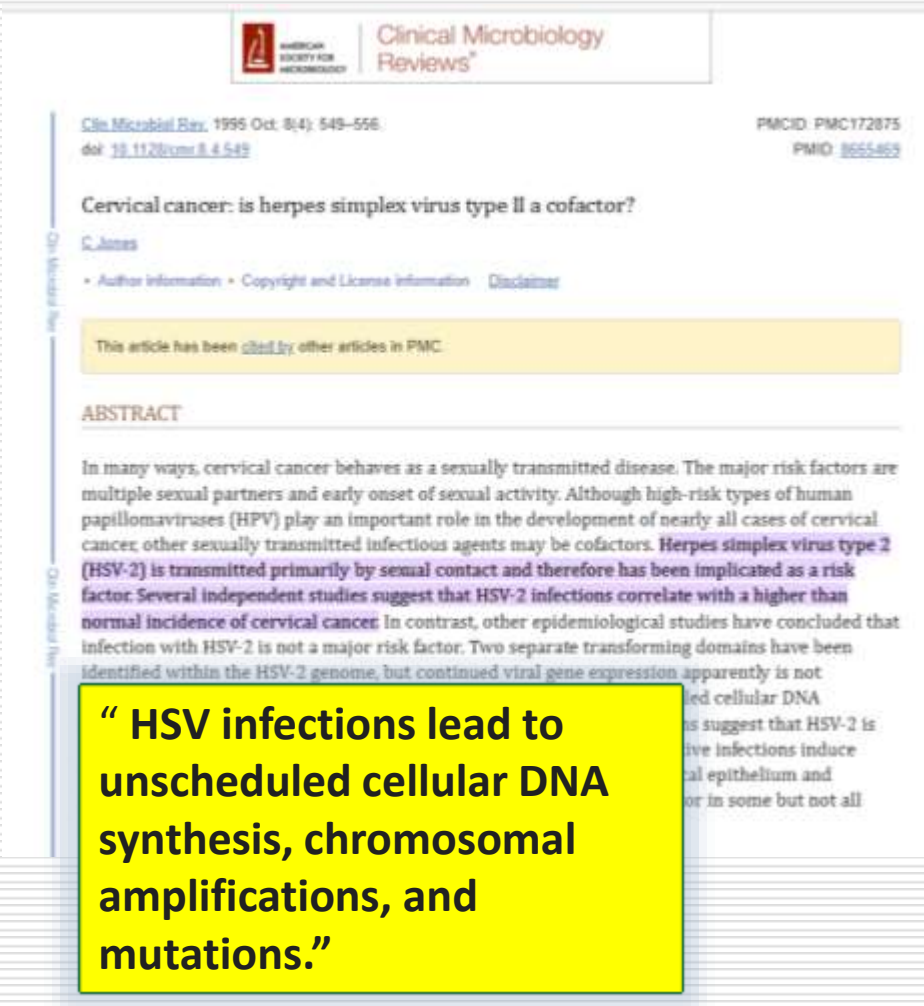
Several independent studies suggest that HSV-2 infections correlate with a higher than normal incidence of cervical cancer, and with HPV



Clinical Microbiology Reviews

Clin Microbiol Rev. 1995 Oct; 8(4): 549–556
doi: 10.1128/cmr.8.4.549
PMCID: PMC172875
PMID: 8665469

Cervical cancer: is herpes simplex virus type II a cofactor?

C Jones

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ABSTRACT

In many ways, cervical cancer behaves as a sexually transmitted disease. The major risk factors are multiple sexual partners and early onset of sexual activity. Although high-risk types of human papillomaviruses (HPV) play an important role in the development of nearly all cases of cervical cancer, other sexually transmitted infectious agents may be cofactors. **Herpes simplex virus type 2 (HSV-2) is transmitted primarily by sexual contact and therefore has been implicated as a risk factor. Several independent studies suggest that HSV-2 infections correlate with a higher than normal incidence of cervical cancer.** In contrast, other epidemiological studies have concluded that infection with HSV-2 is not a major risk factor. Two separate transforming domains have been identified within the HSV-2 genome, but continued viral gene expression apparently is not ...led cellular DNA ...s suggest that HSV-2 is ...ive infections induce ...al epithelium and ...or in some but not all

" HSV infections lead to unscheduled cellular DNA synthesis, chromosomal amplifications, and mutations."

