Cancer and Infection Literature

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This collects some iteratures on cancer and infection studies.
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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Literatures

Abol-Enein, H. (2008). "Infection: is it a cause of bladder cancer?" Scand J Urol Nephrol Suppl(218): 79-84.

This article reviews the literature regarding the possible correlation between infection and occurrence of bladder cancer. The PubMed literature database was searched from inception to January 2008. Keywords of bladder, cancer, parasitic, bacterial, viral and infection, were used. Forty studies were included in the review. Several investigators support the idea that schistosomiasis is aetiologically related to the development of bladder cancer in individuals infected with Schistosoma haematobium. Approximately 70% of those with chronic schistosomiasis who have bladder cancer develop squamous cell rather than transitional cell carcinoma. Several investigators suggest that bacteria may play a role in inducing bladder cancer. Clinically, researchers have linked the development of infection, urinary stones and indwelling catheters with bladder cancer. Nevertheless, to date, no prospective study has examined the association between urinary tract infection and bladder cancer risk. The possibility that infection by human papilloma virus (HPV) is a risk factor contributing to bladder cancer has been investigated but no definite conclusions have been drawn. Thus, the debate remains open as to whether there is any direct link between chronic HPV infection and bladder cancer. Only 15 cases of vesical carcinoma have been reported, to date, in the setting of human immunodeficiency virus (HIV). The rare occurrence of bladder cancer during HIV infection and the lack of correlation with the laboratory markers of HIV disease progression may suggest a trivial association between two unrelated disorders. BK virus is oncogenic in newborn hamsters and can transfer to mammalian cells in vitro, but there is little consistent evidence of a link with human bladder cancer. Studies showed no correlation between herpes simplex virus (HSV) and bladder cancer, but bladder cancer becomes infected with HSV much more easily than non-neoplastic urothelium. In conclusion, with the exception of chronic infection with S. haematobium, the association between the occurrence of bladder cancer and chronic bacterial or viral infections could not be confirmed. Prospective studies with large numbers of patients and controls are required to confirm this issue.

Adami, H. O., H. Kuper, et al. (2003). "Prostate cancer risk and serologic evidence of human papilloma virus infection: a population-based case-control study." Cancer Epidemiol Biomarkers Prev **12**(9): 872-5.

Epidemiological evidence is accumulating that sexual history may be associated with prostate cancer, and some studies have suggested a relation between human papilloma virus (HPV) infections and prostate cancer. We measured the presence of antibodies to the major oncogenic HPV types 16, 18, and 33 among 238 subjects with untreated prostate cancer and 210 population-based control subjects.

Odds ratios (ORs) were estimated from multivariate logistic regression models, controlling for age and HPV types 16, 18, and 33, simultaneously. HPV types 16 and 18 were not associated with prostate cancer [OR, 0.7; 95% confidence interval (CI), 0.4-1.3 for HPV 16; OR, 0.9; 95% CI, 0.5-1.9 for HPV 18]. There was a possible association between HPV 33 and prostate cancer (OR, 1.6; 95% CI, 1.0-2.7), and there was a significant excess risk for subjects with high antibody levels against HPV 33 (OR when the difference in absorbance exceeded 0.2, 2.3; 95% CI, 1.2-4.1). When HPV antibody levels were modeled as continuous variables, the results were qualitatively similar. The data do not support previous studies that have suggested an association with HPV 16 or 18 and prostate cancer risk. Inconsistent associations with different HPV types seen in different studies suggest that the association may be because of chance, bias, or confounding by some unknown risk factor that may associate with different HPV infections in different populations. Additional studies of the relationship between prostate cancer and other HPV types, notably HPV 33, could be helpful for clarifying the possible role of sexual risk factors.

Agrez, M. V., D. R. Shafren, et al. (1997). "Integrin alpha v beta 6 enhances coxsackievirus B1 lytic infection of human colon cancer cells." Virology **239**(1): 71-7.

Viral entry into host cells depends upon specific interactions between virus attachment proteins and cell surface receptors that enable virus binding and internalization of virus and/or the virus-receptor complex. We have recently reported that the ubiquitous cell surface molecule, decay-accelerating factor (DAF), is a major cell attachment receptor for Coxsackieviruses B1, B3, and B5. However, DAF permits only virus binding and not virus internalization, invoking the presence of secondary or accessory receptors. Among the known receptors for enteroviruses are members of the cell adhesion molecule family known as integrins. In the present study, we found that expression of the epithelial-restricted integrin, alpha v beta 6, on colonic epithelial cells significantly enhanced Coxsackievirus B1-mediated cell lysis. Importantly, the viral-mediated cell killing required the presence of the 11-amino-acid C-terminal cytoplasmic extension unique to the beta 6 subunit, providing the first evidence of regulation of viral infectivity by integrin cytoplasmic domains. These results indicate that alpha v beta 6 expression on intestinal epithelial cells critically affects Coxsackievirus B1 infectivity. This may be essential in the conversion of asymptomatic enterovirus infection into clinically apparent disease.

Ando, T., T. Ishikawa, et al. (2009). "Synergistic effect of HLA class II loci and cytokine gene polymorphisms on the risk of gastric cancer in Japanese patients with Helicobacter pylori infection." Int J Cancer **125**(11): 2595-602.

It has been reported that polymorphisms of human leukocyte antigen (HLA) genes and several cytokine genes are associated with an increased risk of developing gastric cancer (GC). However, the results of studies from different geographic regions, ethnic groups and study groups are inconsistent. The aim of this study was to evaluate the influence of H. pylori infection and host genetic factors on GC susceptibility in Japanese patients with GC. We analyzed genotypes for HLA class I and II, tumor necrosis factor alpha, interleukin (IL)-1beta, IL-1 receptor, IL-4, IL-4Ralpha and IL-10 in 330 H. pylori-infected noncardia patients with GC and 190 H. pylori-infected nonulcer dyspeptic controls. Haplotype analyses indicated that the frequencies of the HLA DRB1*0405 and DQB1*0401 alleles were increased in the patients with intestinal-type GC when compared with controls (both DRB1*0405 and DQB1*0401: p = 0.015, OR = 1.57, 95% CI = 1.09-2.26), but the changes were not statistically significant after correction for multiple comparisons. None of the cytokine gene polymorphisms were associated with GC susceptibility, whether patients with GC were analyzed as a group according to the histological subtype. Of interest was the comparison of controls and patients with intestinal-type GC. The frequency of an IL-10-592AA homozygote showing concomitant carriage of the HLA DRB1*0405-DQB1*0401 haplotype was significantly higher in patients with intestinal-type GC (chi(2) = 6.369, p = 0.0116, p(c) = 0.0464, OR = 2.43, 95% CI = 1.21-4.48). Our results suggest that the HLA class II and IL-10-592A/C polymorphisms synergistically affect the susceptibility to GC development of H. pylori-infected individuals in the Japanese population.

Argent, R. H., R. J. Thomas, et al. (2008). "Toxigenic Helicobacter pylori infection precedes gastric hypochlorhydria in cancer relatives, and H. pylori virulence evolves in these families." Clin Cancer Res **14**(7): 2227-35.

PURPOSE: Helicobacter pylori infection by virulent strains is associated with gastric adenocarcinoma. We aimed to determine whether infection with virulent H. pylori preceded precancerous gastric hypochlorhydria and atrophy in gastric cancer relatives and quantify the extent of virulence factor evolution. EXPERIMENTAL DESIGN: H. pylori strains from 51 Scottish gastric cancer relatives were characterized by genetic fingerprinting and typing the vacuolating cytotoxin

gene (vacA), the cytotoxin-associated gene (cagA), and housekeeping genes. We phenotyped strains by coculture with gastric epithelial cells and assessing vacuolation (microscopy), CagA tyrosine phosphorylation (immunoblot), and interleukin-8 secretion (ELISA). RESULTS: Toxigenic (vacA type s1/m1) H. pylori was associated with precancerous gastric hypochlorhydria (P<0.01). Adult family members with this type of H. pylori had the same strain as currently noncohabiting adult family members in 68% cases, implying acquisition during childhood from each other or a common source. We analyzed different isolates of the same strain within families and showed that H. pylori commonly microevolved to change virulence: this occurred in 22% individuals and a striking 44% cases where the strain was shared within families. Microevolution in vacA occurred by extragenomic recombination and in cagA by this or duplication/deletion. Microevolution led to phenotypic changes in virulence. Passage of microevolved strains could be tracked within families. CONCLUSIONS: Toxigenic H. pylori infection precedes and so likely causes gastric hypochlorhydria, suggesting that virulent H. pylori increases cancer risk by causing this condition. Microevolution of virulence genes is common within families of gastric cancer patients and changes H. pylori virulence.

Balcerczak, E., T. Jankowski, et al. (2005). "Expression of the P65 gene in gastric cancer and in tissues with or without Helicobacter pylori infection." Neoplasma **52**(6): 464-8.

A 65-kDa tumor-associated protein (P65) is a potential non- specific tumor marker expressed by many types of tumor cells. Our recent studies indicate that P65 gene expression is connected with poor prognosis for the patients with colorectal cancer. In the present study P65 gene expression was determined by means of RT-PCR in the group of 22 gastric cancer and adjacent normal gastric mucosa. Its presence was correlated with some parameters of clinical staging. P65 gene expression was also determined in 102 tissue antral gastric endoscopic biopsy specimens from the patients suspected of H. pylori infection. The presence of H. pylori infection was determined by urease test. We found that in the group of gastric cancers, similarly to colorectal cancer, P65 gene expression was connected with poor clinicopathological parameters as T3, lymph nodes and distant metastases. There was no dependence between P65 gene expression and H. pylori infection. However, more often P65 gene expression was detected in the group of infected men than women. There was also a statistically significant dependence between age and P65 gene expression in the group of people above 60 years old. It could be then postulated that P65 gene expression is connected with poor prognosis for the patients suffering from gastric cancer and that this expression does not depend on H. pylori infection.

Baritaki, S., S. Sifakis, et al. (2007). "Overexpression of VEGF and TGF-beta1 mRNA in Pap smears correlates with progression of cervical intraepithelial neoplasia to cancer: implication of YY1 in cervical tumorigenesis and HPV infection." Int J Oncol **31**(1): 69-79.

The screening of neo-angiogenesis related gene expression has uncovered many disrupted molecular pathways which may significantly confer to malignant transformation of various cell types including cervical cells. The objective of the present study was to delineate whether changes in certain gene expression profiles during the malignant conversion of the uterine cervix can be potentially used to predict the clinical course and outcome of the cervical pathology. Total RNA was isolated from Pap smears obtained from healthy females or patients diagnosed with low-grade squamous cervical intraepithelial lesions (LG-SIL), high-grade (HG)-SIL or cervical carcinoma. VEGF, TGF-beta1 and YY1 mRNA expression levels were assessed by QRT-PCR. Confirmation of YY1 protein discrepancy among cervical tissues of different histopathology was performed by immunohistochemistry. All tested genes showed statistically significant expression variations among the indicated groups. VEGF and TGF-beta1 mRNA overexpression was found to be associated with progression from low-grade to high-grade cervical intraepithelial neoplasia (CIN), while YY1 showed constitutively elevated transcript levels in CIN and cervical cancer compared to controls. At the protein level YY1 was also overexpressed in HG-SIL and cancer tissues compared to LG-SIL. Both YY1 transcript and protein overexpression were associated with HPV18- or HPV16-infected samples. Spearman analysis revealed a co-expression pattern for VEGF and TGF-beta1 mRNAs in normal cervix and LG-SIL; however, YY1 expression correlated negatively with VEGF and TGF-beta1 transcript levels upon the onset of the cervical neoplastic transformation. Our findings provide for the first time evidence for the implication of YY1 in uterine cervix carcinogenesis and suggest that VEGF, TGF-beta1 and YY1 could be useful biomarkers of cervical malignant transformation as well as potential targets for therapeutic approaches.

Barreto-Zuniga, R., M. Maruyama, et al. (1997). "Significance of Helicobacter pylori infection as a risk factor in gastric cancer: serological and histological studies." J Gastroenterol **32**(3): 289-94.

We conducted a case-control study to examine the association of Helicobacter pylori

infection as a risk factor in gastric cancer in the Japanese population. Serum IgG antibodies for Helicobacter pylori were determined in 55 consecutive patients with gastric cancer and in 75 age- and sex-matched mass survey subjects and 57 age- and sex-matched cancer-free patients with conditions considered at a high risk for development of gastric cancer (precancerous condition). We examined the histology in all subjects and particular focus was placed on the extent of Helicobacter pylori-associated gastritis. The seroprevalence of Helicobacter pylori in gastric cancer patients (82%) and those with a precancerous condition (89%) was significantly higher ($P < 0.005$) than that in the mass survey subjects (60%). Positive relative risk associations were found for patients with gastric cancer (odds ratio, 3, with 95% confidence intervals of 1.69-5.33) and those with a precancerous condition (odds ratio, 5.66, with 95% confidence intervals 2.66-12.03). Significant differences were found when comparisons were made among the case-control groups who were H. pylori-positive and had inflammatory cell infiltration ($P = 0.0127$). The characteristics of Helicobacter pylori in histologically examined gastric mucosa showed differences between Helicobacter pylori-infected and uninfected persons in all groups. However, for none of these groups was there a significant differences between background mucosa for Helicobacter pylori-infected persons with or without gastric cancer. Helicobacter pylori seroprevalence is strongly associated with an increased risk of gastric cancer and with a precancerous condition; histological investigation did not define additional factors that might be associated with increased cancer risk.

Bjorge, T., A. Engeland, et al. (2002). "Human papillomavirus infection as a risk factor for anal and perianal skin cancer in a prospective study." Br J Cancer **87**(1): 61-4.

Human papillomavirus has emerged as the leading infectious cause of cervical and other anogenital cancers. We have studied the relation between human papillomavirus infection and the subsequent risk of anal and perianal skin cancer. A case-cohort study within two large Nordic serum banks to which about 760 000 individuals had donated serum samples was performed. Subjects who developed anal and perianal skin cancer during follow up (median time of 10 years) were identified by registry linkage with the nationwide cancer registries in Finland and Norway. Twenty-eight cases and 1500 controls were analysed for the presence of IgG antibodies to HPV 16, 18, 33 or 73, and odds ratios of developing anal and perianal skin cancer were calculated. There was an increased risk of developing anal and perianal skin cancer among subjects seropositive for HPV 16 (OR=3.0; 95%CI=1.1-8.2) and HPV 18 (OR=4.4; 95%CI=1.1-17). The highest risks were seen for HPV 16 seropositive patients above the age of 45 years at serum sampling and for patients with a lag time of less than 10 years. This study provides prospective epidemiological evidence of an association between infection with HPV 16 and 18 and anal and perianal skin cancer.

Bodey, G. P., E. Anaissie, et al. (1993). "Role of granulocyte-macrophage colony-stimulating factor as adjuvant therapy for fungal infection in patients with cancer." Clin Infect Dis **17**(4): 705-7.

A pilot study was conducted to evaluate the role of granulocyte-macrophage colony-stimulating factor (GM-CSF) as adjuvant therapy for fungal infections in patients with cancer. GM-CSF was added to amphotericin B in the treatment of cancer patients with proven major-organ or disseminated fungal infection. The dose of GM-CSF ranged from 100 to 750 micrograms/(m2.d). Of eight evaluable patients, six had a neutrophil response to GM-CSF. Four of these patients were completely cured of the fungal infection, and two had a partial response. However, a capillary-leak syndrome developed in three patients, an adverse effect suggesting that the dose of GM-CSF was excessive.

Branca, M., M. Ciotti, et al. (2008). "Predicting high-risk human papillomavirus infection, progression of cervical intraepithelial neoplasia, and prognosis of cervical cancer with a panel of 13 biomarkers tested in multivariate modeling." Int J Gynecol Pathol **27**(2): 265-73.

Comprehensive multivariate models were used to disclose whether any of our previously analyzed 13 markers would be independent predictors of intermediate end point markers in cervical carcinogenesis. The expression of the following biomarkers, E-cadherin, extracellular signal-regulated kinase 1, 67-kd laminin receptor (LR67), matrix metalloproteinase 2, tissue inhibitor of metalloproteinase 2, nuclear factor-kappaB, nm23-H1, p16, proliferating cell nuclear antigen, survivin, human telomerase reverse transcriptase, topoisomerase 2alpha, and vascular endothelial growth factor (VEGF) C in 150 cervical cancer (CC) and 152 cervical intraepithelial neoplasia (CIN) lesions were determined immunohistochemically. Multivariate models were constructed to test predictive power of the markers for 3 outcomes: (1) high-grade CIN, (2) high-risk human papillomavirus (HR-HPV), and (3) CC survival. Performance indicators were calculated and compared by the areas under receiver operating characteristic (ROC) curve. Three marker panels were identified consisting of 5

independent predictors of CIN2 (E-cadherin, extracellular signal-regulated kinase 1, LR67, topoisomerase 2alpha, and VEGF-C), 3 predictors of HR-HPV (survivin, p16, and human telomerase reverse transcriptase), and 2 predictors of CC survival (nm23-H1 and tissue inhibitor of metalloproteinase 2). In predicting CIN2, the best balance between sensitivity (SE) and specificity (SP) was obtained by combining the 2 most powerful predictors in panel 1 (VEGF-C and LR67), giving the area under ROC curve, 0.897 (95% confidence interval [CI], 0.847-0.947); odds ratio, 86.27 (95% CI, 19.71-377.47); SE, 86.0%; SP, 93.3%; positive predictive value (PPV), 99.1%; and negative predictive value (NPV), 43.1%. In a hypothetical screening setting (10,000 women; CIN2 prevalence, 1%), this marker combination should theoretically detect CIN2 with 86.0% SE, 100% SP, 99.1% PPV, and 99.6% NPV, area under ROC curve of 0.930 (95% CI, 0.909-0.951), and odds ratio, 29998.0 (95% CI, 7,879.0-37,338.0). Combining 2 markers (LR67 and VEGF-C) enables accurate detection of high-grade CIN in a clinical setting. However, testing the performance of this marker combination in a screening setting necessitates their analysis in cytological samples.

Brandt, K., P. B. Singh, et al. (2007). "Interleukin-21: a new modulator of immunity, infection, and cancer." Cytokine Growth Factor Rev **18**(3-4): 223-32.

Interleukin-21 is the most recently discovered member of the type-I cytokine family. Structurally, IL-21 shows homology to IL-2, IL-4, and IL-15 proteins. IL-21 shares the common gamma-chain with the other three cytokines but, in addition, binds to a unique IL-21Ralpha chain, and activates the JAK/STAT pathway. IL-21 is mainly produced by activated T-cells but targets a broad range of lymphoid and myeloid cells of the immune system and therefore is able to regulate innate and acquired immune responses. This review intends to give the reader an overview of the recent findings concerning the biology of IL-21 and its physiological role in immunity, infection, and cancer.

Brenner, H., G. Bode, et al. (2000). "Helicobacter pylori infection among offspring of patients with stomach cancer." Gastroenterology **118**(1): 31-5.

BACKGROUND & AIMS: A positive family history is associated with an increased risk of stomach cancer. We compared the prevalence of Helicobacter pylori infection, a known risk factor for stomach cancer, between subjects with and without parental history of stomach cancer to evaluate a potential role of H. pylori infection in familial aggregation of stomach cancer. METHODS: A total of 1351 men and women aged 30-74 years who participated in the German Health and Nutrition Survey conducted in the western part of Germany in 1987-1988 were included in the study. Detailed information on sociodemographic factors, nutritional factors, and parental history of cancer was obtained by standardized interviews. Serum samples were analyzed for immunoglobulin G antibodies against H. pylori by enzyme-linked immunosorbent assay. RESULTS: The prevalence of H. pylori infection was much higher (69%) among subjects with a parental history of stomach cancer than among other subjects (44%). This association persisted after control for potential confounders by multiple logistic regression (adjusted odds ratio, 2.7; 95% confidence interval, 1.3-5.9), and was particularly strong among subjects below age 55 (adjusted odds ratio, 5.1; 95% confidence interval, 1.6-16.1). CONCLUSIONS: These results suggest that familial aggregation of stomach cancer may be explained at least partly by familial clustering of H. pylori infection.

Buyru, N., A. Tezol, et al. (2006). "Coexistence of K-ras mutations and HPV infection in colon cancer." BMC Cancer **6**: 115.

BACKGROUND: Activation of the ras genes or association with human papillomavirus infection have been extensively studied in colorectal cancer. However, the correlation between K-ras mutations and HPV in colorectal cancer has not been investigated yet. In this study we aimed to investigate the presence of K-ras mutations and their correlation with HPV infection in colon cancer. METHODS: K-ras mutations were analyzed by a mutagenic PCR assay and digestion with specific restriction enzymes to distinguish the wild-type and mutant codons. HPV infection was analyzed by PCR amplification and hybridization with specific probes by Southern blotting. Statistical analyses were performed by the chi-square and Fisher's exact tests RESULTS: HPV gene fragments were detected in 43 tumors and 17 normal tissue samples. HPV 18 was the prevalent type in the tumor tissue. A mutation at codon 12 of the K-ras gene was present in 31 patients. 56% of the HPV-positive tumors also harbored a K-ras mutation. Codon 13 mutations were not observed. These data indicate that infection with high risk HPV types and mutational activation of the K-ras gene are frequent events in colorectal carcinogenesis. CONCLUSION: Our findings suggest that mutational activation of the K-ras gene is a common event in colon carcinogenesis and that HPV infection may represent an important factor in the development of the premalignant lesions leading to the neoplastic phenotype.

Camargo, M. C., M. C. Yepez, et al. (2004). "Age at acquisition of Helicobacter pylori infection:

comparison of two areas with contrasting risk of gastric cancer." Helicobacter **9**(3): 262-70.

BACKGROUND: Helicobacter pylori infection is usually acquired during childhood and is a known risk factor for the development of gastric malignancies in adulthood. It has been reported that early age at first infection may determine a neoplastic outcome in adults. The purpose of this study was to determine the prevalence of Helicobacter pylori infection in children residing in areas with high (Pasto) and low risk (Tumaco) of gastric cancer in Colombia to evaluate whether differences in the age of acquisition of H. pylori infection were present in the two populations. MATERIALS AND METHODS: The study sample was based on a census taken in 1999. Using the (13)C-urea breath test, we compared the prevalence of H. pylori infection among children aged 1-6 years. RESULTS: Among 345 children in Pasto, 206 (59.7%) were H. pylori-positive, compared with 188 (58.6%) among 321 children in Tumaco. The two populations share a common pattern of very early age at infection and marked increase in prevalence during the first 4 years of life. No differences in any one year were observed when comparing the two groups. CONCLUSIONS: The prevalence of infection was similarly high and increased with age in both populations. In these populations the age of acquisition of H. pylori after 1 year of age does not appear to be a primary factor responsible for the differences in the rates of gastric cancer incidence in adults. Previous findings in adults showed lower prevalence of the most virulent genotypes in Tumaco compared to Pasto, and bacterial virulence may play a key role in determining cancer outcome.

Chang, Y. W., Y. S. Han, et al. (2002). "Role of Helicobacter pylori infection among offspring or siblings of gastric cancer patients." Int J Cancer **101**(5): 469-74.

A positive family history is an increased risk factor for gastric cancer within family members, and one of the possible causes of this is the intrafamilial clustering of Helicobacter pylori infection. Our study examined the prevalence of H. pylori infection, serum antibodies to CagA and VacA and atrophic gastritis and/or intestinal metaplasia in the offspring or siblings of gastric cancer patients. A total of 726 subjects included 300 relatives of 300 separate gastric cancer patients and 426 controls. All subjects underwent upper gastrointestinal endoscopic examination with a rapid urease test. Blood samples were obtained to test for the presence of serum antibodies to the CagA and VacA proteins of H. pylori. The prevalence of H. pylori infection was higher in relatives of cancer patients (75.3%) than in controls (60.1%), and the adjusted odds ratio was 2.1 (95% CI 1.5-2.9). When either siblings or 2 or more family members were gastric cancer patients, the prevalence of H. pylori infection was much higher compared to the prevalence in controls. There was no specific relationship between CagA and VacA, and H. pylori infection. Atrophic gastritis and/or intestinal metaplasia were more frequently found in H. pylori-infected relatives of cancer patients (26.1%) than in H. pylori-infected controls (12.9%). These results strongly support a role for H. pylori infection in familial aggregation of gastric cancer. The prophylactic eradication of H. pylori infection in the offspring or siblings of gastric cancer patients may be clinically beneficial.

Chen, A., C. N. Li, et al. (2004). "Risks of interleukin-1 genetic polymorphisms and Helicobacter pylori infection in the development of gastric cancer." Aliment Pharmacol Ther **20**(2): 203-11.