JNCI JOURNAL of the NATIONAL CANCER INSTITUTE

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Volume 94, Issue 21
6 November 2002

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Abstract
Subjects and Methods
Results
Discussion
Appendix
References

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JOURNAL ARTICLE

Herpes Simplex Virus-2 as a Human Papillomavirus Cofactor in the Etiology of Invasive Cervical Cancer

Jennifer S. Smith, Rolando Herrero, Cristina Bosetti, Nubia Muñoz, F. Xavier Bosch, José Eluf-Neto, Xavier Castellsagué, Chris J. L. M. Meijer, Adriaan J. C. Van den Brule, Silvia Franceschi ... Show more

JNCI: Journal of the National Cancer Institute, Volume 94, Issue 21, 6 November 2002, Pages 1604–1613, https://doi.org/10.1093/jnci/94.21.1604
Published: 06 November 2002 **Article history**

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Abstract

Background: Human papillomavirus (HPV) infection is the main cause of invasive cervical cancer, but cofactors may act in conjunction with HPV. We performed a pooled analysis of seven case–control studies to examine the effect of one possible HPV cofactor, herpes simplex virus-2 (HSV-2) infection, in the etiology of invasive cervical cancer. *Methods:* Blood and exfoliated cervical specimens were obtained from 1263 case patients with invasive cervical cancer (1158 with squamous-cell carcinomas and 105 with adeno- or adenosquamous-cell carcinomas) and 1117 age-matched control subjects. Western blot analysis and/or an enzyme-linked immunosorbent assay were

"Among the HPV DNA-positive women, HSV-2 seropositivity was associated with increased risks of squamous-cell carcinoma."

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Tailored testing protocol for the possibility of infection-associated cervical cancer

» Cervical cancer:

1. Chlamydia trachomatis EliSpot and IgG/IgA antibodies
2. HSV I/2 EliSpot and IgG/IgA antibodies

What cancers have infections been associated with?

Part 2:

- Lung
- Colorectal
- Gastric
- Oesophageal
- Cervical
- **Liver**

More than half of the world's cases of liver cancer are due to viral liver infections

OUTLOOK | 30 March 2022

Hepatitis B and the liver cancer endgame

More than half of the world's cases of liver cancer are due to viral liver infections. Detecting and treating hepatitis B could help to reverse the global increase in fatal liver cancer.

Kristina Campbell

Jason Bahary (left) studies changes in the gut microbiome in people who develop liver cancer. Credit: Jason Bahary

"Hepatitis B virus causes cancer by integrating its DNA into human cells. Delving further, his group found that the viral break-ins led to chromosome rearrangements, wiping out genes that suppress tumours and allowing cancer cells to proliferate."

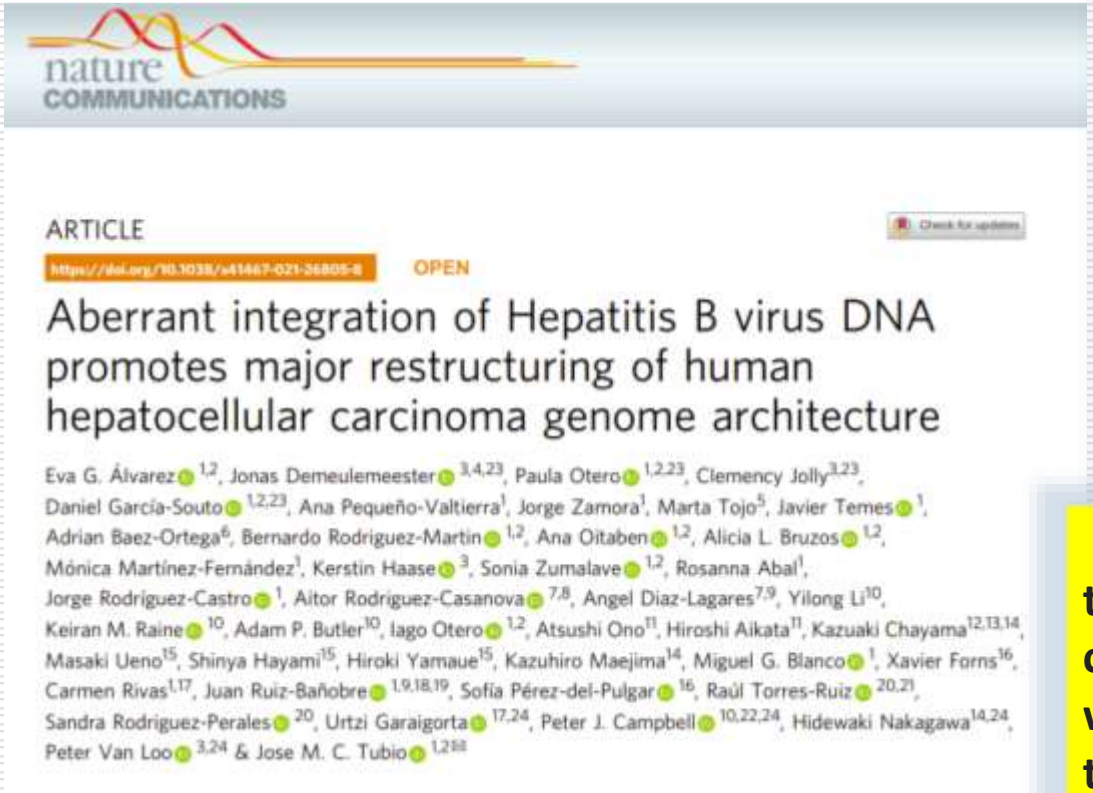
Source: https://www.nature.com/articles/d41586-022-00821-0?proof=t

Most common risk factor for liver cancer is chronic infections with hepatitis B or C

”Individuals chronically infected with hepatitis B have a 25% to 40% lifetime risk of developing liver cancer.”

Source: **https://www.cancer.org/cancer/liver-cancer/causes-risks-prevention/risk-factors.html**; https://www.hepb.org/research-and-programs/liver/risk-factors-for-liver-cancer/#:~:text=The%20most%20common%20risk%20factor,risk%20of%20developing%20liver%20cancer.

Over half of cases of liver cancer – the 3rd leading cause of cancer deaths globally – are due to viral liver infections



nature COMMUNICATIONS

ARTICLE

OPEN

Aberrant integration of Hepatitis B virus DNA promotes major restructuring of human hepatocellular carcinoma genome architecture

Eva G. Álvarez[1,2], Jonas Demeulemeester[3,4,23], Paula Otero[1,2,23], Clemency Jolly[3,23], Daniel García-Souto[1,2,23], Ana Pequeño-Valtierra[1], Jorge Zamora[1], Marta Tojo[5], Javier Temes[1], Adrian Baez-Ortega[6], Bernardo Rodriguez-Martin[1,2], Ana Oitaben[1,2], Alicia L. Bruzos[1,2], Mónica Martínez-Fernández[1], Kerstin Haase[3], Sonia Zumalave[1,2], Rosanna Abal[1], Jorge Rodríguez-Castro[1], Aitor Rodríguez-Casanova[7,8], Angel Diaz-Lagares[7,9], Yilong Li[10], Keiran M. Raine[10], Adam P. Butler[10], Iago Otero[1,2], Atsushi Ono[11], Hiroshi Aikata[11], Kazuaki Chayama[12,13,14], Masaki Ueno[15], Shinya Hayami[15], Hiroki Yamaue[15], Kazuhiro Maejima[14], Miguel G. Blanco[1], Xavier Forns[16], Carmen Rivas[1,17], Juan Ruiz-Bañobre[1,9,18,19], Sofía Pérez-del-Pulgar[16], Raúl Torres-Ruiz[20,21], Sandra Rodriguez-Perales[20], Urtzi Garaigorta[17,24], Peter J. Campbell[10,22,24], Hidewaki Nakagawa[14,24], Peter Van Loo[3,24] & Jose M. C. Tubio[1,25]

Worldwide, the most common risk factor for liver cancer is chronic (long-term) infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
In the US, infection with hepatitis C is the more common cause of hepatocellular carcinoma, while in Asia and developing countries, hepatitis B is more common.