BACKGROUND: The host genetic factors that determine the clinical outcomes of Helicobacter pylori-infected individuals remain unclear. AIM: To elucidate the risks of host interleukin-1 (IL-1) genetic polymorphisms and H. pylori infection in the development of gastric cancer. METHODS: In a case-control study of 164 controls and 142 patients with gastric cancer, the IL-1B-511 biallelic polymorphisms and the IL-1RN penta-allelic variable number of tandem repeats were genotyped. RESULTS: The carriage of IL-1RN*2, male gender, old age and H. pylori infection independently increased the risk of gastric cancer, with odds ratios of 3.3 [95% confidence interval (CI), 1.4-7.7], 2.1 (95% CI, 1.2-3.8), 5.3 (95% CI, 3.1-9.0) and 2.2 (95% CI, 1.3-3.8), respectively. H. pylori-infected individuals who were carriers of IL-1RN*2 showed increased risks of both intestinal and diffuse types of gastric cancer, with odds ratios of 11.0 and 8.7, respectively. In addition, these individuals also had a higher score of intestinal metaplasia in the corpus than did uninfected non-carriers. CONCLUSIONS: This study is the first to verify IL-1RN*2 as an independent factor governing the development of gastric cancer in Asian individuals. A combination of H. pylori testing and host genotyping may target the eradication of H. pylori to high-risk individuals.

Chen, D., B. Stenstrom, et al. (2007). "Does Helicobacter pylori infection per se cause gastric cancer or duodenal ulcer? Inadequate evidence in Mongolian gerbils and inbred mice." FEMS Immunol Med Microbiol **50**(2): 184-9.

A role for Helicobacter pylori infection in the development of gastric cancer in humans is well established; however, evidence for its carcinogenicity in animals remains inadequate. Mongolian gerbils and mice are commonly used to investigate the

carcinogenicity of H. pylori, yet it is unclear whether H. pylori infection per se causes gastric cancer or duodenal ulcers in these animal models. Gastric adenocarcinoma in the gerbils was reported over 10 years ago, but this species has proved an unreliable model for studying H. pylori infection-associated gastric cancer. Helicobacter pylori infection alone appears insufficient to induce gastric cancer in these animals; additional carcinogenic insult is required. The development of invasive adenocarcinoma in inbred mice is rare regardless of the mouse or bacterial strain, and many long-term studies have failed to induce gastric cancer in these animals. Helicobacter pylori infection is also an established causative factor for duodenal ulcer in humans. However, few studies have attempted to develop animal models of H. pylori infection-induced duodenal ulcer. We therefore conclude that both Mongolian gerbils and inbred mice may be inadequate models for studying H. pylori infection-associated gastric cancer and that there is no animal model of H. pylori infection-induced duodenal ulcer.

Chen, M., A. Lee, et al. (1993). "Immunisation against gastric infection with Helicobacter species: first step in the prophylaxis of gastric cancer?" Zentralbl Bakteriol **280**(1-2): 155-65.

The discovery of the gastric bacterium, Helicobacter pylori and the demonstration of its role in the pathogenesis of gastroduodenal disease, has been one of the major microbiological advances in the last decade. Recent demonstration of long term infection with this bacterium as a risk factor in gastric carcinoma suggests that intervention in a disease of major morbidity and mortality is possible. Using a model of Helicobacter infection in mice it has been shown that oral immunisation with a sonicate of Helicobacter felis plus the adjuvant cholera toxin results in protection against an oral challenge with large numbers of viable bacteria. The success of the immunising regimen has been shown to correlate with the development of local immunity. Formulation of equivalent safe vaccines of H. pylori will make possible the immunisation of children in countries such as China, Japan and Columbia and so prevent the establishment of long term inflammation and thus significantly reduce the incidence of gastric cancer in those societies. This animal model is proposed as a major tool in the development of effective oral immunisation.

Cheng, Y. W., H. L. Chiou, et al. (2001). "The association of human papillomavirus 16/18 infection with lung cancer among nonsmoking Taiwanese women." Cancer Res **61**(7): 2799-803.

Lung cancer is the leading cause of cancer death in Taiwanese women since 1982. High lung cancer mortality ratio of male:female in Taiwan (2:1) was observed, although less than 10% of female lung cancer patients are smokers. Until now, the etiological factor remains unknown. We hypothesize that high-risk human papillomavirus (HPV) 16/18 may be associated with lung cancer development based on high prevalence of p53 negative immunostainings in female lung tumors compared with that of male lung tumors. In this study, 141 lung cancer patients and 60 noncancer control subjects were enrolled to examine whether HPV 16/18 DNA existed in lung tumor and normal tissues by nested PCR and in situ hybridization (ISH), respectively. The concordant detection of HPV 16 and 18 DNA between nested PCR and ISH method was 73 and 85.5%, respectively. Our data showed that 77 (54.6%) of 141 lung tumors had HPV 16/18 DNA compared with 16 (26.7%; P = 0.0005) of 60 noncancer control subjects. In addition, ISH data showed that HPV 16/18 DNA was uniformly located in lung tumor cells, but not in the adjacent nontumor cells. When study subjects were stratified by gender, age, and smoking status, nonsmoking female lung cancer patients who were older than 60 years old had significantly high prevalence of HPV 16/18 infection. The odds ratio of HPV 16/18 infection of nonsmoking female lung cancer patients is much higher at 10.12 (95% confidence interval, 3.88-26.38) compared with 1.98 (95% confidence interval, 0.84-4.76) of nonsmoking male lung cancer patients. This result strongly suggests that HPV infection is associated with lung cancer development of nonsmoking female lung cancer patients. The high prevalence of HPV 16/18 infection may explain to a certain extent why Taiwanese women nonsmokers had a higher lung cancer mortality rate.

Chualain, C. N., M. Hayes, et al. (2009). "Hematodinium sp. in Irish Cancer pagurus fisheries: infection intensity as a potential fisheries management tool." Dis Aquat Organ **83**(1): 59-66.

Infection of Cancer pagurus by a parasitic dinoflagellate of the genus Hematodinium is described for the first time in Ireland. An industry-based monitoring programme was established to determine seasonality of infection intensity and prevalence in the country's 3 largest brown crab fisheries in the southwest, north and southeast. The parasite was present in all areas for the majority of sampling periods, with highest prevalences recorded in pre-recruit animals of both sexes. Microscopic examination of haemolymph revealed trophont, plasmodial and dinospore stages of the parasite. Overall prevalence in males (16%) was higher than in females (9%). Prevalence of Hematodinium sp.

infection ranged from 0 to 51%, but a distinct seasonal trend was not apparent. Infection intensity was seasonal with significantly higher peaks occurring in late autumn/early winter months than in other quarters, corresponding to industry reports of moribund and dead pink-shelled crabs in commercial catches. We postulate that seawater temperature or a temperature-linked process is a key factor in triggering the final stages of infection, as significant autumn peaks were followed by a reduction in infection intensity as temperature decreased in the late winter/early spring months with no increase in intensity again until the following autumn. We propose that infection intensity, rather than prevalence, provides a more appropriate indication of the period when there is greatest potential for biological and economic impacts; the parameter's application as a fisheries management tool is discussed.

Chuang, S. C., C. La Vecchia, et al. (2009). "Liver cancer: descriptive epidemiology and risk factors other than HBV and HCV infection." Cancer Lett **286**(1): 9-14.

The incidence of liver cancer is high in all low-resource regions of the world, with the exception of Northern Africa and Western Asia. The estimated worldwide number of new cases of liver cancer in 2002 is 600,000, of which 82% are from developing countries. Given the poor survival from this disease, the estimated number of deaths is similar to that of new cases. Hepatocellular carcinoma (HCC) is the main form of liver cancer. A part from chronic infections with Hepatitis B and Hepatitis C viruses, which are the main causes of HCC, contamination of foodstuff with aflatoxins, a group of mycotoxins produced by the fungi Aspergillus flavus and Aspergillus parasiticus, is an important contributor to HCC burden in many low-income country. Alcoholic cirrhosis is an important risk factor for HCC in populations with low prevalence of HBV and HCV infection, and the association between tobacco smoking and HCC is now established. Diabetes is also related to an excess risk of HCC and the increased prevalence of overweight and obesity likely contributes to it. The second most important type of liver cancer is cholangiocarcinoma, whose main known cause is infestation with the liver flukes, Opistorchis viverrini and Clonorchis sinensis, which is frequent in some areas in South-East Asia. Angiosarcoma is a rare form of liver cancer whose occurence is linked to occupational exposure to vinyl chloride.

Ciardiello, F., C. Bianco, et al. (1993). "Infection with a transforming growth factor alpha anti-sense retroviral expression vector reduces the in vitro growth and transformation of a human colon cancer cell line." Int J Cancer **54**(6): 952-8.

Transforming growth factor alpha (TGF alpha) is a growth factor produced by colon cancer cells which may function as an autocrine growth regulator. Therefore, the proliferation and transformation of colon cancer cells might be attenuated by blocking the production of endogenous TGF alpha. GEO cells, from a human colon carcinoma cell line that expresses TGF alpha and functional epidermal growth factor (EGF) receptors, were infected with a replication-defective, recombinant amphotropic retroviral expression vector containing the neomycin-resistance gene and a 435-bp ApaI-EcoRI coding fragment of the human TGF alpha cDNA oriented in the 3' to 5' direction under the transcriptional control of the heavy-metal-inducible mouse metallothionein I promoter. Following antibiotic selection, G418-resistant colonies were pooled and expanded into a cell line (GEO TGF alpha AS cells). A 50 to 70% inhibition in the production of secreted and cell-associated TGF alpha protein was observed in GEO TGF alpha AS cells that had been maintained in CdCl2-supplemented medium. Moreover, a growth inhibition of 70% and 50% was observed in CdCl2-treated GEO TGF alpha AS cells under anchorage-dependent and anchorage-independent culture conditions, respectively. In contrast, CdCl2 treatment of parental GEO cells had no significant effect upon these parameters. Our results suggest that TGF alpha may be involved in modulating the in vitro cell growth and transformation of human colon cancer cells that express both this growth factor and its cognate receptor.

Clarke, P., S. M. Meintzer, et al. (2001). "Caspase 8-dependent sensitization of cancer cells to TRAIL-induced apoptosis following reovirus-infection." Oncogene **20**(47): 6910-9.

TRAIL (TNF-related apoptosis-inducing ligand) induces apoptosis in susceptible cells by binding to death receptors 4 (DR4) and 5 (DR5). TRAIL preferentially induces apoptosis in transformed cells and the identification of mechanisms by which TRAIL-induced apoptosis can be enhanced may lead to novel cancer chemotherapeutic strategies. Here we show that reovirus infection induces apoptosis in cancer cell lines derived from human breast, lung and cervical cancers. Reovirus-induced apoptosis is mediated by TRAIL and is associated with the release of TRAIL from infected cells. Reovirus infection synergistically and specifically sensitizes cancer cell lines to killing by exogenous TRAIL. This sensitization both enhances the susceptibility of previously resistant cell lines to

TRAIL-induced apoptosis and reduces the amount of TRAIL needed to kill already sensitive lines. Sensitization is not associated with a detectable change in the expression of TRAIL receptors in reovirus-infected cells. Sensitization is associated with an increase in the activity of the death receptor-associated initiator caspase, caspase 8, and is inhibited by the peptide IETD-fmk, suggesting that reovirus sensitizes cancer cells to TRAIL-induced apoptosis in a caspase 8-dependent manner. Reovirus-induced sensitization of cells to TRAIL is also associated with increased cleavage of PARP, a substrate of the effector caspases 3 and 7.

Clarke, P. and K. L. Tyler (2007). "Down-regulation of cFLIP following reovirus infection sensitizes human ovarian cancer cells to TRAIL-induced apoptosis." Apoptosis **12**(1): 211-23.

Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) shows promise as a chemotherapeutic agent. However, many human cancer cells are resistant to killing by TRAIL. We have previously demonstrated that reovirus infection increases the susceptibility of human lung (H157) and breast (ZR75-1) cancer cell lines to TRAIL-induced apoptosis. We now show that reovirus also increases the susceptibility of human ovarian cancer cell lines (OVCAR3, PA-1 and SKOV-3) to TRAIL-induced apoptosis. Reovirus-induced increases in susceptibility of OVCAR3 cells to TRAIL require virus uncoating and involve increased activation of caspases 3 and 8. Reovirus infection results in the down-regulation of cFLIP (cellular FLICE inhibitory protein) in OVCAR3 cells. Down-regulation of cFLIP following treatment of OVCAR3 cells with antisense cFLIP oligonucleotides or PI3 kinase inhibition also increases the susceptibility of OVCAR3 cells to TRAIL-induced apoptosis. Finally, over-expression of cFLIP blocks reovirus-induced sensitization of OVCAR3 cells to TRAIL-induced apoptosis. The combination of reovirus and TRAIL thus represents a promising new therapeutic approach for the treatment of ovarian cancer.

de Martel, C., A. E. Llosa, et al. (2008). "Helicobacter pylori infection and development of pancreatic cancer." Cancer Epidemiol Biomarkers Prev **17**(5): 1188-94.

BACKGROUND: Infection with Helicobacter pylori is an established risk factor for gastric cancer. Results from two studies suggest that it may also be a risk factor for pancreatic cancer. METHODS: We conducted a nested case control study among 128,992 adult subscribers to the Kaiser Permanente Medical Care Program who had been enrolled in a multiphasic health checkup from 1964 to 1969. Serum collected during the checkup was maintained frozen, and subjects were followed for cancer. Cases consisted of 104 randomly selected subjects among 507 who developed pancreatic cancer in the cohort. Controls consisted of 262 pancreatic cancer-free subjects from a pool of 730 controls previously tested for studies conducted on this cohort. Controls were individually matched to cases on age, gender, race, site, and date of multiphasic health checkup. Control sera were compared with cases for antibodies to H. pylori and the CagA protein. The effects of smoking, alcohol consumption, obesity, and years of education were also investigated. RESULTS: Neither H. pylori [odds ratio (OR), 0.85; 95% confidence interval (95% CI), 0.49-1.48] nor its CagA protein (OR, 0.96; 95% CI, 0.48-1.92) was associated with subsequent development of pancreatic cancer. Smoking (OR, 2.09; 95% CI, 1.17-3.74) and greater number of years of education (OR, 2.13; 95% CI, 1.23-3.69) were risk factors for pancreatic cancer, whereas alcohol consumption and obesity were not. CONCLUSION: Our results suggest that H. pylori infection is not associated with development of pancreatic cancer.

Deguchi, R., A. Takagi, et al. (2001). "Association between CagA+ Helicobacter pylori infection and p53, bax and transforming growth factor-beta-RII gene mutations in gastric cancer patients." Int J Cancer **91**(4): 481-5.

We assessed the possible association between CagA+ Helicobacter pylori infection and gastric carcinogenesis in gastric cancer patients. Gastric biopsy specimens were obtained from 64 patients with gastric cancer and were histologically classified into intestinal and diffuse types. H. pylori infection was determined by cultivation, flaA-PCR and serum antibody against CagA. p53, BAX and transforming growth factor-beta-RII (TGFbeta-RII) gene mutations were analyzed by PCR-SSCP and direct sequencing. Intestinal and diffuse types of cancer were detected in 45 and 19 patients, respectively. H. pylori infection was found in 55 (85.9%) of 64 patients. There was no significant difference in H. pylori positivity between intestinal and diffuse types. However, the CagA antibody was positive in 15 (78.9%) of 19 patients with the diffuse type and in 22 (48.9%) of 45 patients with the intestinal type ($p = 0.030$). Among the 55 H. pylori-positive cases, 11 (29.7%) of the 37 patients in the CagA+ group were found to have p53 alterations, compared with 2 (11.1%) in the 18 CagA- group ($p = 0.182$). Moreover, among the 64 gastric cancer patients, p53 alterations were more frequently found in the CagA+ group (29.7%) than in the H. pylori-positive CagA- and H. pylori-negative groups (7.4%; $p = 0.033$). BAX gene mutations were found in 19

(29.7%) of 64 patients and there was no relationship among CagA seropositivity, cancer stages and histopathological phenotypes. In contrast, the TGFbeta-RII gene mutation was only detected in one CagA- patient. The results suggest that CagA+ H. pylori infection may have an important role in the development of gastric cancer patients with p53 mutations

Dillner, J., P. Knekt, et al. (1998). "Sero-epidemiological association between human-papillomavirus infection and risk of prostate cancer." Int J Cancer **75**(4): 564-7.

Some epidemiological studies of prostate cancer have suggested the existence of a sexually transmitted risk factor, and some studies have reported the presence of human papillomavirus (HPV) DNA in prostate-cancer tissue. To perform a sero-epidemiological evaluation of whether HPV infection is associated with increased risk for prostate cancer, we performed a nested case-control study within a serum bank containing samples from 20,243 healthy Finnish men. We identified 165 cases of prostate cancer that were diagnosed up to 24 years after donation of the serum sample. Two control subjects per case were selected, matched for gender, age and municipality of residence. Serum samples were analyzed for the presence of IgG antibodies against 4 HPV types and against Chlamydia. The presence of antibodies against HPV type 18 was associated with a 2.6-fold increased risk of developing prostate cancer during follow-up ($p < 0.005$). HPV type 16 tended to be associated with subsequent prostate-cancer occurrence (relative risk: 2.4, $p = 0.06$), whereas seropositivity for HPV type 11 or type 33 or for Chlamydia was not associated with risk. The results suggest that infection with oncogenic HPV might be involved in the etiology of a minority of prostate cancers.

Dillner, J., M. Lehtinen, et al. (1997). "Prospective seroepidemiologic study of human papillomavirus infection as a risk factor for invasive cervical cancer." J Natl Cancer Inst **89**(17): 1293-9.

BACKGROUND: Major risk factors for invasive cervical cancer include infection with human papillomavirus (HPV), infection with other sexually transmitted pathogens (e.g., Chlamydia trachomatis), and smoking. Since exposures to these risk factors can be related, the contribution of any single factor to cervical carcinogenesis has been difficult to assess. We conducted a prospective study to define the role of HPV infection in cervical carcinogenesis, with invasive cancer as an end point. METHODS: A nested case-control study within a joint cohort of 700,000 Nordic subjects was performed. The 182 women who developed invasive cervical cancer during a mean follow-up of 5 years were matched with 538 control women on the basis of age and time of enrollment. Serum samples taken at enrollment were analyzed for evidence of tobacco use (i.e., cotinine levels); for antibodies against HPV types 16, 18, and 33; and for antibodies against C. trachomatis. Relative risks (RRs) were estimated by use of conditional logistic regression. RESULTS: Presence of antibodies against HPV in serum (seropositivity) was associated with an increased risk of cervical cancer, and adjustment for smoking and for C. trachomatis seropositivity did not affect this finding (RR = 2.4; 95% confidence interval [CI] = 1.6-3.7). HPV16 seropositivity was associated primarily with an increased risk of squamous cell carcinoma (RR = 3.2; 95% CI = 1.7-6.2). In contrast, risk associated with HPV18 seropositivity tended to be higher for cervical adenocarcinoma (RR = 3.4; 95% CI = 0.8-14.9). In populations with a low prevalence of antibodies against C. trachomatis, the HPV16-associated risk of cervical cancer was very high (RR = 11.8; 95% CI = 3.7-37.0); in contrast, in populations with a high prevalence of antibodies against C. trachomatis, no excess risk was found. CONCLUSION: Past infection with HPV16 increases the risk of invasive cervical squamous cell carcinoma, most clearly seen in populations with a low prevalence of sexually transmitted diseases.

Egi, Y., M. Ito, et al. (2007). "Role of Helicobacter pylori infection and chronic inflammation in gastric cancer in the cardia." Jpn J Clin Oncol **37**(5): 365-9.

BACKGROUND: Helicobacter pylori-induced gastritis is an important factor for gastric carcinogenesis. However, it is still controversial whether it is also applicable for cardiac cancer development. Recently, we reported that H. pylori is an important factor for the induction of cardiac inflammation. We examined the status of H. pylori-induced gastritis in patients with cardiac cancer. METHODS: Seventy-five Japanese patients (58 men; mean age, 64.2 years) with cardiac cancer were studied. Cardiac cancer was defined as that mainly located within 2 cm from the squamo-columnar junction (SCJ). Histological gastritis including the cardiac region was evaluated using the biopsy or surgically resected sections. Cardiac inflammation was evaluated at 1 cm distal from SCJ in lesser curvature. Sera were collected and several markers were evaluated. The status of H. pylori infection was evaluated by histology and serum antibodies. Expressions of cytokeratins were examined by immunohistochemical analysis. RESULTS: Out of 75 patients with cardiac cancer, H. pylori was positive in 71 (95%) patients. The cardiac inflammation was examined in 30 patients (26 with H. pylori and four

without H. pylori infection) and we found cardiac inflammation was present in all cases with H. pylori infection. Histologically, H. pylori-related gastritis was also found in the gastric corpus and antrum. Serological data were consistent with the presence of chronic atrophic gastritis. Intestinal metaplasia was found in 18 cases in the cardiac mucosa, and their cytokeratin 7/20 pattern was judged as a gastric pattern in all cases. CONCLUSION: H. pylori infection is closely associated with cardiac cancer.

el-All, H. S., A. Refaat, et al. (2007). "Prevalence of cervical neoplastic lesions and Human Papilloma Virus infection in Egypt: National Cervical Cancer Screening Project." Infect Agent Cancer **2**: 12.

BACKGROUND: Data from Egyptian studies provide widely varying estimates on the prevalence of pre-malignant and malignant cervical abnormalities and human papilloma virus (HPVs) infection. To define the prevalence and risk factors of pre-invasive and invasive cervical cancer (cacx), a community based full-scale cross sectional, household survey including 5453 women aged between 35 and 60 years was conducted. METHODS: The study period was between February 2000 and December 2002. Initially, conventional Papanicolaou (Pap) smears were evaluated using the Bethesda system (TBS), followed by colposcopic guided biopsy (CGB) for all epithelial abnormalities (EA). In a third step, HPV was tested on all EA by in-situ hybridization (ISH) using first the broad spectrum HPV probe recognizing HPVs 6, 11, 16, 18, 30, 31, 35, 45, 51 and 52 followed by subtyping with probes 6/11, 16/18 and 31/33. Lastly, unequivocal cases were immunostained for herpes simplex type-2 (HSV-2), cytomegalovirus (CMV), and human immunodeficiency virus (HIV). RESULTS: EA representing 7.8% (424/5453), were categorized into atypical squamous cell of undetermined significance (ASCUS) (34.4%), atypical glandular cell of undetermined significance (AGCUS) (15.3%), combined ASCUS and AGCUS (3.1%), low grade squamous intraepithelial lesions (SIL) (41.0%), high grade SIL (5.2%) and invasive lesions (1%). CGB of EA (n = 281) showed non neoplastic lesions (12.8%), atypical squamous metaplasia (ASM) (19.2%), cervical intraepithelial neoplasia I (CIN) (44.4%), CIN II (4.4%), CINIII (2.8%), endocervical lesions (5.2%), combined squamous and endocervical lesions (10.0%), invasive squamous cell carcinoma (SCC) (0.02%) and extranodal marginal zone B cell lymphoma (MZBCL) (0.02%). The overall predictive value of cytology was 87% while the predictive value for high grade lesions was 80%. On histological basis, HPVs were present in 94.3% of squamous lesions while it was difficult to be identified in endocervical ones. ISH revealed positivity for pan HPV in 65.9% of the studied biopsies (n = 217), with incorporation of the viral genome HPV 6/11, 16/18 and 31/33 in 11.1%, 33.3% and 17.1% respectively. Multiple HPVs infections were identified in 0.02%. CONCLUSION: Pre-invasive high grade lesions and invasive cervical carcinoma represent 0.5% and 0.04% respectively in Egyptian women. HPV mostly 16/18 as a risk factor ($p < 0.001$), was frequently associated with mixed infections ($p < 0.001$) and bilharzial infestation ($p < 0.001$).

Endo, S., T. Ohkusa, et al. (1995). "Detection of Helicobacter pylori infection in early stage gastric cancer. A comparison between intestinal- and diffuse-type gastric adenocarcinomas." Cancer **75**(9): 2203-8.

BACKGROUND: Helicobacter pylori (H pylori) infection has been suggested to be a risk factor for gastric carcinogenesis. However, those previous studies have been concerned with advanced cancer cases. To the authors' knowledge, no detailed investigation on the prevalence of H pylori in early stage gastric cancer tissue has been performed. The relationship between early stage gastric cancer and the prevalence of H pylori was studied by a immunohistochemical staining analysis. METHODS: Sixty-eight patients who were endoscopically and surgically diagnosed as having early stage gastric cancer were enrolled in this study. All tissue specimens were obtained from patients by endoscopic biopsy, and were classified histopathologically as the intestinal-type of early stage gastric cancer in 34 patients (male-to-female ratio, 28:6; age, 64 +/- 11 years) and the diffuse-type of early stage gastric cancer (male-to-female ratio, 23:11; age, 57 +/- 14 years) in the other 34 patients. The amount of H pylori in tissue samples was graded from 0 (no characteristic bacteria) to 3 (numerous bacteria) using the fluorescent microscopic and an immunohistochemical technique. RESULTS: Twenty-nine of the 34 cases of the intestinal-type of gastric cancer had H pylori infection, as compared with 11 of the 34 cases of diffuse-type early stage gastric cancer. A significantly higher incidence (85%; $P < 0.001$) of H pylori infection and, thus, higher grading scores of the number of H pylori were found in the intestinal-type early stage gastric cancer. CONCLUSIONS: These findings suggest that the infection of H pylori may have a crucial relationship to the early stages of carcinogenesis of intestinal-type gastric cancer.