”Tubio’s … group found that the viral break-ins led to chromosome rearrangements, wiping out genes that suppress tumours and allowing cancer cells to proliferate.”

Source: https://www.nature.com/articles/d41586-022-00821-0; Álvarez EG, Tubio JMC et al. Aberrant integration of Hepatitis B virus DNA promotes major restructuring of human hepatocellular carcinoma genome architecture. Nat Commun. 2021 Nov 25;12(1):6910; **https://pubmed.ncbi.nlm.nih.gov/34824211/; https://www.cancer.org/cancer/liver-cancer/causes-risks-prevention/risk-factors.html;** https://www.hepb.org/research-and-programs/liver/risk-factors-for-liver-cancer/#:~:text=The%20most%20common%20risk%20factor,risk%20of%20developing%20liver%20cancer.

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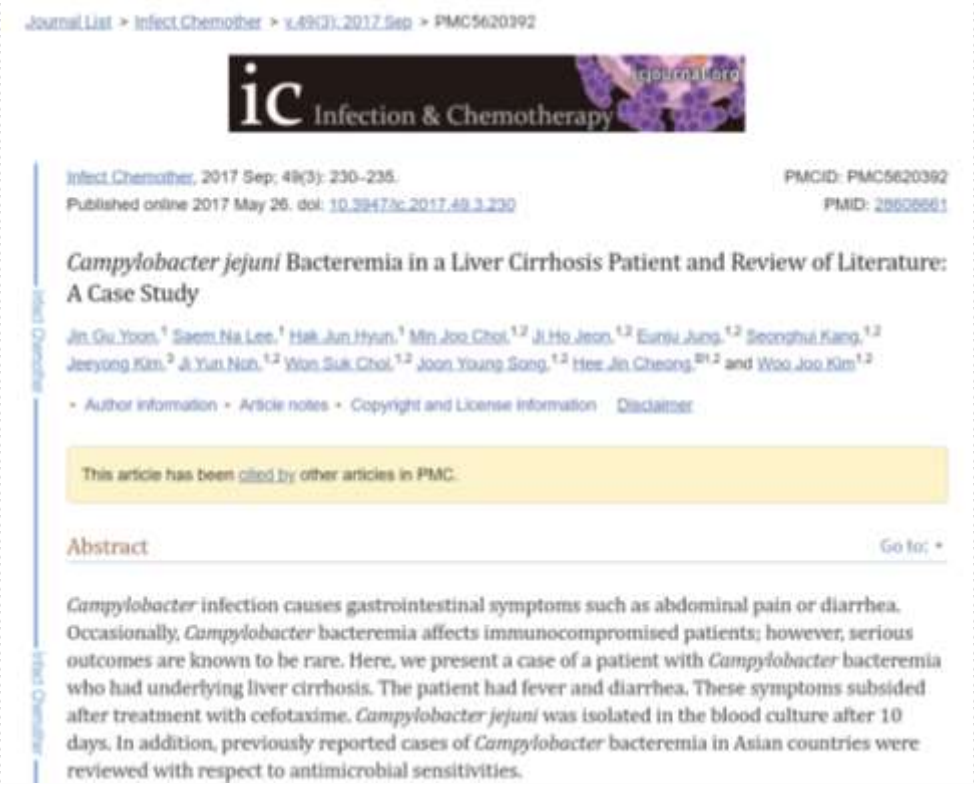
Campylobacter also an association: 38% of patients had liver cancer in a study of 183 patients with C. bacteremia



Journal List > Infect Chemother > v.49(3); 2017 Sep > PMC5620392

ic Infection & Chemotherapy

Infect Chemother. 2017 Sep; 49(3): 230–236.
Published online 2017 May 26. doi: 10.3947/ic.2017.49.3.230

PMCID: PMC5620392
PMID: 28608661

Campylobacter jejuni Bacteremia in a Liver Cirrhosis Patient and Review of Literature: A Case Study