Fioredda, F., A. R. Gigliotti, et al. (2005). "HCV infection in very-long-term survivors after cancer chemotherapy and bone marrow transplantation: a single-center experience." J Pediatr Hematol Oncol **27**(9): 481-5.

The long-term evolution of hepatitis C virus (HCV) infection in oncologic and/or transplanted patients is still unknown. Patients treated for cancer are different from the general HCV-infected population because of the immunosuppression and the hepatotoxic treatments, which act as co-factors of liver damage. Recently it was observed that antimetabolites play a role in accelerating the process of hepatic fibrosis. The aims of this retrospective study were to describe the clinical course of chronic hepatitis C acquired during anticancer treatment in a group of patients referred to a single center, and to correlate the course of hepatic disease to the type of treatment they received. Among the 17 children who underwent very long follow-up (range 10-18.5 years), the authors identified a group with more active hepatic cytolysis through the serial observation of mean ALT values, HCV RNA determination, and histologic data when available. During follow-up, none of them developed hepatic failure, cirrhosis, or hepatocarcinoma. No single risk factor, such as exposure to antimetabolites, alkylating agents, or other chemotherapy, radiotherapy to the abdomen, exposure to other hepatotoxic drugs, appearance of vaso-occlusive disease, acute and/or chronic graft-versus-host disease, or length of immunosuppression, correlated with a worse course of hepatitis. No definitive conclusions can be drawn. However, multivariate analysis of hepatic risk factors in larger cohorts of patients will be able to provide us with more precise information about the clinical outcome of chronic hepatitis in survivors.

Forman, D. (1998). "Review article: Is there significant variation in the risk of gastric cancer associated with Helicobacter pylori infection?" Aliment Pharmacol Ther **12 Suppl 1**: 3-7.

Helicobacter pylori infection is a risk factor for gastric cancer and most epidemiological studies have estimated a relative risk associated with infection in the order of two to four-fold. There is interest in the extent to which this risk estimate might vary between different populations especially as several populations have been identified with low rates of gastric cancer despite a high infection prevalence. Methodological differences between studies make it difficult to compare the results of retrospective case-control studies to quantify the variation in risk, but prospective studies indicate that there may be a six-fold variation in risk between different populations. It is likely that genetic and/or environmental co-factors are important in modifying the risk associated with H. pylori infection but there are few studies that have fully investigated the role of such co-factors.

Fruchter, R. G., M. Maiman, et al. (1998). "Is HIV infection a risk factor for advanced cervical cancer?" J Acquir Immune Defic Syndr Hum Retrovirol **18**(3): 241-5.

OBJECTIVES: To compare HIV-infected and HIV-negative women with invasive cervical cancer with respect to predictors of advanced disease. METHODS: A retrospective analysis of 28 HIV-positive and 132 HIV-negative women with invasive cervical carcinoma was conducted and the two groups were compared with regard to stage of disease, demographic and behavioral variables, and risk factors for advanced disease. RESULTS: Overall, HIV-infected women were more likely to have advanced disease, because 78% of HIV-positive women had Stage II to IV compared with 55% of HIV-negative women (odds ratio [OR] = 3.1; p = .03). Substance abuse was strongly associated with HIV infection, as were high-risk sexual variables. Although HIV infection was associated with a threefold increase in advance stage cervical cancer in a univariate analysis, only symptom duration and lack of a recent Papanicolaou smear were significant predictors of advanced disease in a multiple logistic regression analysis. CONCLUSIONS: The major predictors of advanced cervical cancer are similar in HIV-positive and HIV-negative women, although the reasons for these predictors may be very different. It is likely that a large proportion of HIV-positive patients with cervical cancer acquire HIV infection after initiation of the neoplastic process.

Fujita, T., K. Matai, et al. (1996). "Impact of splenectomy on circulating immunoglobulin levels and the development of postoperative infection following total gastrectomy for gastric cancer." Br J Surg **83**(12): 1776-8.

Splenectomy increases the postoperative morbidity of total gastrectomy for carcinoma of the stomach. The reasons for this increased risk of postoperative infection are unknown. The aim of this study was to evaluate the impact of splenectomy on circulating immunoglobulin levels and to determine whether splenectomy was an independent risk factor for the development of postoperative infection in 154 patients undergoing total gastrectomy for carcinoma of the stomach. Splenectomy reduced circulating immunoglobulin M levels in the early postoperative period following total gastrectomy. However, it was not identified as an independent risk factor for the development of postoperative infection by multivariate analysis.

Garza-Gonzalez, E., F. J. Bosques-Padilla, et al. (2004). "Association of gastric cancer, HLA-DQA1, and infection with Helicobacter pylori CagA+ and VacA+ in a Mexican population." J Gastroenterol **39**(12): 1138-42.

BACKGROUND: The goal of this study was to determine the importance of Helicobacter pylori CagA+, VacA+, and HLA-DQA1 alleles in a Mexican population with gastric cancer (GC). METHODS: We studied a group of Mexican patients (cases) with distal GC (n=22) or high-grade dysplasia (HGD; n=8) (mean age, 62.7 years, F : M=0.3; age range, 33-84 years) and 77 ethnically matched non-GC controls (mean age, 47.1 years; F : M=1.96; age range, 17-92 years). Both cases and controls were H. pylori-positive by at least two of the following diagnostic tests: rapid urease test, histology, culture, or serology. The presence of antibodies to CagA and VacA proteins was determined by Western blot, and the HLA-DQA1 typing was carried out by a polymerase chain reaction (PCR) sequence-specific primer method. RESULTS: The carriage of H. pylori CagA+, VacA+ strains was associated with GC or HGD (odds ratio [OR], 6.07; 95% confidence interval [CI], 1.56-27.57; P=0.005). The allele frequency of DQA1*0503 was significantly lower in the GC-HGD group than in the non-GC group (OR, 0.13; 95% CI, 0.02-0.59). Logistic regression analysis identified the carriage of HLA-DQA1*0503 as an independent protective factor for GC (OR, 0.19; 95% CI, 0.04-0.94) and colonization with H. pylori CagA+, VacA+ strains as an independent risk factor for GC (OR, 6.15; 95% CI, 1.69-22.37). CONCLUSIONS: Infection with H. pylori CagA+, VacA+ strains represents a significant risk for the development of GC. The absence of HLA-DQA1*0503 could be a host risk factor for the development of GC in Mexican patients.

Gerhartz, H. H. (1993). "Reduction of infection rates in cancer patients associated with the use of haematopoietic growth factors." Eur J Cancer **29A Suppl 3**: S14-7.

As the risk of infection associated with chemotherapy is related to the depth of the fall in neutrophil counts, protection from neutropenia has been used as an endpoint for growth factors in this setting. However, the functional status of these and other myeloid cells are also important. Therefore, more direct measurements of clinical improvement will also be useful. Several studies have suggested that the use of granulocyte-macrophage colony-stimulating factor (GM-CSF) can result in improvements in hospital stay, days of fever, antibiotic use and thrombocytopenia. Similar findings have been confirmed by our own work which indicates that GM-CSF not only shortens the period of leukopenia, but also reduces the complications of infection. More sensitive and appropriate endpoints should be included in future trials, including rate of and survival from infection as well as overall and disease-free survival.

Green, N. K., J. Morrison, et al. (2008). "Retargeting polymer-coated adenovirus to the FGF receptor allows productive infection and mediates efficacy in a peritoneal model of human ovarian cancer." J Gene Med **10**(3): 280-9.

BACKGROUND: Transductional targeting of adenovirus following systemic or regional delivery remains one of the most difficult challenges for cancer gene medicine. The numerical excess and anatomical advantage of normal (non-cancer) cells in vivo demand far greater detargeting than is necessary for studies using single cell populations in vitro, and this must be coupled with efficient retargeting to cancer cells. METHODS: Adenovirus (Ad5) particles were coated with reactive poly[N-(2-hydroxypropyl)methacrylamide] copolymers, to achieve detargeting, and retargeting ligands were attached to the coating. Receptor-mediated infection was characterised in vitro and anticancer efficacy was studied in vivo. RESULTS: Polymer coating prevented the virus binding any cellular receptors and mediated complete detargeting in vitro and in vivo. These fully detargeted vectors were efficiently retargeted with the model ligand FGF2 to infect FGFR-positive cells. Specific transduction activity was the same as parental virus, and intracellular routing appeared unaffected. Levels of transduction were up to 100-fold greater than parental virus on CAR negative cells. This level of specificity permitted good efficacy in intraperitoneal cancer virotherapy, simultaneously decreasing peritoneal adhesions seen with parental virus. Following intravenous delivery FGF2 mediated unexpected binding to erythrocytes, improving circulation kinetics, but preventing the targeted virus from leaving the blood stream. CONCLUSIONS: Polymer cloaking enables complete adenovirus detargeting, providing a versatile platform for receptor-specific retargeting. This approach can efficiently retarget cancer virotherapy in vivo. Ligands should be selected carefully, as non-specific interactions with non-target cells (e.g. blood cells) can deplete the pool of therapeutic virus available for targeting disseminated disease.

Gutierrez, J., A. Jimenez, et al. (2006). "Meta-analysis of studies analyzing the relationship between bladder cancer and infection by human papillomavirus." J Urol **176**(6 Pt 1): 2474-81; discussion 2481.

PURPOSE: Studies have been done of the possibility that infection by human papillomavirus is a risk factor contributing to bladder cancer but no definite conclusions have yet been drawn. We performed a meta-analysis of observational studies published until July 2005 to ascertain the degree of association between bladder cancer and human papillomavirus infection. MATERIALS AND

METHODS: The MEDLINE database was searched using the key words bladder cancer and virus. Strict criteria were applied to select studies revealing the prevalence in serum of human papillomavirus infection or its direct detection in patients. A total of 44 articles with these methodological criteria were chosen. RESULTS: In 39 studies the investigators determined the presence of human papillomavirus DNA, and found a prevalence of between 0% and 100% and significant homogeneity analysis ($p < 0.001$). Pooled estimation of the presence of the infection was 16.0% (95% CI 12.8 to 19.1). Pooled OR estimation was 2.3 (95% CI 1.3 to 4.1) with no significant publication bias. In 7 studies human papillomavirus infection was studied by detecting the antigen or antibodies and a prevalence of between 14% and 60% was found with significant homogeneity analysis ($p < 0.001$). Pooled estimation of the prevalence of infection was 32.4% (95% CI 17.0 to 47.8). Pooled OR estimation was 2.9 (95% CI 1.7 to 5.3). CONCLUSIONS: Finding a relationship between bladder cancer and human papillomavirus depends on the method used. In the literature examined there are insufficient cases and samples compared to controls and studies rely on a combination of various microbiological techniques in the same patient and sample, making it difficult to draw any definite conclusion.

Han, C., G. Qiao, et al. (1996). "Serologic association between human papillomavirus type 16 infection and esophageal cancer in Shaanxi Province, China." J Natl Cancer Inst **88**(20): 1467-71.

BACKGROUND: The existence of large geographic variations in the prevalence of esophageal cancer in some countries, such as China, indicates that environmental risk factors may be important in the development of this disease. Some studies have implicated genital-mucosal strains of human papillomaviruses (HPVs) in the etiology of this cancer. PURPOSE: We conducted a case-control study in Shaanxi Province, China, an area with a population at high risk for esophageal cancer, to assess the association of this disease with infection by HPV type 16 (HPV16), the most common cancer-associated genital-mucosal HPV type. METHODS: Ninety individuals with esophageal cancer and 121 cancer-free control subjects were identified among the patients in two hospitals in Xi'an, Shaanxi Province. The control subjects were matched to the case patients on the basis of age and sex. Blood specimens were drawn from all study subjects, and serum was isolated by routine methods. The presence of HPV16 antibodies in serum samples was determined by use of an enzyme-linked immunosorbent assay (ELISA) that used baculovirus-derived HPV16 virus-like particles as the antigen. A similar ELISA that used bovine papillomavirus type 1 (BPV1) virus-like particles as the antigen controlled for the specificity of HPV16 seroreactivity. Data from the HPV16 and the BPV1 assays were normalized with respect to results obtained in each assay with a control serum of known HPV16 seroreactivity. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to examine the association between HPV16 seroreactivity and esophageal cancer. Reported P values are two-sided. RESULTS: The mean seroreactivity to HPV16 virus-like particles was significantly higher for the cancer patients than for the control subjects (mean value +/- standard deviation = 0.85 +/- 0.22 versus 0.74 +/- 0.18; $P < .0001$). When the cancer patients and control subjects were compared by sex and age groups, the differences in mean seroreactivity remained statistically significant. The difference in mean seroreactivity to BPV1 virus-like particles between cancer patients and control subjects was not statistically significant (0.81 +/- 0.28 versus 0.88 +/- 0.32; $P = .12$); this result was not altered when sex and age groups were compared. By use of a cutoff point for HPV16 seropositivity that was established in studies of cervical neoplasia, 24% of the cancer patients were seropositive compared with 7% of the control subjects, yielding a sex- and age-adjusted OR of 4.5 (95% CI = 1.8-11.9). In general, the OR for esophageal cancer increased with increasing HPV16 seroreactivity. CONCLUSIONS AND IMPLICATIONS: HPV16 infection may be a risk factor for esophageal cancer. Further studies of the association between HPV16 infection and the incidence of esophageal cancer are needed.

Hansen, S., K. K. Melby, et al. (1999). "Helicobacter pylori infection and risk of cardia cancer and non-cardia gastric cancer. A nested case-control study." Scand J Gastroenterol **34**(4): 353-60.

BACKGROUND: Helicobacter pylori infection is an established risk factor for gastric adenocarcinoma. Potential confounding by socioeconomic factors has not been adequately assessed, and the magnitude of the relative risk in relation to gastric subsites, morphologic subtypes, sex, age, and follow-up time need further study. METHODS: We conducted a serologic case-control study nested within the Norwegian JANUS cohort. Between 1972 and 1986 serum was collected from 101,601 subjects who were followed up with regard to cancer development through 1992. RESULTS: Among 208 gastric adenocarcinoma cases, we found a strong positive association between H. pylori infection and non-cardia gastric cancer (odds ratio (OR), 5.15; 95% confidence interval (CI), 2.83-9.37), and a statistically significant negative association with

cardia cancer (OR, 0.40; 95% CI, 0.20-0.77). Adjustment for socioeconomic factors and smoking did not materially alter the effect estimates. The association between the infection and non-cardia cancer was stronger for tumors distal to the angulus and tended to be stronger in women than in men. The results were similar across Lauren morphologic subtypes. CONCLUSIONS: These results strengthen the evidence of H. pylori infection as a risk factor in non-cardia gastric cancer. A negative association with H. pylori infection was found for cardia cancer.

Hartwich, A., S. J. Konturek, et al. (2001). "Helicobacter pylori infection, gastrin, cyclooxygenase-2, and apoptosis in colorectal cancer." Int J Colorectal Dis **16**(4): 202-10.

Helicobacter pylori (HP) infection is usually accompanied by an increased plasma level of gastrin, a potent mitogen able to induce cyclooxygenase (COX)-2. This study examined (a) the seroprevalence of HP, its cytotoxic protein, CagA, and cytokines (tumor necrosis factor alpha, interleukins 1beta and 8) in 80 patients with colorectal cancers, before and after the removal of tumor, compared with 160 age- and gender-matched controls; (b) the gene expression of gastrin and its receptors (CCKB-R) in the cancer tissue, (c) the plasma levels and tumor tissue contents of gastrin, and (d) the mRNA expression of COX-1, COX-2, and apoptotic proteins (Bax and Bcl2) in cancer tissue and intact colonic mucosa. Anti-HP IgG, anti-CagA IgG seroprevalence, and cytokine levels were analyzed by enzyme-linked immunosorbent assay tests; gene expressions of gastrin, CCKB-R, COX-1, COX-2, Bax, and Bcl2 by reverse transcriptase polymerase chain reaction; and gastrin by radioimmunoassay. The seroprevalence of HP, especially that expressing CagA, was significantly higher in cancer patients than in controls and did not change 1 week after tumor resection while plasma cytokines were significantly reduced after this operation. Both gastrin and CCKB-R mRNA were detected in the cancer tissue and the resection margin; similarly, COX-2 mRNA was expressed in most of cancers and their resection margin but not in intact colonic mucosa, where only COX-1 was detected. The colorectal cancer tissue contained several folds more immunoreactive gastrin than cancer resection margin and many folds more than the intact colonic mucosa. We conclude that colon adenocarcinoma and its resection margin overexpress gastrin, its receptors, CCKB-R, and COX-2, and that HP infection may contribute to colonic cancerogenesis via overexpression of gastrin and COX-2, which may account for the stimulation of the tumor growth and the reduction in apoptosis as documented by enhanced mRNA expression of anti-apoptotic Bcl2 over proapoptotic Bax proteins.

Hengge, U. R., B. Benninghoff, et al. (2001). "Topical immunomodulators--progress towards treating inflammation, infection, and cancer." Lancet Infect Dis **1**(3): 189-98.

Immunomodulators include both immunostimulatory and immunosuppressive agents. Only recently have the basic mechanisms of topical immunotherapy been elucidated. Besides topical contact sensitisers (eg, diphencyprone or dinitrochlorobenzene), newer agents of the imidazoquinoline family such as imiquimod and resiquimod act by inducing cytokine secretion from monocytes or macrophages (interferon-alpha, interleukin-12, tumour-necrosis factor-alpha). The locally generated immune milieu leads to a Th1-dominance and cell-mediated immunity that have been used clinically to treat viral infections such as human papillomavirus (HPV), herpes simplex virus (HSV), mollusca, and cancerous lesions including initial squamous cell and basal cell carcinoma in immunocompetent and immunosuppressed patients. While these agents improve antigen-presentation by dendritic cells, they also act on B cells and lead to the synthesis of antibodies such as IgG2a much like the recently discovered immunostimulatory CpG-sequences that stimulate innate immunity. These sequences act as "danger signals" since they occur in bacterial and viral DNA, but are selectively methylated and inactivated in the mammalian genome. They share the induction of the same cytokines as imidazoquinolines but they show different magnitudes and kinetics of response. Topical immunotherapy with immunostimulatory agents shows potential for effective and patient-friendly treatment of inflammatory, infectious, and cancerous skin diseases. Immunoenhancers such as imdazoquinolines and CpG-sequences also have adjuvant properties that could improve conventional (protein) and DNA vaccination against cancer, atopy, and allergies.

Hirata, T., K. Kishimoto, et al. (2007). "Association between Strongyloides stercoralis infection and biliary tract cancer." Parasitol Res **101**(5): 1345-8.

Infectious agents, including parasites, often have oncogenic potential. However, there has been no study on the association between Strongyloides stercoralis infection and cancer risk. Therefore, we investigated the relationship between S. stercoralis infection and the occurrence of hepato-pancreato-biliary cancer. This case-control study examined 1,654 patients aged>or=50 years in the Department of Medicine and Therapeutics, Ryukyu University Hospital, Okinawa, Japan, between 1991 and 2005.

There were 196 patients with hepato-pancreato-biliary cancer and 1,458 control patients without cancer. The association between S. stercoralis infection and cancer was analyzed by logistic regression analysis adjusted for human T cell lymphotropic virus type 1 infection, age, and sex. The prevalence of S. stercoralis infection in controls and biliary tract cancer was significantly different at 7.5 and 18.4%, respectively (P=0.03, adjusted odds ratio 2.7, 95% confidence intervals 1.1-6.3). In conclusion, our study indicates that the prevalence of S. stercoralis infection in patients with biliary tract cancer appears significantly higher than that in control patients. Thus, we propose that S. stercoralis infection is a risk factor for biliary tract cancer.

Holmes, R. S., S. E. Hawes, et al. (2009). "HIV infection as a risk factor for cervical cancer and cervical intraepithelial neoplasia in Senegal." Cancer Epidemiol Biomarkers Prev **18**(9): 2442-6.

Cervical cancer is the second leading cause of cancer mortality in women worldwide, and the leading cause in Africa. There is uncertainty in the role of HIV infection as a risk factor for invasive and preinvasive cervical lesions, particularly in African populations. In a case-control study in Dakar, Senegal, we studied 150 women with invasive cervical cancer (ICC), 92 with cervical intraepithelial neoplasia (CIN) 2 or 3, 70 with CIN 1, and 515 control women. We used logistic regression analysis to estimate associations between HIV-1 and HIV-2 infection and the risk of cervical neoplasia. We found large increases in the risk of ICC and CIN 2-3, but not of CIN 1, associated with the presence of either HIV-1 or HIV-2 infection (odds ratios of 6.5 and 10.4 for ICC and CIN 2-3). Our analysis thus shows increases in the risk of both advanced and early cervical pathology associated with HIV infection in an African population.

Howell, P. B., P. E. Walters, et al. (1995). "Risk factors for infection of adult patients with cancer who have tunnelled central venous catheters." Cancer **75**(6): 1367-75.

BACKGROUND: Long-dwelling tunnelled central venous catheters provide reliable access for infusion therapy of patients with cancer, but can result in serious bloodstream infections. The incidence of such infections has been documented, but few studies have assessed potential risk factors, and to the authors' knowledge, none have measured the effect of neutropenia upon the incidence of these infections. METHODS: A cohort of 71 adult patients with cancer with long-dwelling tunnelled central venous catheters was followed for a total of 12,410 catheter days until catheter removal, death, or end of study for the occurrence of catheter-related infection or sepsis of unknown origin. Fifteen factors were assessed for association with these infections. RESULTS: Thirteen patients (18%) experienced a catheter-related infection (1.0/1000 catheter days), and 23 (32%) experienced sepsis of unknown origin. Neutropenia was associated significantly with risk for catheter-related infection (relative risk [RR] = 15.1, 95% confidence interval [CI] 2.7-86.9) and sepsis of unknown origin (RR = 10.3, 95% CI 4.0-26.8). Inpatient status, acute leukemia, and cytosine arabinoside therapy also were associated with sepsis of unknown origin, but not when adjusted for neutropenia. CONCLUSION: Of the 15 potential risk factors studied, neutropenia was the only independent risk factor for infection related to long-dwelling tunnelled central venous catheters and for sepsis of unknown origin.

Hundsberger, H., A. Verin, et al. (2008). "TNF: a moonlighting protein at the interface between cancer and infection." Front Biosci **13**: 5374-86.

The remarkable ability of TNF, especially in combination with Interferon-gamma or melphalan, to inhibit the growth of malignant tumor cells is so far unmatched. Unfortunately, its high systemic toxicity and hepatotoxicity prevent its systemic use in cancer patients. An elegant manner to circumvent this problem is the isolated limb and liver perfusion for the treatment of melanoma, soft tissue sarcoma and liver tumors, respectively, although the latter method can lead to a reversible hepatotoxicity. In order to allow also the treatment of other cancers with TNF, new strategies have to be developed that aim at sensitizing tumor cells to TNF and at reducing its systemic and liver toxicity, without losing its antitumor efficiency. Moreover, the lectin-like domain of TNF, which is spatially distinct from the receptor binding sites, could be useful in reducing cancer treatment-related pulmonary edema formation. This review will discuss some recent developments in these areas, which can lead to a renewed interest in TNF for the systemic treatment of cancer.

Ikeda, F., Y. Doi, et al. (2009). "Hyperglycemia increases risk of gastric cancer posed by Helicobacter pylori infection: a population-based cohort study." Gastroenterology **136**(4): 1234-41.

BACKGROUND & AIMS: Although diabetes mellitus and hyperglycemia are considered to be possible risk factors for various types of malignancy, the epidemiologic evidence concerning gastric cancer is scarce. The aim of this study was to evaluate the impact of hemoglobin A1c (HbA1c) levels on gastric cancer occurrence and their interaction with Helicobacter pylori infection. METHODS: A total of 2603 Japanese subjects

aged>or=40 years were stratified into 4 groups according to baseline HbA1c levels (<or=4.9%, 5.0%-5.9%, 6.0%-6.9%, and >or=7.0%) and followed up prospectively for 14 years. RESULTS: During the follow-up, 97 subjects developed gastric cancer. The age- and sex-adjusted incidence of gastric cancer significantly increased in the 6.0%-6.9% (5.1 per 1000 person-years; P<.05) and >or=7.0% groups (5.5 per 1000 person-years; P<.05) compared with the 5.0%-5.9% group (2.5 per 1000 person-years), whereas it was slightly but not significantly high in the <or=4.9% group (3.6 per 1000 person-years). This association remained substantially unchanged even after adjusting for the confounding factors including Helicobacter pylori seropositivity, (multivariate-adjusted hazard ratio [HR], 2.13; 95% confidence interval [CI]: 1.30-3.47 for the 6.0%-6.9% group and HR, 2.69; 95% CI: 1.24-5.85 for the >or=7.0% group). Among subjects who had both high HbA1c levels (>or=6.0%) and Helicobacter pylori infection, the risk of gastric cancer was dramatically elevated (interaction term, P=.004). CONCLUSIONS: Our findings suggest that casual hyperglycemia is a risk factor for gastric cancer and is a possible cofactor increasing the risk posed by Helicobacter pylori infection.

Ilhan, N., N. Ilhan, et al. (2004). "C-reactive protein, procalcitonin, interleukin-6, vascular endothelial growth factor and oxidative metabolites in diagnosis of infection and staging in patients with gastric cancer." World J Gastroenterol **10**(8): 1115-20.

AIM: The current study was to determine the serum/plasma levels of VEGF, IL-6, malondialdehyde (MDA), nitric oxide (NO), PCT and CRP in gastric carcinoma and correlation with the stages of the disease and accompanying infection. METHODS: We examined the levels of serum VEGF, IL-6, PCT, CRP and plasma MDA, NO in 42 preoperative gastric cancer patients and 23 healthy subjects. There were infection anamneses that had no definite origin in 19 cancer patients. RESULTS: The VEGF levels (mean+/-SD; pg/mL) were 478.05+/-178.29 and 473.85+/-131.24 in gastric cancer patients with and without infection, respectively, and these values were not significantly different (P>0.05). The levels of VEGF, CRP, PCT, IL-6, MDA and NO in cancer patients were significantly higher than those in healthy controls and the levels of CRP, PCT, IL-6, MDA and NO were statistically increased in infection group when compared with non-infection group (P<0.001). CONCLUSION: Although serum VEGF concentrations were increased in gastric cancer, this increase might not be related to infection. CRP, PCT, IL-6, MDA and NO have obvious drawbacks in the diagnosis of infections in cancer patients. These markers may not help to identify infections in the primary evaluation of cancer patients and hence to avoid unnecessary antibiotic treatments as well as hospitalization. According to the results of this study, IL-6, MDA, NO and especially VEGF can be used as useful parameters to diagnose and grade gastric cancer.

Imrie, C., M. Rowland, et al. (2001). "Is Helicobacter pylori infection in childhood a risk factor for gastric cancer?" Pediatrics **107**(2): 373-80.

Helicobacter pylori infection is associated with chronic gastritis and peptic ulcer disease. Furthermore, the World Health Organization has classified this organism as a carcinogen for gastric cancer. H pylori infection is mainly acquired in childhood. Children with H pylori infection are asymptomatic except for a very small number that develop peptic ulcer disease. However, if H pylori gastritis is associated with gastric cancer, do pediatricians need to screen children for this infection and treat those who are infected? In an attempt to determine the significance of the association between H pylori and gastric cancer, we have reviewed all of the English language literature on this topic. H pylori infection seems to be associated with an increased risk of developing gastric cancer. However, only a small number of infected individuals (~1%) will develop gastric cancer. Furthermore, there are potential cofactors other than H pylori that could be equally important. The effect of the eradication of H pylori alone on the development of gastric cancer is unknown. Based on our knowledge to date, we suggest that it is not indicated to treat all children with H pylori infection because of the risk of developing gastric cancer or to institute a screening and treatment program.

Iseki, K., M. Tatsuta, et al. (1998). "Helicobacter pylori infection in patients with early gastric cancer by the endoscopic phenol red test." Gut **42**(1): 20-3.

BACKGROUND: An endoscopic procedure that uses a pH indicator called phenol red to assess Helicobacter pylori infected gastric mucosa has recently been developed. This test makes it possible to take biopsy specimens from H pylori infected areas. AIM: This test was applied to patients with early gastric cancers to clarify the role of H pylori in gastric carcinogenesis. SUBJECTS: Sixty five patients with early gastric cancer (50 with differentiated adenocarcinoma and 15 with undifferentiated adenocarcinoma). METHODS: Patients with early gastric cancer underwent the endoscopic phenol red test before their operation. In this test, areas infected with H pylori can be observed as "coloured" areas where phenol red was turned from yellow to red. RESULTS: H pylori infection was significantly (p <

0.001) more frequent in patients with differentiated adenocarcinomas than in those with undifferentiated adenocarcinomas. Differentiated adenocarcinomas were usually located in areas of mucosa infected with H pylori, but undifferentiated adenocarcinomas were frequently located in non-infected areas. CONCLUSION: H pylori may be a strong risk factor for differentiated early gastric cancer.

Ishizuka, M., H. Nagata, et al. (2008). "Total parenteral nutrition is a major risk factor for central venous catheter-related bloodstream infection in colorectal cancer patients receiving postoperative chemotherapy." Eur Surg Res **41**(4): 341-5.

PURPOSE: To clarify the risk factors for central venous catheter-related bloodstream infection (CVCR-BSI) in patients receiving chemotherapy after surgery for colorectal cancer (CRC). METHODS: CVCR-BSI was evaluated retrospectively from a database of patients who had received postoperative chemotherapy using central venous catheters (CVC). RESULTS: One hundred and nine patients received 542 CVC for a total of 5,558 catheter-days. There were no significant differences in background between the patients who had CVCR-BSI and those who did not, except for the administration of total parenteral nutrition (TPN) ($p < 0.0001$). Moreover, univariate analyses (using factors including type of catheter, sex, age, troubles with insertion, kinds of disinfectant, kinds of catheter, length of inserted catheter, term of catheter insertion and administration of TPN) revealed that the administration of TPN (odds ratio, 12.74; 95% CI, 2.489-62.26; $p = 0.0023$) was the only risk factor for CVCR-BSI. CONCLUSIONS: TPN is a major risk factor for CVCR-BSI in CRC patients receiving postoperative chemotherapy.

Jaafar, F., E. Righi, et al. (2009). "Correlation of CXCL12 expression and FoxP3+ cell infiltration with human papillomavirus infection and clinicopathological progression of cervical cancer." Am J Pathol **175**(4): 1525-35.

Human cervical cancer is an immunogenic tumor with a defined pattern of histopathological and clinical progression. Tumor-infiltrating T cells contribute to immune control of this tumor; however, cervical cancer dysregulates this immune response both through its association with human papillomavirus (HPV) infection and by producing cytokines and chemokines. Animal tumor models have revealed associations between overproduction of the chemokine stromal cell-derived factor-1 (SDF-1 or CXCL12) and dysregulation of tumor-specific immunity. We therefore proposed that CXCL12 expression by cervical precancerous and cancerous lesions correlates with histopathological progression, loss of immune control of the tumor, and HPV infection. We found a significant association between cancer stage and CXCL12 expression for squamous and glandular lesions as well as with the HPV16+ (high-risk) status of the neoplastic lesions. Cancer progression was correlated with increasing levels of FoxP3 T-cell infiltration in the tumor. FoxP3 and CXCL12 expression significantly correlated for squamous and glandular neoplastic lesions. These observations were supported by enzyme-linked immunosorbent assay and Western blotting. In addition, we demonstrated CXCL12 expression by dyskaryotic cells in ThinPrep cervical smears. This study robustly links increased CXCL12 expression and FoxP3(+)-cell infiltration to HPV infection and progression of cervical cancer. It supports the detection of CXCL12 in cervical smears and biopsies as an additional biomarker for this disease.

Jung, W. W., T. Chun, et al. (2004). "Strategies against human papillomavirus infection and cervical cancer." J Microbiol **42**(4): 255-66.

Papillomaviruses infect a wide variety of animals, including humans. The human papillomavirus (HPV), in particular, is one of the most common causes of sexually transmitted disease. More than 200 types of HPV have been identified by DNA sequence data, and 85 HPV genotypes have been well characterized to date. HPV can infect the basal epithelial cells of the skin or inner tissue linings, and are, accordingly, categorized as either cutaneous or mucosal type. HPV is associated with a panoply of clinical conditions, ranging from innocuous lesions to cervical cancer. In the early 1980s, studies first reported a link between cervical cancer and genital HPV infection. Genital HPV infections are now recognized to be a major risk factor in at least 95% of cervical cancers. 30 different HPV genotypes have been identified as causative of sexually transmitted diseases, most of which induce lesions in the cervix, vagina, vulva, penis, and anus, as the result of sexual contact. There is also direct evidence demonstrating that at least four of these genotypes are prerequisite factors in cervical cancer. The main aim of this review was to evaluate the current literature regarding the pathovirology, diagnostics, vaccines, therapy, risk groups, and further therapeutic directions for HPV infections. In addition, we reviewed the current status of HPV infections in South Korean women, as evidenced by our data.

Kameshima, H., A. Yagihashi, et al. (2000). "Helicobacter pylori infection: augmentation of telomerase activity in cancer and noncancerous tissues." World J Surg **24**(10): 1243-9.

Telomerase adds hexameric repeats of 5'-TTAGGG-3' to the ends of chromosomal DNA (telomere) and has been implicated in cell immortalization and cellular senescence. The aim of this study was to measure quantitatively the telomerase activity and human telomerase RNA component (hTR) content in gastric cancer and to examine the relation between these values and histologic factors including Helicobacter pylori as a risk factor for gastric cancer. Telomerase activity was measured by a modified telomeric repeat amplification protocol in cancerous and noncancerous tissues (intestinal metaplasia, chronic gastritis, normal mucosa) from 27 gastric cancer patients; hTR expression was examined by the quantitative reverse transcriptase-polymerase chain reaction using fluorescent probes. Telomerase activity was higher in cancers (total product generated: 33.7) than in noncancerous tissues. Telomerase activity was higher in intestinal metaplasia (16.7) and chronic gastritis (10.6) than in normal mucosa (3.5). In patients with intestinal-type gastric cancer, telomerase activity was higher in intestinal metaplasia with H. pylori infection than in that without infection. hTR expression was not correlated with telomerase activity. H. pylori infection may influence telomerase activity in cancer and noncancerous tissues.

Karube, A., M. Sasaki, et al. (2004). "Human papilloma virus type 16 infection and the early onset of cervical cancer." Biochem Biophys Res Commun **323**(2): 621-4.

Human papilloma viruses (HPV), particularly type 16, have been associated with cervical cancer. It has been noted that the average onset of cervical cancer is occurring in younger women coupled with a higher prevalence of cervical HPV infection. However, the correlation between HPV 16 infection and the early onset of cervical cancer is still unclear. We hypothesize that HPV infection is an indicator of early onset of cervical cancer. To test this hypothesis, cervical smears from 197 women were evaluated by the polymerase chain reaction for HPV 16. These data revealed that the HPV 16-positive women were significantly younger than the HPV 16-negative women. Moreover, the average age of HPV 16-positive women with CIN 3 or invasive cancer was significantly younger compared with the other groups. These data clearly suggest that HPV 16 infection is a significant risk factor for the progression for cervical cancer in a young population of women.

Kato, S., M. Onda, et al. (1996). "Genetic polymorphisms of the cancer related gene and Helicobacter pylori infection in Japanese gastric cancer patients. An age and gender matched case-control study." Cancer **77**(8 Suppl): 1654-61.

BACKGROUND: Gastric cancer is a multistage process, each caused by numerous factors. The objective of this study was to elucidate the risk factors for gastric cancer by using molecular epidemiologic techniques and serum markers. METHODS: Serum pepsinogen I levels, pepsinogen I/pepsinogen II (I/II) ratios, serum IgG antibody against Helicobacter pylori (H. pylori), and genetic polymorphisms of cytochrome p450 2E1 (CYP2E1), glutathione-S-transferase M1 (GSTM1), and L-myc protooncogenes were analyzed in 82 persons with gastric cancer and in 151 age- and sex-matched controls, who were selected from 208 gastric cancer patients and 375 noncancer patients, respectively. Statistical analysis was performed to elucidate which risk factors for gastric cancer were contributing the most to gastric carcinogenicity. RESULTS: Serum pepsinogen I level (odds ratio [OR] = 1.81; 95% confidence interval [CI], 1.04-3.16) and pepsinogen I/II ratios (OR = 3.09; 95% CI, 1.74-5.49) were significantly associated with gastric cancer risk in a case-control study. Seropositivity of serum IgG antibody against H. pylori (OR = 1.25; 95% CI, 0.84-1.85) and specific genotypes of a L-myc genetic polymorphism (OR = 1.33; 95% CI, 0.59-2.99) were more commonly observed in gastric cancer cases, but this was not statistically significant. Specific genotypes of the CYP2E1 RsaI polymorphism and GSTM1 gene deletion were not associated with gastric cancer. CONCLUSIONS: Atrophic mucosal change, indicated by serum pepsinogen levels, is possible a risk factor for gastric cancer. H. pylori infection and genetic polymorphisms of CYP2E1, L-myc, and GSTM1 genetic polymorphisms were not risk factors in this study.

Kato, S., M. Onda, et al. (1997). "Helicobacter pylori infection and genetic polymorphisms for cancer-related genes in gastric carcinogenesis." Biomed Pharmacother **51**(4): 145-9.

The development of gastric cancer is a multistep process that is multi-factorial. An association with the Helicobacter pylori infections, gastric atrophy and gastric cancer has received recent attention. The objective of this study was to elucidate the risk factors for gastric cancer by using molecular epidemiological techniques for genetic susceptibility, gastric atrophy and serum markers including H pylori infection. We used an age- and gender-matched case-control study, where patients with benign gastric lesions were the controls. Low serum pepsinogen I levels (cut-off < 50 ng/mL) and low pepsinogen I/pepsinogen II ratios (cut-off < 3.0) were significantly associated with the risk of gastric cancer (odds ratio

[OR] = 3.53: 95% confidence interval [CI] = 2.46-5.09 and OR = 4.73: 3.26-6.88, respectively). However, seropositivity of serum immunoglobulin G (IgG) antibody against H pylori (OR = 1.09: 0.74-1.61) was not associated with gastric cancer, even when analyzed by age greater than or less then 50 years. Specific genotypes of the cytochrome p450 2E1 (CYP2E1) RsaI polymorphism and glutathione-S-transferase (GST) M1 gene deletion were determined but were not associated with gastric cancer; however, a Lmyc genetic polymorphism was associated with gastric cancer (OR = 1.55: 1.03-2.34). Therefore, in this Japanese study, atrophic mucosal change, indicated by serum pepsinogen levels, is a possible risk factor for gastric cancer.

Khaled, H. M., A. Raafat, et al. (2001). "Human papilloma virus infection and overexpression of p53 protein in bilharzial bladder cancer." Tumori **87**(4): 256-61.

AIMS AND BACKGROUND: An association between human papilloma virus (HPV) and bladder cancer has been reported. However, the role of HPV in bilharzial bladder cancer and its prevalence have not yet been clarified. STUDY DESIGN: We investigated 50 cases for HPV types 16/18 by in situ hybridization. Also, p53 protein expression by immunohistochemistry was evaluated in 41 of the 50 cases, with correlation of these factors to clinicopathologic parameters and tumor relapse after primary treatment. RESULTS: HPV was detected in 46% of Egyptian bladder carcinomas (23/50 cases). Positivity was 47.8% for squamous cell carcinoma and 36.4% for transitional cell carcinoma. There was a possible viral-bilharzial association as 52.8% of Bilharzial cases, whereas only 12.5% of non-Bilharzial cases were HPV positive (P <0.05). P53 protein was found in 19/41 (46.3%) cases. There was a concordance between HPV and p53 in 58.5% of cases. Neither factor was related to tumor recurrence after primary treatment. CONCLUSIONS: HPV may thus be implicated in the etiology of bilharzial bladder cancer, but a definite causal relationship remains to be demonstrated. HPV together with p53 alterations work in synergy to accelerate the carcinogenic process, as there was concordance in the results of both parameters in 24/41 (58.5%) cases.

Kim, H. J., M. K. Kim, et al. (2005). "Effect of nutrient intake and Helicobacter pylori infection on gastric cancer in Korea: a case-control study." Nutr Cancer **52**(2): 138-46.

To examine the effects of dietary factor and Helicobacter pylori (H. pylori) infection with emphasis on vitamin intake on the risk of gastric cancer (GC), we conducted a case-control study in South Korea, a high-risk area for GC. Trained dietitians interviewed 136 cases histologically diagnosed with GC. An equal number of hospital controls was selected by matching sex and age. High dietary intakes of vegetable fat [odds ratio (OR) = 0.35; 95% confidence interval (CI) = 0.15-0.83], folate (OR = 0.35; 95% CI = 0.13-0.96), and antioxidants, such as vitamin A (OR = 0.34; 95% CI = 0.13-0.83), beta-carotene (OR = 0.33; 95% CI = 0.13-0.82), vitamin C (OR = 0.26; 95% CI = 0.09-0.72), and vitamin E (OR = 0.41; 95% CI = 0.17-1.01), were shown to have a protective effect on GC risk using a multivariate model adjusting for foods significantly related to GC in our previous study (charcoal grilled beef, spinach, garlic, mushroom, and a number of types of kimchi) and supplement use. When stratified according to H. pylori infection, high intakes of vitamin C (OR = 0.10; 95% CI = 0.02-0.63) and vitamin E (OR = 0.16; 95% CI = 0.03-0.83) exhibited highly significant inverse associations with GC among the H. pylori-infected subjects compared with noninfected individuals. GC risk was significantly decreased only when consumption levels for two of these vitamins were high. Our findings suggest that high intake of antioxidant vitamins contribute to the reduction of GC risk and that GC risk in Korea may be decreased by encouraging those with H. pylori infection to increase their intake of antioxidant vitamins.

Kim, H. Y., Y. B. Kim, et al. (1997). "Co-existing gastric cancer and duodenal ulcer disease: role of Helicobacter pylori infection." Helicobacter **2**(4): 205-9.

BACKGROUND: The association of gastric cancer and chronic duodenal ulcer disease is considered rare. In fact duodenal ulcer disease is believed to somehow "protect" against the development of gastric cancer. Helicobacter pylori infection is an important factor in the development of gastric cancer. No detailed investigation on the prevalence of H. pylori in coexistence of gastric cancer and duodenal ulcer disease has been performed. We evaluated the frequency of H. pylori infection in the patients with co-existence of gastric cancer and duodenal ulcer disease. MATERIALS AND METHODS: During the period March 1994 to February 1995, we collected data from 3,652 patients in whom esophagogastroduodenoscopy was done. During this period, when the cancerous or ulcerative lesions in stomach or duodenum were found, rapid urease tests were performed. RESULTS: Six patients had concurrent gastric carcinoma and duodenal ulcer disease. Three of the cases had early gastric carcinoma; 2 had active duodenal ulcers and one had a duodenal ulcer scar; all 3 had positive rapid urease

tests. The patients with early gastric cancer were younger than the individuals with advanced gastric cancer. CONCLUSIONS: The co-existence of both diseases may be higher than reported from Western countries or from Peru which may either reflect the high prevalence of circulation of H. pylori ulcer and cancer strains in Korea and the co-infection with both types of organism in some individuals.

Kim, N., R. Y. Park, et al. (2008). "Helicobacter pylori infection and development of gastric cancer in Korea: long-term follow-up." J Clin Gastroenterol **42**(5): 448-54.

BACKGROUND AND AIM: Infection of Helicobacter pylori is viewed as a major driver of progression to the precancerous state or to gastric cancer. This study was performed to investigate the effect of H. pylori infection on gastric cancer development and to determine to what extent H. pylori eradication is likely to reduce the prevalence of gastric cancer. METHODS: Gastric cancer development was investigated in 1790 Korean subjects who underwent gastroscopy and H. pylori testing between 1992 and 1998. The effects of H. pylori-positive and eradicated states on gastric cancer development were analyzed. RESULTS: Gastric cancer developed in 5 of the study cohort during a mean follow-up period of 9.4 years. All of these patients were positive for H. pylori infection, and 4 of the 5 had antral intestinal metaplasia (IM) at the time of study enrollment. One of these 5 patients was in an eradicated state when the gastric cancer was diagnosed, and had histologic IM before eradication therapy was performed. Gastric cancer was found to develop 10.9 times more frequently in the presence of IM than in its absence. CONCLUSIONS: The present study shows a close relationship between H. pylori infection and IM, and between IM and the development of gastric cancer. In addition, our finding suggests that chronic H. pylori infection looks like an important risk factor for the development of gastric cancer in Korea, where the prevalence of H. pylori remains high. This study indicates that to prevent gastric cancer H. pylori eradication is best performed before the development of IM.

Kirk, G. D., C. Merlo, et al. (2007). "HIV infection is associated with an increased risk for lung cancer, independent of smoking." Clin Infect Dis **45**(1): 103-10.

BACKGROUND: Human immunodeficiency virus (HIV)-infected persons have an elevated risk for lung cancer, but whether the increase reflects solely their heavy tobacco use remains an open question. METHODS: The Acquired Immunodeficiency Syndrome (AIDS) Link to the Intravenous Experience Study has prospectively observed a cohort of injection drug users in Baltimore, Maryland, since 1988, using biannual collection of clinical, laboratory, and behavioral data. Lung cancer deaths were identified through linkage with the National Death Index. Cox proportional hazards regression was used to examine the effect of HIV infection on lung cancer risk, controlling for smoking status, drug use, and clinical variables. RESULTS: Among 2086 AIDS Link to the Intravenous Experience Study participants observed for 19,835 person-years, 27 lung cancer deaths were identified; 14 of the deaths were among HIV-infected persons. All but 1 (96%) of the patients with lung cancer were smokers, smoking a mean of 1.2 packs per day. Lung cancer mortality increased during the highly active antiretroviral therapy era, compared with the pre-highly active antiretroviral therapy period (mortality rate ratio, 4.7; 95% confidence interval, 1.7-16). After adjusting for age, sex, smoking status, and calendar period, HIV infection was associated with increased lung cancer risk (hazard ratio, 3.6; 95% confidence interval, 1.6-7.9). Preexisting lung disease, particularly noninfectious diseases and asthma, displayed trends for increased lung cancer risk. Illicit drug use was not associated with increased lung cancer risk. Among HIV-infected persons, smoking remained the major risk factor; CD4 cell count and HIV load were not strongly associated with increased lung cancer risk, and trends for increased risk with use of highly active antiretroviral therapy were not significant. CONCLUSIONS: HIV infection is associated with significantly increased risk for developing lung cancer, independent of smoking status.

Kitajima, Y., K. Ohtaka, et al. (2008). "Helicobacter pylori infection is an independent risk factor for Runx3 methylation in gastric cancer." Oncol Rep **19**(1): 197-202.

Runx3, a member of the human runt-related transcription factor family, is known as a possible tumor suppressor gene for gastric cancer. Runx 3 expression is frequently suppressed by the promoter hypermethylation in gastric cancer cell lines and tissues. However, the precise mechanism of the induction of Runx3 methylation, which is considered to be a critical step in gastric carcinogenesis, remains to be elucidated. In the present study, we evaluated runx3 gene methylation in 57 resected early gastric cancer specimens. Then, we correlated Runx3 methylation in the cancer tissue specimens with clinicopathological factors as well as the mucosal backgrounds, such as intestinal metaplasia surrounding the cancer cells and Helicobacter pylori (H. pylori) infection. Runx3 methylation was observed in 30 of the 57 (52.6%) cancer specimens, whereas

methylation was detected in 10 of the 57 (17.5%) corresponding non-cancerous mucosae. In comparison to the clinicopathological factors, Runx3 methylation was significantly correlated with both age and tumor location. A multivariate analysis demonstrated that age and tumor location as well as H. pylori infection were independent risk factors for Runx3 methylation. We demonstrated for the first time that H. pylori infection contributes to Runx3 methylation in gastric cancer tissues. When a persistent infection by H. pylori continues in the middle/lower stomach for a long period, Runx3 methylation may be induced and the subsequent loss of Runx3 expression may therefore affect gastric carcinogenesis.

Knekt, P., H. Adlercreutz, et al. (2000). "Does antibacterial treatment for urinary tract infection contribute to the risk of breast cancer?" Br J Cancer **82**(5): 1107-10.

Low lignan status has been reported to be related to an elevated risk of breast cancer. Since lignan status is reduced by antibacterial medications, it is plausible to hypothesize that repeated use of antibiotics may also be a risk factor for breast cancer. History of treatment for urinary tract infection was studied for its prediction of breast cancer among 9,461 Finnish women 19-89 years of age and initially cancer-free. During a follow-up in 1973-1991, a total of 157 breast cancer cases were diagnosed. Women reporting previous or present medication for urinary tract infection at baseline showed an elevated breast cancer risk in comparison with other women. The age-adjusted relative risk was 1.34 (95% confidence interval (CI) = 0.98-1.83). The association was concentrated to women under 50 years of age. The relative risk for these women was 1.74 (95% CI 1.13-2.68), whereas it was 0.97 (95% CI 0.59-1.58) for older women. The relative risk in the younger age-group was 1.47 (95% CI 0.73-2.97) during the first 10 years of follow-up, and 1.93 (95% CI 1.11-3.37) for follow-up times longer than 10 years. These data suggest that premenopausal women using long-term medication for urinary tract infections show a possible elevated risk of future breast cancer. The results are, however, still inconclusive and the hypothesis needs to be tested by other studies.

Kocazeybek, B. (2003). "Chronic Chlamydophila pneumoniae infection in lung cancer, a risk factor: a case-control study." J Med Microbiol **52**(Pt 8): 721-6.