Jin Gu Yoon,[1] Saem Na Lee,[1] Hak Jun Hyun,[1] Min Joo Choi,[1,2] Ji Ho Jeon,[1,2] Eunju Jung,[1,2] Seonghui Kang,[1,2] Jeeyong Kim,[3] Ji Yun Noh,[1,2] Won Suk Choi,[1,2] Joon Young Song,[1,2] Hee Jin Cheong,[1,2] and Woo Joo Kim[1,2]

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Abstract

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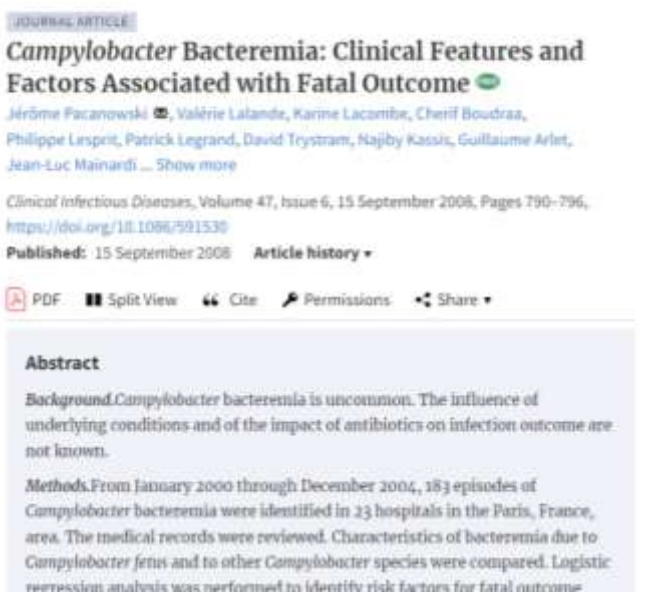
Campylobacter infection causes gastrointestinal symptoms such as abdominal pain or diarrhea. Occasionally, *Campylobacter* bacteremia affects immunocompromised patients; however, serious outcomes are known to be rare. Here, we present a case of a patient with *Campylobacter* bacteremia who had underlying liver cirrhosis. The patient had fever and diarrhea. These symptoms subsided after treatment with cefotaxime. *Campylobacter jejuni* was isolated in the blood culture after 10 days. In addition, previously reported cases of *Campylobacter* bacteremia in Asian countries were reviewed with respect to antimicrobial sensitivities.



JOURNAL ARTICLE

Campylobacter Bacteremia: Clinical Features and Factors Associated with Fatal Outcome

Jérôme Pacanowski, Valérie Lalande, Karine Lacombe, Cherif Boudraa, Philippe Lesprit, Patrick Legrand, David Trystram, Najiby Kassis, Guillaume Arlet, Jean-Luc Mainardi ... Show more

Clinical Infectious Diseases, Volume 47, Issue 6, 15 September 2008, Pages 790–796, https://doi.org/10.1086/591530

Published: 15 September 2008 **Article history**

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Abstract

Background. *Campylobacter* bacteremia is uncommon. The influence of underlying conditions and of the impact of antibiotics on infection outcome are not known.

Methods. From January 2000 through December 2004, 183 episodes of *Campylobacter* bacteremia were identified in 23 hospitals in the Paris, France, area. The medical records were reviewed. Characteristics of bacteremia due to *Campylobacter fetus* and to other *Campylobacter* species were compared. Logistic regression analysis was performed to identify risk factors for fatal outcome

"The main underlying conditions were liver disease (39%) and cancer (38%)."

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5620392/; https://academic.oup.com/cid/article/47/6/790/325735

Enteroviruses also associated with liver cancer

The coxsackievirus-adenovirus receptor (CAR) is “expressed more in more in liver than in other tissues … These findings indicate that CAR plays an important role in the initiation of CVB infections and is closely associated with hepatotropism and age-specific susceptibility”.