The relationship between chronic Chlamydophila (formerly Chlamydia) pneumoniae infection and lung carcinoma was investigated. A total of 123 patients who were smokers and diagnosed with lung carcinoma based on clinical and laboratory (radiological, cytological) findings were examined. Of these patients, 70 had small-cell, 28 squamous-cell and seven large-cell carcinomas, while 18 had adenocarcinoma. A total of 123 healthy persons matching patients in age, sex, duration of smoking and locality were chosen as controls. Blood samples (5 ml) were withdrawn at the time of diagnosis and 1 month later. The values between IgG >/= 512 and IgA >/= 40 were set as the criteria for chronic Chlamydophila pneumoniae infections. In male patients with lung carcinoma, Chlamydophila pneumoniae IgG antibody titres of >/= 512 and IgA antibody titres of >/= 40 were found at a higher rate than in the control group. This ratio was not significant for the female patients. In chronic Chlamydophila pneumoniae infections, Chlamydophila pneumoniae antibody titres with values IgG >/= 512 and IgA >/= 40 were found in a total of 62 (50.4 %) cases. Chronic Chlamydophila pneumoniae infections were seen statistically more often in male patients with carcinoma who were aged 55 years or younger. This study supports the idea that chronic Chlamydophila pneumoniae infection increases the risk of lung carcinoma.

Konturek, P. C., S. J. Konturek, et al. (2006). "Gastric cancer and Helicobacter pylori infection." J Physiol Pharmacol **57 Suppl 3**: 51-65.

The Nobel prize in Physiology and Medicine in 2005 was presented to Barry Marshall and Robin Warren for their discovery of Helicobacter pylori (Hp), but only the involvement of this germ in gastritis and peptic ulcer has been mentioned in the award sentence, while numerous epidemiological, clinical and experimental studies and reports emphasized the crucial role of Hp in pathogenesis of gastric cancer (GC). This review is based on the old concept proposed by P. Correa much before the discovery of spiral bacteria in the stomach, postulating the cascade of mucosal changes from acute/chronic gastritis into the atrophic gastritis with intestinal metaplasia and finally to dysplasia and GC. It is now widely accepted view that Hp infection is the major initiator of the inflammatory and atrophic changes in gastric mucosa accompanied by an over-expression of certain growth factors such as gastrin as well as of cyclooxygenase-2 (COX-2) and anti-apoptotic proteins including survivin and B-cl(2), leading to proliferation of mutated atrophic cells, excessive angiogenesis, inhibition of apoptosis and formation of gastric tumour. All the morphological and biochemical changes associated with the transformation of mucosal cells into the cancer cells can be traced in excellent experimental model of gastric cancerogenesis induced by infection of Hp in Mongolian gerbils. Since the eradication therapy was proved in several prospective clinical trials to greatly reduce the incidence of GC and this was confirmed on the gerbil model of Hp-

induced GC, it has been postulated; a) that Hp is the major causal factor in pathogenesis of GC and b) that the only rational approach in attempt to reduce the occurrence of GC is the global eradication of Hp.

Korodi, Z., X. Wang, et al. (2005). "No serological evidence of association between prostate cancer and infection with herpes simplex virus type 2 or human herpesvirus type 8: a nested case-control study." J Infect Dis **191**(12): 2008-11.

Sexual history has consistently been found to be a risk factor for the development of prostate cancer. An association between prostate cancer and herpes simplex virus type 2 (HSV-2) or Kaposi sarcoma-associated herpesvirus/human herpesvirus type 8 (HHV-8) infections has also been reported. Linkage of data on a cohort of 20,243 healthy Finnish men identified 165 cases of prostate cancer that were diagnosed up to 24 years after donation of a serum sample. Two control subjects were matched by age, sex, and municipality of residence to each case patient. Serum levels of immunoglobulin G against HSV-2 and HHV-8 were determined. Neither HSV-2 infection (odds ratio [OR], 0.93 [95% confidence interval {CI}, 0.44-1.96]) nor HHV-8 infection (OR, 0.74 [95% CI, 0.19-2.88]) was associated with prostate cancer.

Koskela, P., T. Anttila, et al. (2000). "Chlamydia trachomatis infection as a risk factor for invasive cervical cancer." Int J Cancer **85**(1): 35-9.

Cervical carcinoma is a sexually transmitted disease most strongly linked with human-papillomavirus (HPV) infection. We conducted a prospective sero-epidemiologic study to evaluate the role of Chlamydia trachomatis infection in the development of cervical carcinoma, with invasive cancer as an end point. A nested case-control study within a cohort of 530000 Nordic women was performed. Linking data files of 3 Nordic serum banks and the cancer registries of Finland, Norway and Sweden identified 182 women with invasive cervical carcinoma diagnosed during a mean follow-up of 5 years after serum sampling. The serum samples of the cases and matched cancer-free controls were analyzed for IgG antibodies to C. trachomatis, C. pneumoniae (a control microbe) and HPV types 16, 18 and 33, as well as for serum cotinine (an indicator of tobacco smoking). Serum antibodies to C. trachomatis were associated with an increased risk for cervical squamous-cell carcinoma (HPV- and smoking-adjusted OR, 2.2; 95% CI, 1.3-3.5). The association remained also after adjustment for smoking both in HPV16-seronegative and -seropositive cases (OR, 3.0; 95% CI, 1.8-5.1; OR, 2.3, 95% CI, 0. 8-7.0 respectively). No such association was found for C. pneumoniae. Our prospective study provides sero-epidemiologic evidence that infection with C. trachomatis confers an increased risk for subsequent development of invasive squamous-cell carcinoma of the uterine cervix.

Koziol-Montewka, M., A. Magrys, et al. (2006). "MPO and cytokines in the serum of cancer patients in the context of Candida colonization and infection." Immunol Invest **35**(2): 167-79.

This study investigated the immunological factors, such as neutrophils number, the level of myeloperoxidase and IL-12, IL-10, TNF-alpha, IFN-gamma, that additionally might correlate with increased susceptibility to Candida infections in cancer patients. A total of 105 cancer patients were evaluated. Patients were examined twice for Candida colonization and presence of Candida antigen and DNA in bloodstream. Serum concentrations of MPO and selected cytokines were quantified by ELISA. The values for myeloperoxidase were decreased in Candida-colonized as well as deep-infected cancer patients groups, compared to healthy persons. In the group of patients suspected of deep candidiasis, we observed significantly elevated level of IFN-gamma compared to control. In the group of Candida-colonized patients, the concentrations of IL-12, TNF-alpha and IFN-gamma were significantly heightened when compared to control.MPO deficiency seems to be one of the important risk factor for deep candidiasis independently of the neutrophil count. The disturbances in cytokines levels in cancer patients group can be connected with underlying cancer disease, its treatment as well as Candida infection. The decreased level of TNF-alpha, in particular may be connected with Candida invasion.

Kuehnert, M. J., J. A. Jernigan, et al. (1999). "Association between mucositis severity and vancomycin-resistant enterococcal bloodstream infection in hospitalized cancer patients." Infect Control Hosp Epidemiol **20**(10): 660-3.

OBJECTIVE: To determine the role of mucositis severity in the development of vancomycin-resistant enterococcal (VRE) bloodstream infection (BSI). SETTING: A tertiary-care university medical center. PARTICIPANTS: Hematology-oncology-unit inpatients. DESIGN: Patients with VRE BSI (case-patients) were compared with VRE-colonized (control) patients from September 1994 through August 1997. Oral mucositis severity was recorded on the day of VRE BSI for case-patients and on hospital day 22 (median day of hospitalization of case-patient VRE BSI) for controls. There were 19 case-patients and 31 controls. RESULTS: In univariate analysis, case-patients were significantly more likely than

controls to have a higher mucositis severity score, diarrhea, or a higher severity of illness score. In multivariate analysis, only mucositis remained as an independent risk factor, and increasing mucositis score was significantly associated with VRE BSI. CONCLUSIONS: Mucositis severity was independently associated with an increasing risk for VRE BSI. Interventions to alter mucositis severity may help to prevent VRE BSI in hospitalized cancer patients.

Kumar, S., S. Kumar, et al. (2006). "Infection as a risk factor for gallbladder cancer." J Surg Oncol **93**(8): 633-9.

Gallbladder cancer is a common hepato-biliary malignancy with poor prognosis. The main associated risk factors identified so far include cholelithiasis (especially mixed gall stone), chronic infections of the gallbladder, obesity, reproductive factors, diet, hepato-biliary anamolies, and environmental exposure to specific chemicals. Genetic and molecular predisposing factors have also been described. This article reviews the association of chronic infection and gallbladder cancer. Most of the studies have shown a good association of mixed bacterial and Salmonella infections in the carcinogenesis of cancer gallbladder especially in the area of high endemicity of typhoid. Bacterial degradation of bile and chronic inflammation may also play some role in the carcinogenic process. Mutations in multiple tumor suppressor gene and oncogenes (P53 and K-ras) have also been found in a few studies. This review seeks to bring out many hidden infective etiological aspects of the pathogenesis of gallbladder cancer. Review of the entire published literature suggests a need for further studies for better understanding of the disease.

Lagergren, J., Z. Wang, et al. (1999). "Human papillomavirus infection and esophageal cancer: a nationwide seroepidemiologic case-control study in Sweden." J Natl Cancer Inst **91**(2): 156-62.

BACKGROUND: Infection with human papillomavirus (HPV) type 16 has been implicated as a risk factor for esophageal squamous cell carcinoma in three seroepidemiologic studies. We conducted a larger, population-based study to verify this association and to investigate possible confounding factors. METHODS: We performed a nationwide case-control study in Sweden of HPV16 or HPV18 infection and risk of esophageal squamous cell carcinoma or esophageal/gastroesophageal adenocarcinoma. Tumors were strictly classified by their location and histologic type. Case subjects with incident cancers and population-based control subjects donated blood samples and were interviewed in person about potential confounding factors. An enzyme-linked immunosorbent assay was used to detect HPV seropositivity. Multivariate analyses were conducted to study relationships between HPV seropositivity, level of education, smoking (all tobacco) status, alcohol consumption, and cancer risk. RESULTS: We compared 121 case subjects with esophageal squamous cell carcinoma and 173 case subjects with adenocarcinoma of the esophagus or gastroesophageal junction with 302 population-based control subjects. The age- and sex-adjusted odds ratios (ORs) for squamous cell carcinoma were 1.0 (95% confidence interval [CI] = 0.5-2.0) for persons seropositive for HPV16 and 0.5 (95% CI = 0.2-1.1) for persons seropositive for HPV18 in comparison with seronegative individuals. The corresponding ORs for adenocarcinoma were 1.2 (95% CI = 0.7-2.2) and 0.2 (95% CI = 0.1-0.7), respectively. Adjustments for smoking status, alcohol consumption, and level of education did not alter the results. CONCLUSIONS: We found no evidence of a positive association between HPV16 or HPV18 infection and either form of esophageal cancer. Our results do not support conclusions from previous studies.

Laurila, A. L., T. Anttila, et al. (1997). "Serological evidence of an association between Chlamydia pneumoniae infection and lung cancer." Int J Cancer **74**(1): 31-4.

Epidemiological evidence suggests that airway obstruction is an independent risk factor for lung cancer and that this cannot be explained by active or passive smoking alone. Chlamydia pneumoniae infection has been associated with chronic bronchitis and its exacerbates. Our aim was to evaluate the association between chronic C. pneumoniae infection and risk of lung cancer among male smokers. Smoking males with lung cancer (n = 230) and their age- and locality-matched controls were selected among participants of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. The presence of C. pneumoniae infection was assessed by analyzing specific antibodies and immune complexes in 2 serum samples collected with a 3-year interval before the lung cancer diagnosis. The diagnosis of chronic infection was based on stable levels of positive specific IgA antibody (titer > or = 16) and immune complex (titer > or = 4). Relative risks were estimated by odds ratios (OR) adjusted for age, locality and smoking history by a conditional logistic regression model. Markers suggesting chronic C. pneumoniae infection were present in 52% of cases and 45% of controls and hence were positively associated with the incidence of lung cancer (OR 1.6; 95% confidence interval [CI] 1.0-2.3). The incidence was especially increased in men younger than 60 years (OR 2.9; 95%

CI 1.5-5.4) but not in the older age group (OR 0.9; 95% CI 0.5-1.6). Before concluding that C. pneumoniae infection is a new independent risk factor for lung cancer, corroboration from other studies with larger number of cases and longer follow-up is needed.

Ligtenberg, A. J., E. C. Veerman, et al. (2007). "Salivary agglutinin/glycoprotein-340/DMBT1: a single molecule with variable composition and with different functions in infection, inflammation and cancer." Biol Chem **388**(12): 1275-89.

Salivary agglutinin (SAG), lung glycoprotein-340 (gp-340) and Deleted in Malignant Brain Tumours 1 (DMBT1) are three names for identical proteins encoded by the dmbt1 gene. DMBT1/SAG/gp-340 belongs to the scavenger receptor cysteine-rich (SRCR) superfamily of proteins, a superfamily of secreted or membrane-bound proteins with SRCR domains that are highly conserved down to sponges, the most ancient metazoa. On the one hand, DMBT1 may represent an innate defence factor acting as a pattern recognition molecule. It interacts with a broad range of pathogens, including cariogenic streptococci and Helicobacter pylori, influenza viruses and HIV, but also with mucosal defence proteins, such as IgA, surfactant proteins and MUC5B. Stimulation of alveolar macrophage migration, suppression of neutrophil oxidative burst and activation of the complement cascade point further to an important role in the regulation of inflammatory responses. On the other hand, DMBT1 has been demonstrated to play a role in epithelial and stem cell differentiation. Inactivation of the gene coding for this protein may lead to disturbed differentiation, possibly resulting in tumour formation. These data strongly point to a role for DMBT1 as a molecule linking innate immune processes with regenerative processes.

Lin, J. T., L. Y. Wang, et al. (1995). "A nested case-control study on the association between Helicobacter pylori infection and gastric cancer risk in a cohort of 9775 men in Taiwan." Anticancer Res **15**(2): 603-6.

A nested case-control study was carried out to investigate the association between Helicobacter pylori infection and gastric cancer risk in Taiwan. A total of 29 patients newly affected with gastric cancer and 220 healthy controls matched with cases on age, sex and residence were selected from a cohort of 9,775 men recruited from 1984 through 1986. Frozen serum samples collected at recruitment examination were tested for IgG antibodies against Helicobacter pylori by an enzyme-linked immunosorbent assay. The average interval between serum collection and cancer diagnosis was 3.1 years. Gastric cancer cases had a higher seropositive prevalence (69%) than matched controls (59%) giving an odds ratio of 1.6 (95%) confidence interval = 0.7-2.6). Compared with previous nested case-control studies, Helicobacter pylori infection in early childhood may be a risk factor for gastric cancer. However, a long induction period seems required for gastro-carcinogenesis associated with Helicobacter pylori infection.

Lin, L. L., C. N. Chen, et al. (2008). "Annexin A4: A novel molecular marker for gastric cancer with Helicobacter pylori infection using proteomics approach." Proteomics Clin Appl **2**(4): 619-34.

Helicobacter pylori was reported to be an important risk factor for the carcinogenesis of gastric cancer. Here, we used a proteomic approach to find differentially expressed proteins between the normal and tumor tissue of gastric cancer patients infected with H. pylori. In our results, we found annexin A4 was over-expressed in patients infected with H. pylori and was found in tumor cells, and over-expressed in gastric cancer SCM-1 cells after H. pylori infection. Ca(2+) can be induced by H. pylori and interact with annexin A4 Ca(2+) binding site to block the calmodulin-activated chloride conductance activation; therefore, it produces a new environment that benefits the malignant existence of H. pylori and raises the risk for gastric cancer. We also found interleuken-8 (IL-8) expression levels were increased in H. pylori infected SCM-1 cells. Combined with previous reports and our results, we summarize that the over-expression of annexin A4 in SCM-1 cells with H. pylori infection may subsequently induce IL-8 which can further cause tumor angiogenesis. In this paper, we show that annexin A4 is a potential novel molecular marker for gastric cancer with H. pylori infection, and our results may provide a new insight in the development of new anti-cancer drugs.

Machida-Montani, A., S. Sasazuki, et al. (2004). "Association of Helicobacter pylori infection and environmental factors in non-cardia gastric cancer in Japan." Gastric Cancer **7**(1): 46-53.

BACKGROUND: Although Helicobacter pylori infection is a major risk factor for gastric cancer, it does not explain the full picture of stomach carcinogenesis. There have been few epidemiological studies, however, which examined both H. pylori and environmental factors simultaneously. The aims of this study were to estimate the association of environmental factors (smoking and dietary factors) with gastric cancer in consideration of H. pylori infection, and to investigate the effects of the interaction between environmental factors and H. pylori infection. METHODS: A multicenter, hospital-based, case-control study of gastric cancer was

conducted at four hospitals in Nagano prefecture, Japan, between October 1998 and March 2002. For 153 newly diagnosed gastric cancer cases, two controls matched by age (within 3 years), sex, and residence area were randomly selected from the participants of a health check-up program during the same period in the same hospitals. We conducted a questionnaire survey and obtained blood samples. Consequently, 122 non-cardia gastric cancer cases and 235 controls were available for this analysis. RESULTS: Results. H. pylori infection was strongly associated with non-cardia gastric cancer after adjustment for possible confounding factors (odds ratio [OR], 8.2; 95% confidence interval [CI], 3.7-18.2). Cigarette smoking (OR, 2.8; 95% CI, 1.2-6.5) and frequent intake of miso (fermented soy bean) soup (OR, 2.1; 95% CI, 0.9-5.1) and rice (OR, 2.5; 95% CI, 1.0-6.1) were determined to be risk factors even after adjusting for possible confounding factors, including H. pylori infection. However, no statistically significant interaction between environmental factors and H. pylori infection was detected. CONCLUSION: This finding suggests that although H. pylori infection is clearly an important risk factor for gastric cancer, smoking cessation and dietary modification may be practical strategies for the prevention of non-cardia gastric cancer among both H. pylori-positive and -negative subjects in Japan.

Maciag, P. C., N. F. Schlecht, et al. (2000). "Major histocompatibility complex class II polymorphisms and risk of cervical cancer and human papillomavirus infection in Brazilian women." Cancer Epidemiol Biomarkers Prev **9**(11): 1183-91.

Infection with high-risk human papillomavirus (HPV) is the major risk factor for the development of malignant lesions in the uterine cervix. Environmental, behavioral, and ill-defined genetic factors also have been implicated in the pathogenesis of this disease. Associations between human leukocyte antigens (HLAs) and cervical cancer, precursor lesions, and HPV infections have been reported in several populations. To verify whether HLA-DRB1, -DQA1, and -DQB1 diversity is related to cervical cancer in the Brazilian population, 161 cases and 257 controls were HLA typed. Variants of DQA1 and DQB1 promoter regions were also typed in 92 cases and 228 controls. Polymorphism in HLA genes and promoters was distinguished by PCR-based methods, and the magnitude of associations was determined by logistic regression analysis. DRB1*15 [confounder-adjusted odds ratio (OR), 2.24; 95% confidence interval (CI), 1.29-3.90], DRB1*1503 (OR, 2.52; 95% CI, 1.16-5.48), and haplotype DRB1*15-DQB1*0602 (OR, 2.04; 95% CI, 1.15-3.61) were positively associated with cervical cancer. When we considered only DR15 haplotypes that did not carry the DQB1*0602 allele, the risk attributed to DRB1*15 more than doubled. A negative association was found between DQB1*05 and cervical cancer (OR, 0.57; 95% CI, 0.35-0.92), and similar trends were observed for DQA1*0101/04, DRB1*0101, and DRB1*1302. HPV positivity among controls was associated with DRB1*1503 (OR, 4.60; 95% CI, 1.33-15.9), DRB1*0405 (OR, 6.21; 95% CI, 1.66-23.2), and DQB1*0602 (OR, 2.48; 95% CI, 1.06-5.80). We suggest that HLA class II polymorphisms are involved in genetic susceptibility to cervical cancer and HPV infection in a Brazilian population from an area with a high incidence of this neoplasia.

Maciag, P. C. and L. L. Villa (1999). "Genetic susceptibility to HPV infection and cervical cancer." Braz J Med Biol Res **32**(7): 915-22.

Squamous cell carcinoma of the cervix (SCCC) is one of the leading causes of death in developing countries. Infection with high-risk human papillomavirus (HPV) is the major risk factor to develop malignant lesions in the cervix. Polymorphisms of the MHC and p53 genes seem to influence the outcome of HPV infection and progression to SCCC, although controversial data have been reported. MHC are highly polymorphic genes that encode molecules involved in antigen presentation, playing a key role in immune regulation, while p53 is a tumor suppressor gene that regulates cell proliferation. The HPV E6 protein from high-risk types binds p53 and mediates its degradation by the ubiquitin pathway. The role of these polymorphisms in genetic susceptibility to HPV infection and to SCCC remains under investigation.

Maggio-Price, L., P. Treuting, et al. (2009). "Bacterial infection of Smad3/Rag2 double-null mice with transforming growth factor-beta dysregulation as a model for studying inflammation-associated colon cancer." Am J Pathol **174**(1): 317-29.

Alterations in genes encoding transforming growth factor-beta-signaling components contribute to colon cancer in humans. Similarly, mice deficient in the transforming growth factor-beta signaling molecule, Smad3, develop colon cancer, but only after a bacterial trigger occurs, resulting in chronic inflammation. To determine whether Smad3-null lymphocytes contribute to increased cancer susceptibility, we crossed Smad3-null mice with mice deficient in both B and T lymphocytes (Rag2(-/-) mice). Helicobacter-infected Smad3/Rag2-double knockout (DKO) mice had more diffuse inflammation and increased incidence of adenocarcinoma compared with Helicobacter-infected Smad3(-/-) or Rag2(-/-) mice alone. Adoptive transfer of WT CD4(+)CD25(+)

T-regulatory cells provided significant protection of Smad3/Rag2-DKO from bacterial-induced typhlocolitis, dysplasia, and tumor development, whereas Smad3(-/-) T-regulatory cells provided no protection. Immunohistochemistry, real-time reverse transcriptase-polymerase chain reaction, and Western blot analyses of colonic tissues from Smad3/Rag2-DKO mice 1 week after Helicobacter infection revealed an influx of macrophages, enhanced nuclear factor-kappaB activation, increased Bcl(XL)/Bcl-2 expression, increased c-Myc expression, accentuated epithelial cell proliferation, and up-regulated IFN-gamma, IL-1alpha, TNF-alpha, IL-1beta, and IL-6 transcription levels. These results suggest that the loss of Smad3 increases susceptibility to colon cancer by at least two mechanisms: deficient T-regulatory cell function, which leads to excessive inflammation after a bacterial trigger; and increased expression of proinflammatory cytokines, enhanced nuclear factor-kappaB activation, and increased expression of both pro-oncogenic and anti-apoptotic proteins that result in increased cell proliferation/survival of epithelial cells in colonic tissues.

Maggio-Price, L., P. Treuting, et al. (2006). "Helicobacter infection is required for inflammation and colon cancer in SMAD3-deficient mice." Cancer Res **66**(2): 828-38.

Accumulating evidence suggests that intestinal microbial organisms may play an important role in triggering and sustaining inflammation in individuals afflicted with inflammatory bowel disease (IBD). Moreover, individuals with IBD are at increased risk for developing colorectal cancer, suggesting that chronic inflammation may initiate genetic or epigenetic changes associated with cancer development. We tested the hypothesis that bacteria may contribute to the development of colon cancer by synergizing with defective transforming growth factor-beta (TGF-beta) signaling, a pathway commonly mutated in human colon cancer. Although others have reported that mice deficient in the TGF-beta signaling molecule SMAD3 develop colon cancer, we found that SMAD3-deficient mice maintained free of the Gram-negative enterohepatic bacteria Helicobacter spp. for up to 9 months do not develop colon cancer. Furthermore, infection of SMAD3(-/-) mice with Helicobacter triggers colon cancer in 50% to 66% of the animals. Using real-time PCR, we found that Helicobacter organisms concentrate in the cecum, the preferred site of tumor development. Mucinous adenocarcinomas develop 5 to 30 weeks after infection and are preceded by an early inflammatory phase, consisting of increased proliferation of epithelial cells; increased numbers of cyclooxygenase-2-positive cells, CD4(+) T cells, macrophages; and increased MHC class II expression. Colonic tissue revealed increased transcripts for the oncogene c-myc and the proinflammatory cytokines interleukin-1alpha (IL-1alpha), IL-1beta, IL-6, IFN-gamma, and tumor necrosis factor-alpha, some of which have been implicated in colon cancer. These results suggest that bacteria may be important in triggering colorectal cancer, notably in the context of gene mutations in the TGF-beta signaling pathway, one of the most commonly affected cellular pathways in colorectal cancer in humans.

Maiche, A. G. and T. Muhonen (1993). "Granulocyte colony-stimulating factor (G-CSF) with or without a quinolone in the prevention of infection in cancer patients." Eur J Cancer **29A**(10): 1403-5.