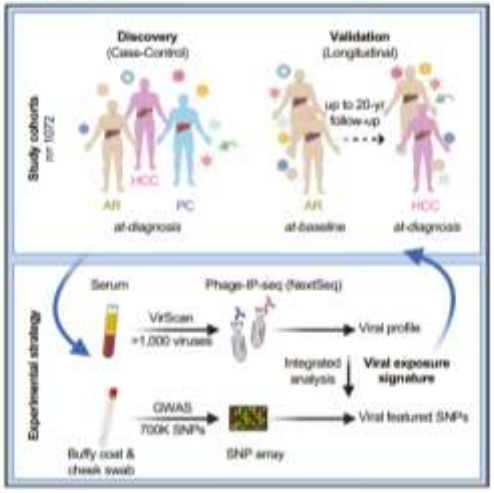
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6350183/; https://academic.oup.com/femspd/article/68/2/52/2398850

Viral infection history can be used to detect hepatocellular cancer (HCC)

Cell
Article

A Viral Exposure Signature Defines Early Onset of Hepatocellular Carcinoma

Graphical Abstract



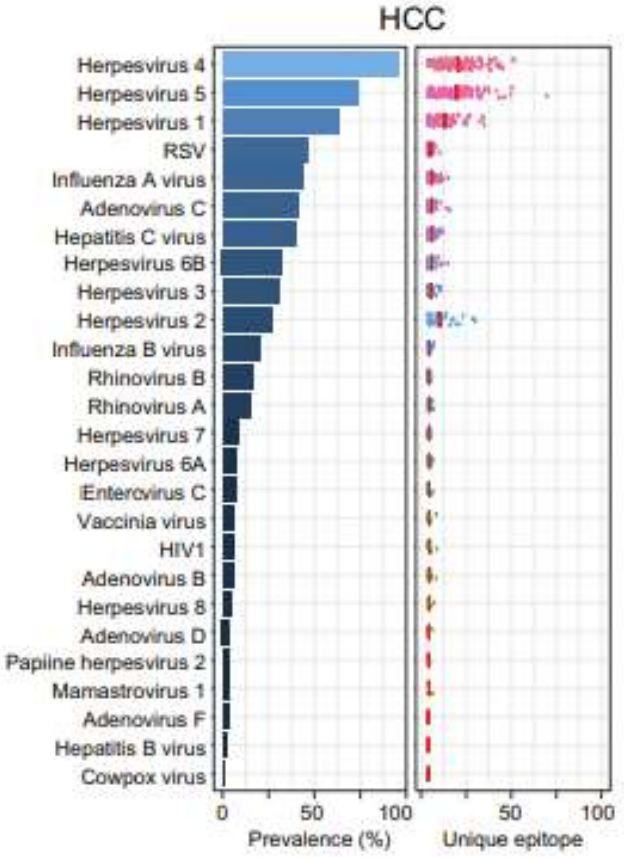
Authors
Jinping Liu, Wei Tang, Anuradha Budhu, ..., Zhanwei Wang, Herbert Yu, Xin Wei Wang

Correspondence
xw3u@nih.gov

In Brief

Lui et al. demonstrate how viral infection history, obtained using human blood samples and VirScan analysis of antiviral antibodies, can be used to detect hepatocellular carcinoma in at-risk patients prior to clinical cancer diagnoses.

Cell
Article



Source: https://www.cell.com/cell/pdf/S0092-8674(20)30671-1.pdf

Tailored testing protocol for the possibility of infection-associated liver cancer

» Liver cancer:

1. Hepatitis B
2. Hepatitis C
3. Camphylobacter
4. Coxsackie A/B IgG/IgA antibodies

Tailored testing protocols available for all the types of cancer mentioned

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Test panels in different cancers

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» Lung cancer

- Chlamydia pneumoniae EliSpot & IgG/IgA antibodies
- Mycoplasma pneumoniae EliSpot & IgG/IgA antibodies
- Epstein Barr Virus EliSpot

» Oesophageal cancer

- Mycoplasma pneumoniae EliSpot & IgG/IgA antibodies

» Gastric cancer

- H. pylori IgG/IgA antibodies
- Epstein Barr Virus EliSpot

» Colorectal cancer

- H. pylori IgG/IgA antibodies
- Epstein Barr Virus EliSpot
- Cytomegalovirus EliSpot

» Cervical cancer

- Chlamydia pneumoniae EliSpot & IgG/IgA antibodies
- Herpes Simplex Virus (HSV) 1/2 EliSpot & IgG/IgA antibodies