59 patients who had earlier developed an infection following antineoplastic chemotherapy were randomised to receive either granulocyte colony-stimulating factor (G-CSF) alone or G-CSF+quinolone as prophylaxis during subsequent identical chemotherapy courses. 30 patients received 48 courses of G+CSF, while 29 patients received 44 courses of G-CSF+ofloxacin or ciprofloxacin. The overall infection rate was 23%. Patients with WHO grade IV leukopenia at the onset of prophylactic treatment developed infection in 61% of cases when on G-CSF, but only in 22% when on G-CSF+quinolone (P = 0.002). Patients with initial leukopenia of grade WHO III-I had only a 11% infection rate showing no significant difference between the treatment groups. The median duration of leukopenia < 1 x 10(9)/l was 4 days for patients receiving G-CSF alone and 3.5 days for those receiving additional quinolone. Patients developing infection had grade IV leukopenia for a median of 5 days. Both prophylactic treatments were well tolerated. We conclude that when prophylactic G-CSF is initiated at WHO grade IV leukopenia, addition of an oral quinolone reduces the risk of infection.

Mathe, G. (1997). "Is the study of human cancer-associated factors, the best or the only model for human carcinogenesis research? I. The question of Helicobacter pylori infection as an accused human gastric carcinogen." Biomed Pharmacother **51**(1): 1-4.

Experimental carcinogenesis has discovered and analyzed the inductive effect for one type of cancer, of single factors in given animal strains. Human carcinogenesis analyses the effect of associated factors on one cancer type incidence. It does not find any direct correlation and finds a lot of intermediary effects and mechanism between the factor and established carcinogenesis. Regarding Helicobacter pylori (HP), one realizes there is no statistical correlation between gastric infection and

carcinoma. The only data which sustain its role is its possible effect in promoting atrophic gastritis with intestinal metaplasia, via the serum pepsinogen 1 reduction due to anti-HP immunoglobulin A (IgA) antibody. Intestinal metaplasia of the stomach is a condition increasing cell proliferation.

Matsuda, A., T. Matsutani, et al. (2009). "Preoperative plasma adiponectin level is a risk factor for postoperative infection following colorectal cancer surgery." J Surg Res **157**(2): 227-34.

BACKGROUND: Adiponectin is produced exclusively by adipose tissues. It is associated with visceral adiposity and various metabolic disorders, and acts as an anti-inflammatory protein that inhibits nuclear factor-kappaB activation. The purpose of this study is to clarify the association between the preoperative plasma adiponectin levels and the development of postoperative infection following colorectal cancer surgery. METHODS: Peripheral blood samples were collected from 41 colorectal cancer patients before surgery and on postoperative days (PODs) 1, 3, 5, and 7. Plasma adiponectin, leptin, and serum C-reactive protein (CRP) levels were measured and the white blood cells (WBCs) were counted. Subcutaneous and visceral fat volumes were quantified by preoperative CT scans. The patients were divided into a group with postoperative infections and an uninfected group. RESULTS: In both groups, the postoperative plasma adiponectin levels decreased transiently and then gradually recovered. However, the infected group had significantly lower adiponectin levels throughout the perioperative period than the uninfected group. Logistic regression analysis revealed that preoperative adiponectin level was an independent risk factor for postoperative infection. CONCLUSIONS: Preoperative adiponectin levels may be useful for anticipating the development of postoperative infection following colorectal cancer surgery.

McColl, K. E. and E. El-Omar (2002). "How does H. pylori infection cause gastric cancer?" Keio J Med **51 Suppl 2**: 53-6.

H. pylori is now recognised to be an important co-factor in the aetiology of non-cardia gastric cancer of both the diffuse and intestinal histological type. The latter type develops via a complex multistage and multifactorial process. The fist stage involves progression from superficial gastritis to atrophic pangastritis with intestinal metaplasia and associated hypochlorhydria. This gastric phenotype may then progress to dysplasia and cancer. Many co-factors are involved in this progression including the strain of H. pylori, host genetic factors, such as interleukin-1 polymorphisms and gender, plus environmental factors such as smoking and diet. Intestinal colonisation with helminthic infection may retard the progression by altering the immune and inflammatory response to H. pylori and colonisation of the achlorhydric stomach with nitrosating bacteria may promote progression to cancer. H. pylori appears to be an obligatory co-factor in the aetiology of most gastric cancers. Consequently, prevention of the infection or its eradication in early life should reduce the incidence of this common and usually fatal tumour.

McNamara, D. and E. El-Omar (2008). "Helicobacter pylori infection and the pathogenesis of gastric cancer: a paradigm for host-bacterial interactions." Dig Liver Dis **40**(7): 504-9.

Helicobacter pylori infection is the most important acquired risk factor for gastric cancer. The infection initiates a chronic inflammatory process that eventually alters the physiology of the gastric environment and leads to achlorohydria. Gastric atrophy may be part of this process but cancer can arise without this precursor. The net effect of decades of inflammation is the establishment of a milieu awash with pro-inflammatory cytokines and characterized by the activation of signalling pathways that cross-talk between inflammation and carcinogenesis. Many of the factors involved in chronic inflammation play a dual role in the process-promoting neoplastic progression but also facilitating cancer prevention. H. pylori bacterial virulence factors as well as host genetic factors play a major role in orchestrating the increased risk of cancer. The study of such host-bacterial interaction is key to uncovering the molecular and cellular pathways involved and will ultimately lead to developing preventive and therapeutic strategies against this global killer.

Menaker, R. J., A. A. Sharaf, et al. (2004). "Helicobacter pylori infection and gastric cancer: host, bug, environment, or all three?" Curr Gastroenterol Rep **6**(6): 429-35.

Helicobacter pylori is a common bacterial pathogen that colonizes the gastric mucosa of over 50% of the world's population. All infected individuals exhibit chronic gastric inflammation, and approximately 1% of patients develop gastric cancers, including adenocarcinomas and mucosal-associated lymphoid tissue lymphomas. In 1994, the World Health Organization International Agency for Research on Cancer classified H. pylori as a type I, or definite carcinogen. Because the prevalence of gastric cancers among H. pylori-infected patients varies between individuals, countries, and geographic areas, H. pylori disease-related outcomes are believed to be determined by an interplay between host factors,

bacterial factors, and their interaction with the environment. This review highlights recent advances in our knowledge on H. pylori disease pathogenesis, focusing on the role of the host, bacteria, and environment in the development of gastric carcinoma.

Mendonca, M. A., A. H. Pereira, et al. (2009). "Neutrophil count is not associated with infection episodes in breast cancer patients treated with anthracycline-based chemotherapy." Eur J Cancer Care (Engl) **18**(2): 184-90.

The aim was to evaluate the impact of anthracycline-based chemotherapy on neutrophil count and infections in breast cancer women. The medical records of patients were retrospectively and prospectively reviewed (8-year period). Patients were grouped according to anthracyclines at different doses: (1) Scheme 1 (n = 56, 224 courses): 50-60 mg/m(2); and (2) Scheme 2 (n = 25, 100 courses): 65-75 mg/m(2), associated to cyclophosphamide and 5-fluorouracil, at 21-day intervals between courses. Neutrophil count was performed on diagnosis and 48-72 h before each chemotherapy course. Patients were followed up for neutrophil count and infection episodes for three consecutive courses. Multivariate analysis was used to determine independent factors for infection. After the first course, neutrophil count was reduced than baseline ($P < 0.001$) and maintained during the subsequent courses, without differences between courses or groups. There were 49 infection episodes (63.2% urinary, 18.4% neutropenic fever and 18.4% diverses), mainly between course 1-2 (39%) and course 3-4 (38%) of chemotherapy. Patients evaluated as presenting or not with infection episodes did not differ in neutrophil count. The number of chemotherapy courses ($P < 0.05$), but not age, neutrophil count or chemotherapy regimen, was associated with infection. We concluded that progressive chemotherapy, but not neutrophil count, was an independent factor for infection.

Milde-Langosch, K., K. Albrecht, et al. (1995). "Presence and persistence of HPV infection and p53 mutation in cancer of the cervix uteri and the vulva." Int J Cancer **63**(5): 639-45.

We studied 51 cervical carcinomas, among them 25 squamous-cell carcinomas (SCC) and 26 cervical adenocarcinomas (AdCa), and 40 vulvar SCC for the presence of HPV and mutant p53. HPV was detected by PCR, and p53 alterations by temperature-gradient gel electrophoresis/direct sequencing and immunohistochemistry. HPV, mostly type 16/18, was found in 80.4% of the cervical tumors (92.0% of the SCC and 69.2% of the AdCa), but in only 27.5% of vulvar carcinomas. In contrast, p53 mutations were found in 7.8% and 52.5% of cervical and vulvar tumors respectively. Mutant p53 occurred in pre-invasive vulvar lesions, indicating that this oncogenic factor is involved early in carcinogenesis. Further analysis of recurrent/metastatic lesions of 9 cervical and 14 vulvar tumors also showed remarkable differences: in cervical cancer, HPV was persistent, and p53 mutations absent, whereas in vulvar tumors, HPV was mostly absent or not persistent, and the p53 mutation rate was very high (78.6%). These observations suggest that HPV persistence is an important event for the evolution and maintenance of cervical cancer, whereas for vulvar cancers p53 mutation and not HPV activity is a central oncogenic event.

Minaguchi, T., Y. Kanamori, et al. (1998). "No evidence of correlation between polymorphism at codon 72 of p53 and risk of cervical cancer in Japanese patients with human papillomavirus 16/18 infection." Cancer Res **58**(20): 4585-6.

Human papillomavirus (HPV)-16 and -18 encode E6 oncoprotein, which binds to and induces degradation of the tumor suppressor protein p53. A common polymorphism of p53, encoding either proline or arginine at position 72, affects the susceptibility of p53 to E6-mediated degradation in vivo; Caucasian women homozygous for arginine 72 reportedly are about seven times more susceptible to HPV-associated carcinoma of the cervix than heterozygotes. To examine whether arginine 72 could be a risk factor for HPV-associated cervical carcinomas in the Japanese population, we used the same PCR-based assay to analyze p53 genotypes of HPV-positive invasive cervical carcinomas from 103 Japanese women versus 110 control samples. Inasmuch as we detected no significant difference in the frequencies of proline or arginine alleles between the two groups, p53 polymorphism at residue 72 does not seem to be involved in the development of HPV-associated cervical carcinomas in women of Japanese ethnicity.

Moulin, F., S. Dumontier, et al. (1996). "Surveillance of intestinal colonization and of infection by vancomycin-resistant enterococci in hospitalized cancer patients." Clin Microbiol Infect **2**(3): 192-201.

OBJECTIVE: To study epidemiologic features of and risk factors for intestinal colonization and infection by vancomycin-resistant enterococci (VRE) in cancer patients. METHODS: During a 41-month period, over 7600 fecal samples and all samples from sterile sites from hospitalized cancer patients were screened for VRE. Species were identified and isolates analyzed by pulsed-field gel electrophoresis (PFGE) of SmaI DNA restriction fragments. Antibiotic resistance was characterized by

MIC determinations, and polymerase chain reaction for vanA, vanB, and vanC1 genes. Plasmid contents were analyzed before and after PstI and HindIII restriction, and by Southern hybridization with a vanA probe. Two case-control studies were performed to identify risk factors for colonization or infection by VRE, respectively. RESULTS: Eighty-two isolates were recovered from 81 patients. Most (72%) isolates were Enterococcus faecium VanA/vanA, with 37 different PFGE types, each of which was found in only one to four patients, except for type P1, which was found in 20 patients hospitalized over a 3-month period in the pediatric wards. Plasmid analysis suggested that only two types of plasmid were carrying gene vanA, as part of a transposon related to transposon Tn 1546 from reference strain E. faecium BM4147. Seventy-seven patients were colonized during the study period. Six of them became infected. Four patients were infected but not colonized. Only one patient died during the course of infection, but intestinal colonization persisted for months in the survivors. Case-control analysis revealed that cephalosporin treatment was a significant risk factor for colonization. No significant risk factor for infection was found in colonized patients. CONCLUSION: Colonization by VRE was mostly endemic and the colonized patients were not often infected. However, when clustered cases of colonization occurred, they were then associated with an increased rate of infection.

Mueller, A., S. Falkow, et al. (2005). "Helicobacter pylori and gastric cancer: what can be learned by studying the response of gastric epithelial cells to the infection?" Cancer Epidemiol Biomarkers Prev **14**(8): 1859-64.

The development of gastric adenocarcinoma is closely linked to chronic infection with the bacterial pathogen Helicobacter pylori. One Helicobacter-specific virulence factor in particular, the CagA protein, has emerged as a main effector molecule in the interaction of H. pylori with gastric epithelial cells and has been implicated in gastric carcinogenesis. This review highlights the latest insights that have been gained into the pathogenesis of the disease by transcriptional profiling approaches studying gene expression in normal gastric tissue and gastric cancer tissue from human biopsy material as well as animal models of Helicobacter infection. The potential role of CagA as a bacterial oncoprotein is also discussed.

Nagatomo, A., K. Watanabe, et al. (1998). "A randomized controlled trial of sulfamethoxazole/trimethoprim plus norfloxacin versus sulfamethoxazole/trimethoprim alone for the prophylaxis of bacteria infection during chemotherapy for lung cancer." Lung Cancer **19**(2): 121-5.

The efficacy of the prophylactic administration of sulfamethoxazole/trimethoprim (ST) plus norfloxacin (NFLX) versus ST alone to prevent the development of bacterial infection during chemotherapy-induced leukopenia was compared in patients with lung cancer. Patients who underwent systemic chemotherapy were randomized into one of the prophylactic regimens when grade 3 or 4 leukopenia occurred. Prophylactic treatment was performed on 133 courses of leukopenia in 75 patients and the efficacy was evaluated on 127 of those courses after excluding those patients who demonstrated a fever within 24 h from the start of the prophylaxis. The number of patients who had leukopenia associated fever was two out of 63 (3.2%) with the ST plus NFLX regimen and 10 out of 64 (15.6%) with ST alone; the difference was statistically significant. The prophylactic use of ST plus NFLX was thus found to be more useful than ST alone for the treatment of chemotherapy-induced leukopenia in patients with lung cancer.

Nakajima, S. and T. Hattori (2004). "Oesophageal adenocarcinoma or gastric cancer with or without eradication of Helicobacter pylori infection in chronic atrophic gastritis patients: a hypothetical opinion from a systematic review." Aliment Pharmacol Ther **20 Suppl 1**: 54-61.

BACKGROUND: As chronic atrophic gastritis is a precancerous condition for gastric cancer and the eradication of Helicobacter pylori infection halts chronic gastritis, eradication of infection may prevent gastric cancer. However, as chronic atrophic gastritis is a risk factor for reflux oesophagitis after eradication of infection, the risk of oesophageal adenocarcinoma may also increase. METHODS: We systematically reviewed papers and estimated the expected annual incidence of oesophageal or gastric cancer with and without eradication of H. pylori infection in patients with chronic atrophic gastritis. RESULTS: The expected annual incidence of gastric cancer in patients with corpus atrophy with persistent infection was at least 5.8-fold higher than that for oesophageal adenocarcinoma after the eradication of infection at all ages. Even for patients with accompanying reflux oesophagitis or Barrett's oesophagus, the expected incidence of either gastric or oesophageal adenocarcinoma with persistent infection was higher than that of oesophageal adenocarcinoma after eradication of infection. CONCLUSION: If eradication of infection lowers the incidence of gastric cancer, it should be recommended for patients with corpus atrophy at all ages irrespective of the presence of reflux oesophagitis or Barrett's oesophagus,

especially in populations having a high prevalence of gastric cancer.

Nakamura, T., H. Mitomi, et al. (2008). "Risk factors for wound infection after surgery for colorectal cancer." World J Surg **32**(6): 1138-41.

BACKGROUND: Among complications after surgery for colorectal cancer, wound infections may prolong hospitalization and increase healthcare costs. This study was designed to clarify the incidence, risk factors, and pathogens responsible for wound infections after surgery for colorectal cancer. METHODS: The study group comprised 144 patients (94 men and 50 women) with colorectal cancer in whom the same surgeon at Kitasato University Hospital performed resection from January 2004 through December 2005. Their mean age was 67.1 years (range = 38-90). To identify risk factors for surgical wound infections, we examined the following 11 variables: gender, age (>65 vs. <or=65 years), body-mass index (>25 vs. <or=25 kg/m(2)), the presence or absence of diabetes mellitus, physical status according to the American Society of Anesthesiologists classification (ASA score), stage of cancer according to the TNM staging system, surgical procedure (laparoscopic colectomy vs. open colectomy), procedure type (right colectomy vs. left colectomy vs. anterior resection), operation time (>180 vs. <or=180 min), intraoperative bleeding volume (>120 vs. <or=120 ml), and the presence or absence of intraoperative transfusion. Tissue specimens of infected wounds were cultured to identify pathogens. RESULTS: Postoperative wound infections occurred in 12% (17/144) of the patients. In univariate analyses, the incidence of wound infection was 26% (11/43) in patients who underwent open colectomy compared with 6% (6/101) in those who underwent laparoscopic colectomy. This difference was significant (P = 0.001). In multivariate analyses, only surgical procedure was identified as an independent risk factor for wound infection. The odds ratio for open colectomy compared with laparoscopic colectomy was 3.322 (P = 0.021). Pus from infected wounds was cultured in 7 of the 17 patients and cultures were positive for pathogens in 5 patients: 1 laparoscopic colectomy and 4 open colectomy. Bacteroides species were the most common pathogen. CONCLUSION: To prevent wound infections after surgery for colorectal cancer, laparoscopic surgery should be performed when indicated.

Ness, R. B., M. T. Goodman, et al. (2003). "Serologic evidence of past infection with Chlamydia trachomatis, in relation to ovarian cancer." J Infect Dis **187**(7): 1147-52.

Pelvic inflammatory disease has been inconsistently linked with ovarian cancer. We measured antibodies to Chlamydia trachomatis, to chlamydial heat shock protein (CHSP) 60, and to CHSP10, in 117 women with ovarian cancer and in 171 age- and ethnicity-matched population-based control subjects from Oahu, Hawaii. IgG antibodies to serovar D of chlamydia elementary bodies (EB) and IgG antibodies to CHSP60-1, CHSP60-2, CHSP60-3, and CHSP10 were detected using an ELISA assay. The probability of having ovarian cancer was 90% greater in women with the highest, compared with the lowest (optical density, >or =0.40 vs. <0.10), levels of chlamydia-EB antibodies (P=.05). There was also a monotonic trend (P=.09) in ovarian cancer risk associated with CHSP60-1 but not with CHSP60-2, CHSP60-3, or CHSP10. These data suggest that past or chronic persistent infection with chlamydia may be a risk factor for ovarian cancer.

Nicolatou-Galitis, O., K. Dardoufas, et al. (2001). "Oral pseudomembranous candidiasis, herpes simplex virus-1 infection, and oral mucositis in head and neck cancer patients receiving radiotherapy and granulocyte-macrophage colony-stimulating factor (GM-CSF) mouthwash." J Oral Pathol Med **30**(8): 471-80.

Oral pseudomembranous candidiasis (OPC) was evaluated in 61 patients receiving head and neck radiotherapy (RT). Herpes simplex virus-1 (HSV-1) reactivation was also investigated in 14 patients. According to the agreed protocol, granulocyte-macrophage colony-stimulating factor (GM-CSF) mouthwash was administered in 46 patients with radiation-induced ulcers. Candidiasis was diagnosed in 31 patients. Candida albicans was the most frequent isolate. Multiple Candida species were isolated from the lesions of four patients. Concurrent candidiasis and radiation-induced ulcers were observed in 17 patients. Viral culture and the polymerase chain reaction disclosed the presence of HSV-1 in five patients. Twenty of the 46 patients, with initial mucositis grade II and grade III, completed RT with mucositis grade I, indicating a beneficial effect of GMCSF mouthwash, although further controlled studies are necessary to verify that. In conclusion, OPC was an important infection in patients undergoing radiotherapy. The role of HSV-1 in oral mucositis during head and neck radiotherapy needs additional study.

Ohata, H., S. Kitauchi, et al. (2004). "Progression of chronic atrophic gastritis associated with Helicobacter pylori infection increases risk of gastric cancer." Int J Cancer **109**(1): 138-43.

We conducted a longitudinal cohort study to determine the association of Helicobacter pylori infection and the progression of chronic atrophic gastritis (CAG) with gastric cancer. A cohort of 4655 healthy asymptomatic subjects was followed for a mean period of 7.7 years. H. pylori infection was established by serum specific antibodies and the presence of CAG was confirmed by serum pepsinogen. During the follow-up period, 45 gastric cancer cases were detected (incidence rate, 126/100000 person-years). A univariate analysis after adjustment for age showed that both H. pylori and CAG were significantly associated with gastric cancer. To clarify the interaction between H. pylori and CAG, an analysis stratified by H. pylori- and CAG-status was performed. No cancer developed in the H. pylori(-)/CAG(-) group during the study period. This supports the theory that it is quite rare for any type of gastric cancer to develop in an H. pylori-free healthy stomach. With the progression of H. pylori-induced gastritis, the risk of gastric cancer increased in a stepwise fashion from CAG-free gastritis [H. pylori(+)/CAG(-) group] (HR=7.13, 95%CI=0.95-53.33) to CAG [H. pylori(+)/CAG(+) group] (HR=14.85, 95%CI=1.96-107.7) and finally to severe CAG with extensive intestinal metaplasia [H. pylori(-)/CAG(+) group] (HR=61.85, 95%CI=5.6-682.64) in which loss of H. pylori from the stomach is observed. Therefore, it is probable that H. pylori alone is not directly associated with stomach carcinogenesis. Instead, H. pylori appears to influence stomach carcinogenesis through the development of CAG. The observed positive correlation between the extent of H. pylori-induced gastritis and the development of cancer was strong, especially for the intestinal type. These results are compelling evidence that severe gastritis with extensive intestinal metaplasia is a major risk factor for gastric cancer, and they confirm the previously described model of stomach carcinogenesis: the gastritis-metaplasia-carcinoma sequence.

Oude Nijhuis, C. S., E. Vellenga, et al. (2003). "Endothelial cells are main producers of interleukin 8 through Toll-like receptor 2 and 4 signaling during bacterial infection in leukopenic cancer patients." Clin Diagn Lab Immunol **10**(4): 558-63.

Cancer patients who are leukopenic due to chemotherapy are susceptible to bacterial infections. Normally, clinical conditions during bacterial infections are caused by pathogen-associated molecular patterns, which are components that bind to Toll-like receptor (TLR) 2 (TLR-2) and TLR-4 on leukocytes, resulting in the production of inflammatory cytokines. The mechanism of this inflammatory response in cancer patients with diminished numbers of leukocytes is not completely clear. The levels of interleukin 1 beta (IL-1 beta) and tumor necrosis factor alpha measured in the circulation of leukopenic cancer patients are lower than those measured in that of nonleukopenic patients during bacterial infections, whereas plasma interleukin 8 (IL-8) levels show distinct identical increases during bacterial infections in both leukopenic and nonleukopenic patients. Normally, these cytokines are mainly secreted by leukocytes. In cancer patients with bacterial infections and a diminished number of leukocytes, other sources of IL-8 production, such as endothelial cells, might be expected. Endothelial cells instead of leukocytes become the most important producers of IL-8 during bacterial infections in patients with chemotherapy-induced leukopenia through TLR-2 and TLR-4 signaling. Whole blood samples from six cancer patients were stimulated with lipopolysaccharide (LPS), and then IL-8 concentrations in supernatants were measured. Further, human umbilical vein endothelial cells (HUVECs) were incubated with sera from leukopenic cancer patients with or without bacterial infections, and then IL-8 concentrations in supernatants were measured (n = 6). In addition, the same HUVEC experiment was performed with the addition of neutralizing antibodies against TLR-2 and TLR-4. During leukopenia (<10(9) cells/liter), LPS stimulation of whole blood did not result in an increase in IL-8 levels. However, when endothelial cells were incubated with sera from leukopenic cancer patients during bacterial infections, a three- to eightfold increase in IL-8 production was found, compared to the IL-8 production found after incubation with sera from patients without signs of infections. This increase did not reflect a higher level of IL-8 already present in the sera. Further, we demonstrated that IL-8 production induced in endothelial cells by sera from patients with documented gram-negative infections could be reduced significantly by up to 40% when the cells were incubated with neutralizing antibodies against TLR-4 (P = 0.028). The addition of TLR-2 antibodies slightly enhanced the reduction of IL-8 production. These results suggest that during bacterial infections in cancer patients with markedly diminished numbers of leukocytes, endothelial cells become important producers of IL-8 through TLR-4 signaling and, to a lesser extent, TLR-2 signaling.

Popescu, M., D. L. Dumitrascu, et al. (2007). "Low prevalence of Helicobacter pylori infection in patients with gastric cancer." Rom J Intern Med **45**(3): 259-62.