» Liver cancer

- Hepatitis B antibodies
- Hepatitis C antibodies
- Camphylobacter IgG/IgA antibodies
- Coxsackie A & B IgG/IgA antibodies

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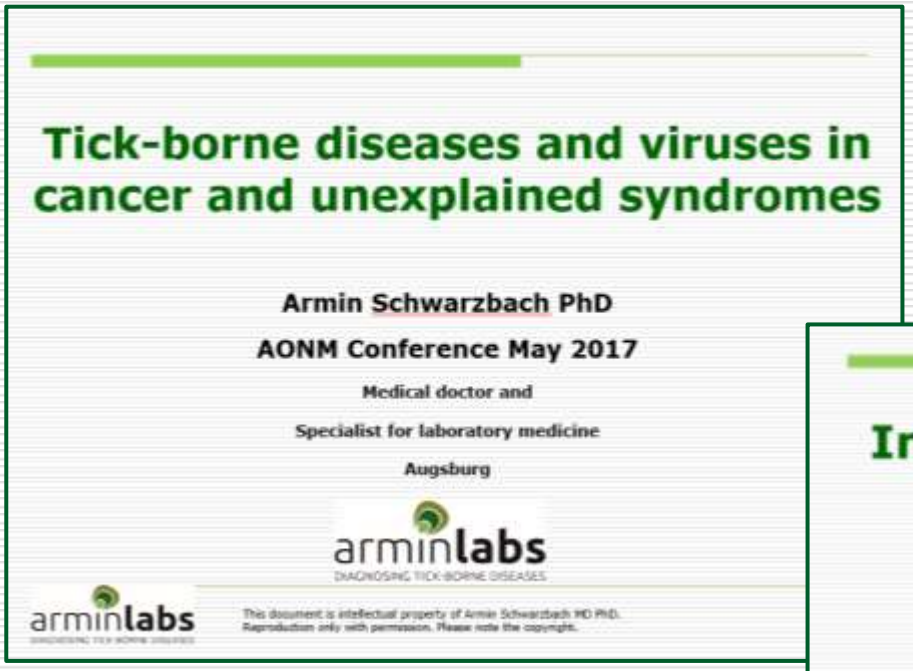
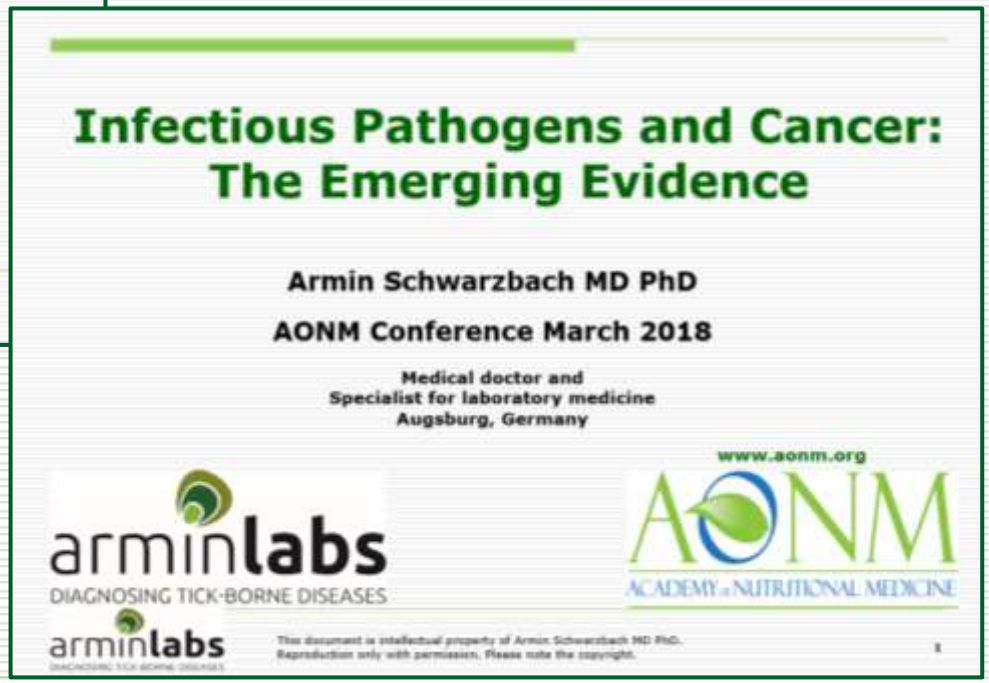
Further presentations on the links between pathogens and cancer available from AONM