The Helicobacter pylori (Hp) infection is a well-known carcinogenic factor. There are only limited data on the presence of Hp infection in gastric

cancer in Romania. AIM: Cross-sectional study of the prevalence of Hp infection in gastric cancer. MATERIAL-METHODS: All cases of gastric cancer confirmed by gastroscopy in an endoscopy unit with national referrals were analysed. The Hp status was checked. The Hp + cases were studied compared with the Hp - cases. RESULTS: From 6768 gastroscopies 84 cases with gastric cancer were detected. Among these in 40 the Hp status was determined. 37 cases were carcinoma, 1 lymphoma, 2 cases without microscopical aspect of malignancy. In 8 cases (20%) Hp was found +. The majority of the patients with gastric cancer did not use PPIs. There were no demographic life style differences between the patients with gastric cancer who were Hp + and Hp -. CONCLUSION: Prevalence of the Hp infection in gastric cancer is lower than that reported in the literature. The investigation of Hp in gastric cancer should be done routinely. These data represent the starting point for a prospective study.

Popov, A. and J. L. Schultze (2008). "IDO-expressing regulatory dendritic cells in cancer and chronic infection." J Mol Med (Berl) **86**(2): 145-60.

Immune evasion and T cell tolerance induction have been associated both with malignant disease and chronic infection. In recent years, increasing evidence has been accumulated that antigen-presenting cells such as dendritic cells (DC) play a major role in immune regulation. They are not only involved in the induction of immunity but also can inhibit immune responses. Interesting parallels for major molecular mechanisms involved in turning DC from stimulatory to regulatory cells have been uncovered between malignant disease and chronic infection. Apparently, not only inhibitory cytokines such as IL-10 seem to play a role, but also metabolic mechanisms dysregulating tryptophan metabolism, thereby, leading to inhibition of T cells and pathogens. We focus here on recent findings establishing the tryptophan catabolizing enzyme indoleamine-pyrrole 2,3 dioxygenase (IDO) as a central feature of DC with regulatory function both in cancer and chronic infection. Induction of enzymatically active IDO can be triggered by various soluble and membrane-bound factors, and in general, require interferon (IFN) signaling. In addition, based on the most recently established link between tumor necrosis factor alpha (TNFalpha), prostaglandin E2 and IDO, a new model of regulation of IDO in context of cancer and infection is proposed. In light of the increasing use of anti-TNFalpha drugs, these findings are also of great interest to the clinician scientist.

Raad, I., D. Abi-Said, et al. (1998). "The risk of infection associated with intra-arterial catheters for cancer chemotherapy." Infect Control Hosp Epidemiol **19**(9): 640-2.

OBJECTIVE: To determine the frequency of, and risk factors for, infections associated with intra-arterial catheters used for cancer chemotherapy. METHODS: Between September 1992 and September 1995, we conducted a surveillance study of all 807 intra-arterial catheters placed for chemotherapy at our center. The insertion site was disinfected with povidone iodine and alcohol, and the arterial catheter was placed using maximal sterile barrier precautions. Upon removal, all intravascular segments were submitted for semi-quantitative culture. RESULTS: No episodes of catheter-related bloodstream infection (95% confidence interval [CI95], 0%-1.6%) were observed. However, the risk of colonization (>15 colony-forming units) of arterial catheters was 15% (CI95, 12%-17%). Retrospective risk-factor analysis conducted on 224 intra-arterial catheters placed for chemotherapy in 1993 showed that colonization was associated significantly with duration of catheterization (median of 1 day for culture-negative catheters vs median of 4 days for culture-positive catheters, P<.001). Age, gender, prior radiotherapy, underlying cancer, neutropenia, and hypoalbuminemia were not associated with catheter colonization. CONCLUSION: Intra-arterial catheters for cancer chemotherapy placed under maximal sterile barrier precautions for a short period of time are associated with a very low risk of bloodstream infection.

Rabkin, C. S., R. J. Biggar, et al. (1993). "Cancer incidence trends in women at high risk of human immunodeficiency virus (HIV) infection." Int J Cancer **55**(2): 208-12.

To determine the types and rates of tumors which may be associated with HIV infection in women, we used cancer incidence data from New York and northern New Jersey. We examined changes in incidence of selected cancers in women aged 20-49 years and compared groups differing in incidence of AIDS. Black women were compared to white women in New York City and in the remainder of New York State; for cervical cancer, rates were also compared for Blacks and Whites in northern New Jersey. The incidence of Kaposi's sarcoma in women increased in New York City, beginning in 1982 for Blacks and in 1984 for Whites, but remained stable in the remainder of New York State. The incidence of non-Hodgkin's lymphoma in New York women doubled in Blacks after 1982 whereas incidence trends in Whites were unchanged. No consistent variation was seen in the incidence of Hodgkin's disease. Cervical cancer in New York and northern New Jersey Blacks declined over the same period by approximately 40% for invasive tumors and 50% for in situ lesions. The HIV

epidemic is associated with substantial excesses of Kaposi's sarcoma and non-Hodgkin's lymphoma in women. The absence of Kaposi's sarcoma in upstate New York women suggests the existence of a geographically restricted co-factor(s) for Kaposi's sarcoma in addition to HIV. If HIV affected cervical cancer incidence through 1988, its impact was small compared to the striking decreases which followed widespread adoption of Papanicolaou screening.

Raderer, M., F. Wrba, et al. (1998). "Association between Helicobacter pylori infection and pancreatic cancer." Oncology **55**(1): 16-9.

PURPOSE: In order to determine whether infection with Helicobacter pylori might be associated with pancreatic adenocarcinoma, we performed a study to compare the H. pylori seroprevalence rate between patients with pancreatic carcinoma and matched control subjects. PATIENTS AND METHODS: Blood samples from 92 patients with histologically confirmed diagnosis of pancreatic adenocarcinoma admitted to our hospital between January 1994 and July 1995 were analyzed for the presence of IgG antibodies against H. pylori by a commercially available enzyme-linked immunosorbent assay. Thirty patients with gastric cancer, 35 patients with colorectal cancer, and 27 healthy volunteers served as controls. In addition to these serological analyses, tumor specimens from 20 patients with pancreatic adenocarcinoma were microscopically investigated for the presence of H. pylori. RESULTS: 65% of pancreatic cancer patients and 69% of those with gastric cancer were found to be seropositive, while only 45% of the other controls tested positive. Statistical analysis revealed no difference in seropositivity between the cohort of patients suffering from pancreatic and gastric cancer. The rate of seropositivity was more prominent, however, in pancreatic cancer patients when compared with those suffering from colorectal cancer combined with normal controls ($p = 0.035$), with an odds ratio of 2.1 (1.1-4.1). Microscopic evaluation of human pancreatic cancer specimens showed no evidence for the presence of H. pylori. CONCLUSION: Our data suggest an association between H. pylori infection and pancreatic cancer. Despite demonstration of a positive relationship and its physiological plausibility, larger prospective studies are needed to confirm our preliminary findings and to assess H. pylori as a potential carcinogenic risk factor.

Randall, R. J. (2001). "Hepatitis C virus infection and long-term survivors of childhood cancer: issues for the pediatric oncology nurse." J Pediatr Oncol Nurs **18**(1): 4-15.

Infection with hepatitis C virus (HCV) represents a major public health concern today because of its prevalence in the United States. Acute HCV is commonly asymptomatic and often results in chronic disease. However, symptoms related to chronic disease may not appear for decades. Patients with HCV have a broad spectrum of symptoms, which vary from elevated liver function test results to cirrhosis, liver cancer and end stage liver disease. Past treatment therapies have not been highly effective; however, a new treatment is currently available. Today, many high-risk activities are associated with HCV infection. Blood transfusions are no longer a risk factor. However, 20% of individuals who received transfused blood products contracted hepatitis C nearly two decades ago. Therefore, cancer survivors who received blood products to combat chemotherapy induced anemia and thrombocytopenia before 1980 represent a population at risk. It is important that nurses caring for these patients understand the pathophysiology, etiology, transmission, and course of HCV. This knowledge will enable nurses to encourage serological testing to identify infected individuals. Once identified, patients with hepatitis C can receive social support and appropriate referrals to help them deal with the psychosocial issues related to long-term effects and secondary illnesses.

Rotstein, C., L. Brock, et al. (1995). "The incidence of first Hickman catheter-related infection and predictors of catheter removal in cancer patients." Infect Control Hosp Epidemiol **16**(8): 451-8.

OBJECTIVE: To describe the incidence and types of first Hickman catheter-related infection (HCRI) in cancer patients and to identify indicators for catheter removal. DESIGN: Retrospective cohort study. SETTING: A regional, tertiary, referral cancer center and its supportive care university teaching hospital. PATIENTS AND METHODS: A retrospective review was conducted of 316 consecutive adult oncology patients who underwent Hickman catheter placement from 1986 to 1990 at a regional oncology center. HCRI was determined on the basis of clinical information incriminating the Hickman catheter as the source of infection. Patient characteristics and data about HCRIs (exit site cellulitis, tunnel infection with concomitant exit site cellulitis, bloodstream infection, and exit site cellulitis with bloodstream infection) were abstracted from patient medical records. Subsequently, univariate and multivariate analyses for the risk of HCRI and catheter removal were completed. RESULTS: The incidence of first HCRI was 5.98 infections per 1,000 catheter days. Overall, 156 (49%) of 316 patients developed their first HCRI prior to catheter removal. The median time to HCRI was 90 days. Male gender ($P = .0004$)

and hematologic malignancy (P = .0001) emerged as significant risk factors for HCRI in the univariate analysis. A cox model verified that male gender (P = .02) and hematologic malignancy (P = .004) were associated with an enhanced risk of HCRI. There were 35 exit site infections (23%), three infections of the tunnel and the exit site (2%), 80 bloodstream infections (51%), and another 38 bloodstream infections with concomitant exist site infections (24%). The incidence of bloodstream infection was 3.05 per 1,000 catheter days. Gram-positive pathogens outnumbered gram-negatives and fungi, with Staphylococcus epidermidis being most common. Fifty (32%) of 156 HCRIs resulted in catheter removal. Predictors of Hickman catheter removal in the univariate analysis were bloodstream infection (P = .046) and pathogen type (P = .006). Multiple regression analysis suggested that having a gram-negative (P = .014) or fungal (P = .057) pathogen was the most important factor for catheter removal. CONCLUSIONS: These data suggest that first HCRIs occur more commonly in male patients with hematologic malignancies than in patients with solid tumors. The removal of Hickman catheters in oncology patients probably is predicated on the causative pathogen, but further investigations are necessary to delineate this issue.

Sasagawa, T., Y. Dong, et al. (1997). "Human papillomavirus infection and risk determinants for squamous intraepithelial lesion and cervical cancer in Japan." Jpn J Cancer Res **88**(4): 376-84.

A case control design was used to investigate human papillomavirus (HPV) prevalence and risk factors associated with development of cervical squamous intraepithelial lesion (SIL) and cervical cancer (CC) in Japan. One hundred and twenty-three women with histologically confirmed SIL or CC were compared to a control group of 778 cytologically normal women. With the use of a polymerase chain reaction (PCR)-based method for detection of low-risk (types 6 and 11) and high-risk (types 16, 18, 31, 33, 35, 52 and 58) HPVs, a high prevalence of HPV infection was observed in smokers among the controls. Logistic regression analysis demonstrated that high-risk HPV infection was the most significant risk determinant for LSIL (OR=9.4, 95% CI=4.5-19), HSIL (OR=77, 95% CI=28-217) and CC (OR=97, 95% CI=35-269). It also showed that unmarried women, women married for 5 to 19 years and smokers represented high risk groups for SIL, while smokers and women with a history of many pregnancies/parities had increased risk for CC. Smoking was the only HPV infection-independent factor for CC, suggesting that smoking may have a carcinogenic effect on the cervix. Since neither history of other cancer nor family cancer history was associated with SIL or CC, genetic factors appear to play little role in cervical carcinogenesis. The risk for cervical neoplasia due to HPV infection increased after marriage in Japan, suggesting a role for husbands as carriers of HPV transmission. Protection from high-risk HPV infection may be of greatest importance for prevention of cervical cancer.

Sayhan, N., H. Yazici, et al. (2001). "P53 codon 72 genotypes in colon cancer. Association with human papillomavirus infection." Res Commun Mol Pathol Pharmacol **109**(1-2): 25-34.

It has been reported that the p53Arg homozygous genotype could be a potential genetic risk factor for cancer. In this study we investigated the proportion of p53 codon 72 genotypes in patients with colon cancer and compared to a control population. A region of the p53 gene containing the polymorphic site was amplified by PCR and the genotypes were determined by restriction enzyme digestion. No significant difference was found between genotype frequencies in the study groups. Infection with human papilloma virus was also investigated in the tumor samples. HPV 18 and HPV 33 infection was observed in a considerable number of the tumor samples. Incidence of HPV infection did not show a correlation with the genotypes. Thus the p53 genotypes do not seem to be associated with risk of colon cancer or HPV infection.

Sayi, A., E. Kohler, et al. (2009). "The CD4+ T cell-mediated IFN-gamma response to Helicobacter infection is essential for clearance and determines gastric cancer risk." J Immunol **182**(11): 7085-101.

Chronic infection with the bacterial pathogen Helicobacter pylori is a risk factor for the development of gastric cancer, yet remains asymptomatic in the majority of individuals. We report here that the C57BL/6 mouse model of experimental infection with the closely related Helicobacter felis recapitulates this wide range in host susceptibility. Although the majority of infected animals develop premalignant lesions such as gastric atrophy, compensatory epithelial hyperplasia, and intestinal metaplasia, a subset of mice is completely protected from preneoplasia. Protection is associated with a failure to mount an IFN-gamma response to the infection and with a concomitant high Helicobacter burden. Using a vaccine model as well as primary infection and adoptive transfer models, we demonstrate that IFN-gamma, secreted predominantly by CD4(+)CD25(-) effector T(H) cells, is essential for Helicobacter clearance, but at the same time mediates the formation of preneoplastic lesions. We further provide evidence that IFN-gamma triggers a common

transcriptional program in murine gastric epithelial cells in vitro and in vivo and induces their preferential transformation to the hyperplastic phenotype. In summary, our data suggest a dual role for IFN-gamma in Helicobacter pathogenesis that could be the basis for the differential susceptibility to H. pylori-induced gastric pathology in the human population.

Scaggiante, B., S. Bonin, et al. (2008). "Prostate-tumor-inducing gene-1 analysis in human prostate cancer cells and tissue in relation to Mycoplasma infection." Cancer Invest **26**(8): 800-8.

The potential role of PTI-1, in the natural story of prostate adenocarcinoma remains to be fully determined. PTI-1 expression was evaluated in human prostate cancer cell lines and in paraffin-embedded archive tissues. PTI-1 expression was found in Mycoplasma infected but not in non-infected cells. The lack of PTI-1 expression was also confirmed in fixed and paraffin-embedded human cancer prostate biopsies. The overall data indicate that, in prostate tumor cell lines, PTI-1 presence parallels Mycoplasma infection suggesting that PTI-1 might not necessarily play a major role in the onset of prostate tumorigenesis.

Schmitz, K. J., J. Wohlschlaeger, et al. (2008). "Activation of the ERK and AKT signalling pathway predicts poor prognosis in hepatocellular carcinoma and ERK activation in cancer tissue is associated with hepatitis C virus infection." J Hepatol **48**(1): 83-90.

BACKGROUND/AIMS: The aim of the study was to determine the prognostic relevance of AKT and extracellular regulated kinases (ERK1/2), which are implied in the regulation of cell proliferation and apoptosis, in hepatocellular carcinoma (HCC). METHODS: This study comprised a series of 208 patients incorporating HCCs treated either by surgical resection (n = 109) or liver transplantation (n = 99). Immunohistochemically demonstrated phospho-ERK1/2 (pERK1/2) and phospho-AKT (pAKT) was correlated with a series of clinico-pathologically relevant parameters (EGFR, Cyclin-D1, HCV/HBV infection, liver cirrhosis, chronic alcohol abuse), proliferative activity, and apoptosis. RESULTS: Activation of ERK1/2 correlated statistically with the presence of HCV infection. pERK1/2 ($P < 0.001$) and pAKT ($P = 0.052$) expression showed a significant correlation with a decreased overall survival (OS). In multivariate Cox regression analysis pERK1/2 was identified as an independent prognostic parameter in HCC ($P = 0.026$). CONCLUSIONS: Activation of ERK1/2 in HCC cancer indicates aggressive tumour behaviour and constitutes an independent prognostic factor. Furthermore our data confirm that HCV infection activates the ERK pathway and thereby might contribute to HCC carcinogenesis. Immunohistochemical determination of pERK1/2 status can thus be proposed as a promising candidate for the identification of high risk patients who may benefit from new anticancer drugs targeting the ERK-pathway.

Shah, M. H., A. G. Freud, et al. (2006). "A phase I study of ultra low dose interleukin-2 and stem cell factor in patients with HIV infection or HIV and cancer." Clin Cancer Res **12**(13): 3993-6.

PURPOSE: Ultra low doses of interleukin-2 (IL-2) can activate the high-affinity IL-2 receptor constitutively expressed on CD56(bright) natural killer (NK) cells, the CD34+ NK cell precursor, and CD4+ CD25+ regulatory T cells (Tregs) in vivo. We have previously shown synergy between IL-2 and stem cell factor (SCF) in the generation of CD56(bright) NK cells from CD34+ hemopoietic progenitor cells in vitro and showed synergistic NK cell expansion in an in vivo preclinical model. To determine the safety, toxicity, and immune modulation of this combination of cytokines in vivo, we conducted a first-in-man phase I study. EXPERIMENTAL DESIGN: A phase I dose escalation study was conducted using IL-2 at 900,000 or 650,000 IU/m2/d for 8 weeks with 5 or 10 microg/kg/d of SCF given thrice a week for 8 weeks in patients with HIV infection and/or cancer. RESULTS: Ten of 13 patients completed therapy; four experienced the dose-limiting toxicities of grade 3 fatigue or urticaria. The maximum tolerated doses of IL-2 and SCF in combination is 650,000 IU/m2/d of IL-2 and 5 microg/kg/d thrice a week of SCF. NK cells were expanded over 2-fold on therapy; Tregs were expanded nearly 6-fold from baseline. CONCLUSIONS: Administration of IL-2 with SCF is safe and well tolerated and leads to expansion of lymphocyte subsets in patients with HIV or HIV and cancer; however, the changes in NK cell and Treg expansion seen with this cytokine combination were no different than those seen with a similar dose of IL-2 alone.

Shanks, A. M. and E. M. El-Omar (2009). "Helicobacter pylori infection, host genetics and gastric cancer." J Dig Dis **10**(3): 157-64.

Helicobacter pylori infects half the world's population and is responsible for a considerable global health burden, including peptic ulcer disease and gastric cancer. The infection causes a chronic gastritis, the severity and distribution of which determine the clinical outcome. Bacterial, environmental and host genetic factors combine to define the degree of gastric damage. Most patients have a limited mild pan-

gastritis with no significant clinical consequences. Antral-predominant gastritis is associated with high gastric acid output and an increased risk of duodenal ulcers. Corpus-predominant gastritis is associated with a reduction in gastric acid, multifocal gastric atrophy and an increased risk of gastric cancer. Host genetic factors are particularly important in defining the severity and extent of Helicobacter-induced gastritis. The most relevant and consistent genetic factors uncovered thus far are in the interleukin-1 and tumor necrosis factor-A gene clusters. These cytokines appear to play a key role in the pathophysiology of gastric cancer and their roles have been confirmed in animal models that mimic human gastric neoplasia. More genetic factors have also been uncovered and, with advancing technology, there is every prospect of defining a full genetic risk profile in the next decade. This will aid in targeting the testing and treatment of Helicobacter pylori, which offers a true opportunity to prevent and defeat this global killer.

Shaw, P. J. (2002). "Suspected infection in children with cancer." J Antimicrob Chemother **49 Suppl 1**: 63-7.

A common complication of the intensive therapy that children with cancer receive is infection. The Oncology Unit of The Children's Hospital at Westmead maintains a comprehensive database of all admissions for suspected sepsis. From July 1994 to June 1999 broad-spectrum antibiotics were commenced in 2331 episodes. With early and aggressive use of empirical amphotericin B, 545 courses were given. Bacteraemia was documented in 701 episodes and invasive fungal disease in 73. Trends seen during the study included: (i) the proportion of febrile neutropenic patients receiving granulocyte colony stimulating factor increased from 40% to 60%; (ii) the mean neutrophil count at cessation of antibiotics fell from 0.97 to 0.63 x 10(9) cells/L for patients not receiving growth factors; (iii) the proportion of non-albicans Candida species infections increased. In addition, an outbreak of infection caused by Scedosporium sp. was documented; (iv) first-line empirical antibiotic combinations containing vancomycin fell from 20% to 7%; and (v) the ability to maintain or escalate anti-fungal therapy with reduced nephrotoxicity through use of lipid formulations of amphotericin was increasingly apparent in high-risk patients. During the study, infection was the primary cause of death in 11 non-bone marrow transplant (BMT) patients (five fungal, four viral, one bacterial infection and one sepsis syndrome) and five BMT patients (two bacterial and three viral). A prospective randomized study of toxicity due to amphotericin B given in either lipid emulsion or dextrose showed no significant difference, but both groups showed a lower incidence of amphotericin B intolerance in comparison with the adult series. The inability to reduce toxicity of amphotericin B by simple mixing with lipid emulsion has led to increasing use of commercially available lipid formulations of amphotericin B.

Shi, Y., J. Li, et al. (1997). "Association of Helicobacter pylori infection with precancerous lesions and stomach cancer: a case-control study in Yangzhong County." Chin Med Sci J **12**(3): 175-80.

Previous study has raised H. pylori infection as a suspected biologic risk factor for gastric cancer. A comparative case-control study involving precancerous lesions and gastric cancer was conducted in Yanzhong county, an area with one of the highest rates of gastric cancer in China to study the relationship between the H. pylori infection and gastric cancer. Subjects in the study were all randomly selected participants of a screening program for gastric cancer sponsored by the Cancer Institute of CAMS in cooperation with Yangzhong county Hospital. Totally, 125 normal controls, 108 superficial gastritis, 111 atrophic gastritis and 110 gastric cancer patients were included in our study according to endoscopy and pathology result. Status of H. pylori infection was evaluated by measuring IgG antibody in plasma with ELISA assay. Our result showed Odds ratios of H. pylori infection were higher among gastritis and cancer groups, 4.5 (95% CI 2.5-7.9) for superficial gastritis, 6.3 (95% CI 3.4-12) for atrophic gastritis, 3.3 (95% CI 1.9-5.9) for gastric cancer. It was found in our study that consumption of pickled vegetables and drinking dirty water increased the relative risk of H. pylori infection for both precancerous lesions and gastric cancer and that H. pylori infection had higher risk of atrophic gastritis and gastric cancer for males and also higher risk of atrophic gastritis for olders. Our results strongly support the casual role played by H. pylori infection in the carcinogenic process of gastric mucosa.

Shin, G. S., B. H. Lee, et al. (2003). "Monokine levels in cancer and infection." Ann Clin Lab Sci **33**(2): 149-55.

The levels of monocyte intracellular monokines (TNFalpha, MIP, and MIG) in patients with cancer or bacterial infection were studied by multiparameter flow cytometry and comparative fluorescence analysis. TNFalpha, MIP, and MIG levels in peripheral blood of patients with cancer or bacterial infection were higher than in normal controls ($p < 0.005$). In normal controls, no significant relationships were found among TNFalpha, MIG, MIP levels, monocyte count, and lymphocyte count in peripheral blood. In cancer patients, TNFalpha was

strongly related to MIP (r = 0.809, p < 0.001) and MIG (r = 0.773, p < 0.001). Of the 3 monokines, TNFalpha and MIG levels were related to monocyte count, but none showed correlation with lymphocyte count in cancer patients. In patients with bacterial infection, TNFalpha was not significantly related to MIP (r = 0.423, p = 0.051), but it was related to MIG (r = 0.457; p = 0.033). None of the monokines (TNFalpha, MIP, MIG) was related to the monocyte count, but the MIP level was related to the peripheral blood lymphocyte count in patients with bacterial infection (r = 0.559, p = 0.008). These results suggest that circulating monocytes may play an important role in both cancer and bacterial infection through increased production of monokines. Moreover, correlations of the monokine levels with each other and their relationships to the monocyte count differ in patients with cancer and bacterial infection.

Song, L., W. Yan, et al. (2005). "Mycobacterium tuberculosis infection and FHIT gene alterations in lung cancer." Cancer Lett **219**(2): 155-62.

Although it is fairly well accepted that pulmonary tuberculosis is a major risk factor of lung cancer, the exact molecular mechanisms involved in its tumorigenesis are unclear. For this purpose, we have examined the relationship between Mycobacterium tuberculosis (M-TB) infection and FHIT gene alteration in lung cancer. Tumors with M-TB infection had a slightly higher abnormal FHIT protein expression compared with tumors without M-TB infection, although not statistically significant (Fisher's exact test, P=0.248). LOH affecting at least one locus of the FHIT gene was significantly more frequent in lung cancer patients with M-TB infection than in patients without M-TB infection whether assessment by univariate testing methods or logistic regression modeling analysis (Fisher's exact test P=0.025, logistic regression analysis P=0.012). These results indicate that M-TB infection is associated with FHIT gene LOH in lung cancer.