See https://aonm.org/cancer-webinar-series/

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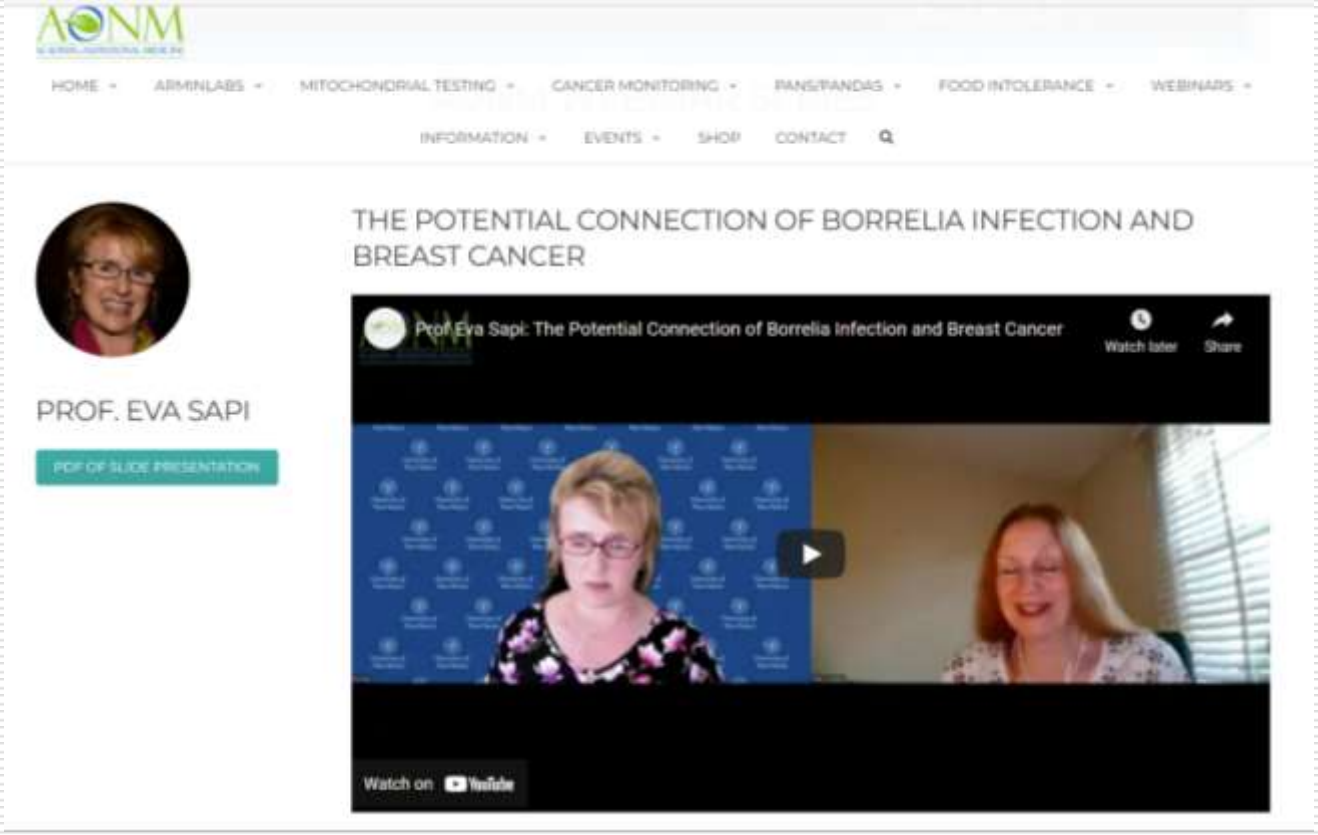
Professor Sapi gave us incredible insights into the possible links between Borrelia and breast cancer



https://aonm.org/view-past-webinars/

Thank you very much for your attention!

For tests, please go to
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or call the AONM helpline
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