Sorensen, L. T., J. Horby, et al. (2002). "Smoking as a risk factor for wound healing and infection in breast cancer surgery." Eur J Surg Oncol **28**(8): 815-20.

AIM: Clinical studies suggest that smoking is associated with wound necrosis after breast cancer surgery. However, the significance of smoking as a risk factor for wound infection, skin flap necrosis, and epidermolysis when adjusting for other potential risk factors remains to be studied. METHODS: From June 1994 through August 1996, 425 patients underwent breast cancer surgery as simple mastectomy, modified radical mastectomy, or breast conserving surgery. The patients were evaluated postoperatively for wound infection, skin flap necrosis, and epidermolysis. Association between these complications and 17 patient, operative, and postoperative variables were analysed by three separate multiple logistic regression analyses. RESULTS: When compared to non-smoking, smoking was significantly associated with wound infection after all types of surgery (light smoking (1-14 grams per day): [odds ratio (OR)=2.95, 95% confidence interval (95% CI)=1.07-8.16], and heavy smoking (>/=15 grams per day): OR=3.46 (1.52-7.85). A similar significant association was found as regards skin flap necrosis and epidermolysis after simple mastectomy and modified radical mastectomy: both light and heavy smoking were predictive for skin flap necrosis: light smoking: OR=6.85 (1.96-23.90), heavy smoking: OR=9.22 (2.91-29.25) and for epidermolysis: light smoking: OR=3.98 (1.52-10.43) and heavy smoking: OR=4.28 (1.81-10.13). No significant dose-response relation was disclosed. Other risk factors and confounders associated with complicated wound healing were adjusted for in the analysis: diabetes, obesity, alcohol, NSAIDs, duration of surgery, and surgical experience. CONCLUSION: Independent of other risk factors, smoking is predictive for post-mastectomy wound infection, skin flap necrosis, and epidermolysis.

Sugimoto, M., T. Furuta, et al. (2005). "Poor metabolizer genotype status of CYP2C19 is a risk factor for developing gastric cancer in Japanese patients with Helicobacter pylori infection." Aliment Pharmacol Ther **22**(10): 1033-40.

BACKGROUND: Cytochrome P450 2C19 (CYP2C19) polymorphism has been associated with the development of lung, liver or oesophageal cancer by detoxification of carcinogen(s) or activation of procarcinogen(s). AIM: To clarify the association between CYP2C19 polymorphisms and gastric cancer development in Japanese. Methods : We determined CYP2C19 genotypes (CYP2C19*1, *2 and *3) in 111 Helicobacter pylori-positive patients with gastric cancer and 315 H. pylori-positive controls without gastric cancer consisting of patients with gastritis only or peptic ulcer. Frequencies of CYP2C19 genotypes and serum pepsinogen I and II levels, a biomarker of gastric atrophy, in the gastric cancers and controls were compared. RESULTS: Frequencies of homozygous extensive metabolizers, heterozygous extensive metabolizers and poor metabolizers were 31.5%, 42.3% and 26.2% in the gastric cancers and 38.1%, 47.0% and 14.9% in the controls, respectively (P = 0.046). Poor metabolizers were associated with an increased risk for developing gastric cancer with the age- and sex-adjusted odds ratio (OR) of 1.975 [95% confidence interval (CI): 1.068-3.649], especially for diffuse type (OR: 3.385, CI: 1.187-9.648). There is no significant association between

CYP2C19 genotypes and serum pepsinogen I level or pepsinogen I/II ratios, although serum pepsinogen I level in gastric cancers were significantly decreased. CONCLUSIONS: In H. pylori-positive Japanese, poor metabolizers of CYP2C19 appear to be at an increased risk for developing gastric cancer, especially diffuse type, and may require an intensive follow-up for scrutinizing possible gastric cancer development.

Sugiyama, T. (2004). "Development of gastric cancer associated with Helicobacter pylori infection." Cancer Chemother Pharmacol **54 Suppl 1**: S12-20.

Helicobacter pylori infection is associated with histological gastritis, gastric atrophy, gastric cancer and mucosa-associated lymphoid tissue lymphoma in the stomach. However, gastric cancer only develops in a minority of infected individuals. Such clinical diversity is caused by variations in the interactions between H. pylori pathogenicity, host susceptibility, and environmental factors. Based on evidence from three prospective epidemiological studies, the International Agency for Research on Cancer and the World Health Organization (IARC/WHO) concluded in 1994 that H. pylori has a causal linkage to gastric carcinogenesis and is a definite carcinogen in humans. Two large-scale, prospective, epidemiological studies have recently been reported in Japan and have confirmed that H. pylori infection constitutes a high risk factor for the development of gastric cancer, at least in males. In order to obtain evidence that eradication of H. pylori leads to a reduction in the occurrence of gastric cancer, reversibility of precancerous lesions, gastric atrophy or intestinal metaplasia should be proven after eradication treatment. A biopsy specimen from the lesser curvature of the corpus is the most sensitive for evaluating the regression of gastric atrophy on histology, and the evaluation needs be conducted at least 13 months after treatment. In a Mongolian gerbil model with or without low-dose chemical carcinogens, it has been demonstrated that H. pylori can lead to the development of gastric cancer. Experimental studies have elucidated that virulence factors of H. pylori interact with gastric epithelial cell signaling related to carcinogenesis. The cag pathogenicity island (cagPAI) is a major virulence gene cluster; it encodes the type IV secretion machinery system forming a cylinder-like structure. The CagA protein is translocated into target cells via this secretion system and induces a hummingbird phenotype, a growth factor-like effect. The other gene products are probably translocated into target cells and accelerate cellular proliferation and apoptosis. The molecular mechanism of the interaction between H. pylori and gastric epithelial cells may provide a new strategy for effective prevention of the development of gastric cancer induced by H. pylori infection.

Sugiyama, T. and M. Asaka (2004). "Helicobacter pylori infection and gastric cancer." Med Electron Microsc **37**(3): 149-57.

Helicobacter pylori infection has an association with histological gastritis, gastric atrophy, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma in the stomach. Gastric cancer occurs in only a minority of infected individuals, however. Such clinical diversities are caused by variations of H. pylori pathogenicity, host susceptibility, environmental factors, and interactions of these factors. By three prospective epidemiological studies, the International Agency for Research on Cancer, World Health Organization (IARC/WHO) concluded in 1994 that H. pylori had a causal linkage to gastric carcinogenesis and is a definite carcinogen in humans. In addition, the Mongolian gerbil model with or without low-dose chemical carcinogens demonstrated that H. pylori infection could develop into gastric cancer. The experimental studies have elucidated that virulence factors of H. pylori have an interaction with gastric epithelial cell signaling related to carcinogenesis. The cag pathogenicity island (cagPAI) is a major virulence gene cluster and codes the type IV secretion machinery system, forming a cylinder-like structure. The CagA protein is translocated into target cells via this secretion system and induces a hummingbird morphology, growth factor-like effect. The other gene products are probably translocated into target cells and accelerate cellular proliferation and apoptosis. Understanding the molecular mechanism of the interaction between H. pylori and gastric epithelial cells will provide us with a new strategy for effective prevention of the development of gastric cancer induced by H. pylori infection.

Summersgill, K. F., E. M. Smith, et al. (2000). "p53 polymorphism, human papillomavirus infection in the oral cavity, and oral cancer." Oral Surg Oral Med Oral Pathol Oral Radiol Endod **90**(3): 334-9.

OBJECTIVES: Human papillomavirus (HPV) infection has emerged as a risk factor in oral carcinogenesis. An arginine-coding polymorphism of the tumor suppressor protein p53 at codon 72 is more readily degraded by the HPV oncoprotein E6. Our objective was to evaluate the association between p53 polymorphism at codon 72 and HPV infection in the oral cavity, as well as its association with oral cancer. Study Design: Oral squamous cells from 202 patients with oral cancer and 333 age-sex frequency matched controls were evaluated by polymerase chain reaction for the presence and type of HPV and for alleles of

codon 72 in p53. Fisher exact test and chi(2) tests were used to evaluate the data. RESULTS: The p53 codon 72 polymorphism is not associated with HPV infection, whether comparing HPV-negative controls with HPV-positive controls or comparing HPV-negative cases with HPV-positive cases. Additionally, we found no association with the codon 72 polymorphism and oral cancer, whether comparing HPV-negative controls with HPV-negative cases or comparing HPV-positive controls with HPV-positive cases. CONCLUSIONS: There is no association between p53 codon 72 polymorphism and HPV infection or between the p53 polymorphism and the risk of oral cancer.

Takayama, S., H. Takahashi, et al. (2007). "Effects of Helicobacter pylori infection on human pancreatic cancer cell line." Hepatogastroenterology **54**(80): 2387-91.

BACKGROUND/AIMS: Helicobacter species has been shown to be commonly present in extragastric human organs by polymerase chain reaction (PCR). To date, a few studies have reported that infection by Helicobacter pylori (H. pylori) was a risk factor for pancreatic malignancies, but this was not investigated very well. Therefore, we examined effects of H. pylori infection on human pancreatic cancer cells. METHODOLOGY: Interleukin (IL)-8 and vascular endothelial growth factor (VEGF) secretions by human pancreatic cancer cells which were co-cultured with H. pylori, were measured by enzyme-linked immunosorbent assay (ELISA). We then examined whether activities of proliferation factors nuclear factor-kappaB (NF-kappaB), activator protein-1 (AP-1), and serum response element (SRE) of human pancreatic cancer cells were increased by H. pylori infection. Furthermore, we examined cytotoxin-associated gene A protein (CagA) secretion into pancreatic cancer cells using Western blotting. RESULTS: IL-8 and VEGF secretion levels and activities of proliferation factors NF-kappaB, AP-1, and SRE of human pancreatic cells increased by H. pylori infection. Moreover, CagA secretion into pancreatic cancer cells was confirmed by Western blotting. CONCLUSIONS: Helicobacter pylori infection of human pancreatic cells may increase malignant potential of pancreatic cells, which seems to involve the same mechanisms as in gastric cancer cells.

Tamamura, H., H. Tsutsumi, et al. (2007). "Development of low molecular weight CXCR4 antagonists by exploratory structural tuning of cyclic tetra- and pentapeptide-scaffolds towards the treatment of HIV infection, cancer metastasis and rheumatoid arthritis." Curr Med Chem **14**(1): 93-102.

The chemokine receptor, CXCR4, is a GPCR that transduces signals of its endogenous ligand, CXCL12 (stromal cell-derived factor-1, SDF-1). The CXCL12-CXCR4 system plays an important role in the migration of progenitors during embryologic development of the cardiovascular, hemopoietic, central nervous systems, etc. This system has recently been proven to be involved in several problematic diseases, including HIV infection, cancer cell metastasis, leukemia cell progression, rheumatoid arthritis (RA) and pulmonary fibrosis. Thus, CXCR4 is thought to be an important therapeutic target to overcome the above diseases. Fourteen-mer peptides, T140 and its analogs, were previously found to be specific CXCR4 antagonists that were characterized as HIV-entry inhibitors, anti-cancer-metastatic agents, anti-chronic lymphocytic/acute lymphoblastic leukemia agents and anti-RA agents. Based on our knowledge of pharmacophores of T140, CXCR4 antagonists, such as FC131, were previously found by the efficient utilization of cyclic pentapeptide libraries. This review article focuses on our recent research on the development of low molecular weight CXCR4 antagonists including FC131 analogs, in which structural tuning of the cyclic peptide ring and chemical modifications were performed for an increase in potency and a reduction of the peptide character.

Thomas-Tikhonenko, A. and C. A. Hunter (2003). "Infection and cancer: the common vein." Cytokine Growth Factor Rev **14**(1): 67-77.

The role of infectious agents in the development of cancer is well documented. The pathogenesis of various human neoplasms ranging from non-Hodgkin lymphoma (NHL) to cervical carcinoma frequently involves a chronic, most often viral, infection. At the same time, there is compelling evidence that certain acute infections result in the inhibition of neoplastic growth. The basis for this phenomenon is often thought to be concomitant anti-tumor immunity. Yet, experimental data supporting this hypothesis are scarce, and other non-immune anti-tumor factors could be involved. For instance, since virtually all aggressive tumors outstrip their blood supply, development of new vessels, or angiogenesis, is a limiting factor during neoplastic growth. In this review, we will discuss recent studies that implicate anti-angiogenesis in infection-mediated tumor suppression and suggest that this mechanism could also complement cytotoxic immunity arising from the use of cancer vaccines.

Tokudome, S., Soeripto, et al. (2005). "Rare Helicobacter pylori infection as a factor for the very

low stomach cancer incidence in Yogyakarta, Indonesia." Cancer Lett **219**(1): 57-61.

To elucidate factors associated with the very low risk of gastric neoplasia in Yogyakarta, Indonesia, approximately 1/50 of the level in Japan, we recruited 52 male and 39 female participants from the general populace in the city of Yogyakarta in October 2003. Helicobacter pylori IgG antibodies were found in only 5% (0-13) (95% confidence interval) and 4% (0-9) for Javanese males and females, respectively, and were statistically lower than the 62% (58-65) and 57% (53-60), respectively, in Japanese. Furthermore, positive findings of pepsinogen test were only 0 and 2% (0-6) for males and females, in Yogyakarta, and were again significantly lower than the 23% (22-25) and 22% (20-23), in Japan. The very low incidence of stomach cancer in Yogyakarta may be due to a low prevalence of H. pylori infection and chronic atrophic gastritis.

Vekemans, M., J. Robinson, et al. (2007). "Low mannose-binding lectin concentration is associated with severe infection in patients with hematological cancer who are undergoing chemotherapy." Clin Infect Dis **44**(12): 1593-601.

BACKGROUND: Mannose-binding lectin (MBL) is a serum lectin involved in innate immune response. Low serum MBL concentration may constitute a risk factor for infection in patients receiving myelosuppressive chemotherapy. METHODS: We conducted a prospective, observational study that assessed MBL concentration as a risk factor for infection in patients with hematological malignancy who were hospitalized to undergo at least 1 chemotherapy cycle. MBL deficiency was defined using an algorithm that considered the serum MBL concentration and the MBL genotype. The primary end point was the ratio of duration of febrile neutropenia to the duration of neutropenia. Secondary end points included the incidence of severe infection (e.g., sepsis, pneumonia, bacteremia, and invasive fungal infection). Logistic regression analysis was conducted, and Fisher's exact test was used to analyze binary outcomes, and Kaplan-Meier estimates and log rank tests were used for time-to-event variables. RESULTS: We analyzed 255 patients who received 569 cycles of chemotherapy. The median duration of neutropenia per cycle was 7 days (interquartile range, 0-13 days). Sixty-two patients (24%) were found to have MBL deficiency. Febrile neutropenia occurred at least once in 200 patients. No difference in the primary outcome was seen. The incidence of severe infection was higher among MBL-deficient patients than among non-MBL-deficient patients (1.96 vs. 1.34 cases per 100 days for analysis of all patients [P=.008] and 1.85 vs. 0.94 cases per 100 days excluding patients with acute leukemia [P<.001]). CONCLUSIONS: MBL deficiency does not predispose adults with hematological cancer to more-frequent or more-prolonged febrile episodes during myelosuppressive chemotherapy, but MBL-deficient patients have a greater number of severe infections and experience their first severe infection earlier, compared with nondeficient patients.

Wang, G., J. W. Barrett, et al. (2006). "Infection of human cancer cells with myxoma virus requires Akt activation via interaction with a viral ankyrin-repeat host range factor." Proc Natl Acad Sci U S A **103**(12): 4640-5.

We demonstrate that the susceptibility of human cancer cells to be infected and killed by an oncolytic poxvirus, myxoma virus (MV), is related to the basal level of endogenous phosphorylated Akt. We further demonstrate that nonpermissive tumor cells will switch from resistant to susceptible for MV infection after expression of ectopically active Akt (Myr-Akt) and that permissive cancer cells can be rendered nonpermissive by blocking Akt activation with a dominant-negative inhibitor of Akt. Finally, the activation of Akt by MV involves the formation of a complex between the viral host range ankyrin-repeat protein, M-T5, and Akt. We conclude that the Akt pathway is a key restriction determinant for permissiveness of human cancer cells by MV.

Wang, T. C., C. A. Dangler, et al. (2000). "Synergistic interaction between hypergastrinemia and Helicobacter infection in a mouse model of gastric cancer." Gastroenterology **118**(1): 36-47.

BACKGROUND & AIMS: Hypergastrinemia occurs frequently in association with acid suppression and Helicobacter infection, but its role in the progression to gastric atrophy and gastric cancer has not been well defined. METHODS: The effects of hypergastrinemia, and possible synergy with Helicobacter felis infection, were investigated in insulin-gastrin (INS-GAS) transgenic mice. RESULTS: INS-GAS mice initially showed mild hypergastrinemia, increased maximal gastric acid secretion, and increased parietal cell number but later progressed to decreased parietal cell number and hypochlorhydria. Development of gastric atrophy was associated with increased expression of growth factors, heparin-binding epidermal growth factor and transforming growth factor alpha. At 20 months of age, INS-GAS mice showed no evidence of increased enterochromaffin-like cell number, but instead exhibited gastric metaplasia, dysplasia, carcinoma in situ, and gastric cancer with vascular invasion. Invasive gastric carcinoma was observed in 6 of 8 INS-GAS mice that were >20 months old.

Helicobacter felis infection of INS-GAS mice led to accelerated (< or = 8 mo) development of intramucosal carcinoma (85%), with submucosal invasion (54%) and intravascular invasion (46%; P < or = 0.05). CONCLUSIONS: These findings support the unexpected conclusion that chronic hypergastrinemia in mice can synergize with Helicobacter infection and contribute to eventual parietal cell loss and progression to gastric cancer.

Wu, M. S., C. T. Shun, et al. (1998). "Gastric cancer risk in relation to Helicobacter pylori infection and subtypes of intestinal metaplasia." Br J Cancer **78**(1): 125-8.

Helicobacter pylori (H. pylori) infection and intestinal metaplasia (IM) are each associated with an increased risk of gastric cancer (GC). To explore further the influences of H. pylori and IM on GC, H. pylori and subtypes of IM were evaluated in 135 sex and age-matched case and control pairs. Odds ratios (ORs) with 95% confidence intervals of developing GC were calculated for each risk factor using multiple logistic regression analysis. ORs for H. pylori infection and IM were 2.43 (1.29-4.65) and 4.59 (2.58-8.16), respectively, and those for different IM subtypes gave values of 0.82 (0.28-2.36) for type I, 2.03 (0.95-4.34) for type II and 39.75 (14.34-110.2) for type III. Stratification analysis by histological subtype and stage of GC showed a particularly high OR for IM in intestinal type (12.8, 4.73-34.83) and early GC (6.40, 2.25-18.18). Our data indicate that both H. pylori and IM are related to GC risk. Type III IM is a more specific marker of premalignancy, with relevance, in particular, to the early and intestinal type of GC.

Yatsuya, H., H. Toyoshima, et al. (2004). "Individual and joint impact of family history and Helicobacter pylori infection on the risk of stomach cancer: a nested case-control study." Br J Cancer **91**(5): 929-34.

We used 202 cases of stomach cancer and 394 controls nested within the Japan Collaborative Cohort Study For Evaluation of Cancer Risk (JACC study) to investigate whether family history has an independent effect on the risk of stomach cancer after controlling for the Helicobacter pylori infection. A positive history of stomach cancer in one or more first-degree relatives was associated with an increased risk of the disease in women, but not in men after controlling for H. pylori infection and other confounding variables. Women with both a family history and H. pylori infection were associated with more than five-fold increased risk of the disease (OR 5.10, 95% CI 1.58-16.5) compared to those without these factors. These results suggest the existence of inherited susceptibility to the disease in women, and that measurements of H. pylori infection together with the family history allow meaningful evaluation of risk beyond that provided by either factor alone.

Yeh, J. M., S. J. Goldie, et al. (2009). "Effects of Helicobacter pylori infection and smoking on gastric cancer incidence in China: a population-level analysis of trends and projections." Cancer Causes Control **20**(10): 2021-9.

OBJECTIVE: Although gastric cancer incidence is declining in China, trends may differ from historical patterns in developed countries. Our aim was to (1) retrospectively estimate the effects of Helicobacter pylori (H. pylori) and smoking on past gastric cancer incidence and (2) project how interventions on these two risk factors can reduce future incidence. METHODS: We used a population-based model of intestinal-type gastric cancer to estimate gastric cancer incidence between 1985 and 2050. Disease and risk factor data in the model were from community-based epidemiological studies and national prevalence surveys. RESULTS: Between 1985 and 2005, age-standardized gastric cancer incidence among Chinese men declined from 30.8 to 27.2 per 100,000 (12%); trends in H. pylori and smoking prevalences accounted for >30% of overall decline. If past risk factor trends continue, gastric cancer incidence will decline an additional 30% by 2050. Yet, annual cases will increase from 116,000 to 201,000 due to population growth and aging. Assuming that H. pylori prevention/treatment and tobacco control are implemented in 2010, the decline in gastric cancer incidence is projected to increase to 33% with universal H. pylori treatment for 20-year-olds, 42% for a hypothetical childhood H. pylori vaccine, and 34% for aggressive tobacco control. CONCLUSIONS: The decline in gastric cancer incidence has been slower than in developed countries and will be offset by population growth and aging. Public health interventions should be implemented to reduce the total number of cases. Electronic supplementary material The online version of this article (doi:10.1007/s10552-009-9397-9) contains supplementary material, which is available to authorized users.

You, W. C., L. Zhang, et al. (1998). "Helicobacter pylori infection, garlic intake and precancerous lesions in a Chinese population at low risk of gastric cancer." Int J Epidemiol **27**(6): 941-4.

BACKGROUND: Cangshan County of Shandong Province has one of the lowest rates of gastric cancer (GC) in China. While intestinal metaplasia (IM) and dysplasia (DYS) are less common in Cangshan than in areas of Shandong at high risk of GC, these precursor lesions nevertheless

affect about 20% of adults age > or = 55. SUBJECTS AND SETTING: In order to evaluate determinants of IM and DYS in Cangshan County, a low risk area of GC a survey was conducted among 214 adults who participated in a gastroscopic screening survey in Cangshan County in 1994. METHOD: A dietary interview and measurement of serum Helicobacter pylori antibodies were performed. RESULTS: The prevalence of H. pylori was lowest (19%) among those with normal gastric mucosa, rising steadily to 35% for superficial gastritis (SG), 56% for chronic atrophic gastritis (CAG), 80% for IM, and 100% for DYS. The prevalence odds of precancerous lesions were compared with the odds of normal histology or SG. The odds ratio (OR) or CAG associated with H. pylori positivity was 4.2 (95% confidence interval [CI] : 1.7-10.0), while the OR of IM/DYS associated with H. pylori positivity was 31.5 (95% CI: 5.2-187). After adjusting for H. pylori infection, drinking alcohol was a risk factor for CAG (OR = 3.2, 95% CI: 1.1-9.2) and IM/DYS (OR = 7.8, 95% CI: 1.3-47.7). On the other hand, consumption of garlic showed non-significant protective effects and an inverse association with H. pylori infection. CONCLUSIONS: The findings of this study suggest that infection with H. pylori is a risk factor and garlic may be protective, in the development and progression of advanced precancerous gastric lesions in an area of China at relatively low risk of GC.

Zhuo, X., Y. Zhang, et al. (2008). "Helicobacter pylori infection and oesophageal cancer risk: association studies via evidence-based meta-analyses." Clin Oncol (R Coll Radiol) **20**(10): 757-62.

AIMS: Infection of Helicobacter pylori, a major cause of various gastric diseases, has been reported to play a role in the process of tumorigenesis and progression of gastric carcinoma. Some studies have been devoted to the relationship between H. pylori infection and oesophageal cancer and have yielded conflicting results. Whether infection of H. pylori is a risk factor for this cancer remains uncertain. In this study we aimed to evaluate the association of H. pylori infection with oesophageal cancer risk. MATERIALS AND METHODS: The associated literature was acquired through deliberate searching and selected based on the established inclusion criteria for publications, then the extracted data were further analysed by systematic meta-analyses. RESULTS: In total, 195 articles were identified, of which 12 case-control studies concerning oesophageal cancer were selected. Oesophageal adenocarcinoma risk for H. pylori infection was 0.58-fold (95% confidence interval 0.48-0.70) (Z=5.79, P<0.01) compared with the controls. Oesophageal squamous cell carcinoma risk was 0.80-fold (95% confidence interval 0.45-1.43) (Z=0.75, P>0.05) compared with the controls. Compared with CagA-negative H. pylori, CagA-positive H. pylori markedly decreased oesophageal cancer risk. CONCLUSION: The pooled data suggest infection of H. pylori as a possible preventive factor for oesophageal adenocarcinoma and failed to suggest a significant association between H. pylori infection and oesophageal squamous cell carcinoma.

Zhuo, X. L., Y. Wang, et al. (2008). "Possible association of Helicobacter pylori infection with laryngeal cancer risk: an evidence-based meta-analysis." Arch Med Res **39**(6): 625-8.

BACKGROUND: Infection with Helicobacter pylori (H. pylori) is a major cause of various gastric diseases and has been reported to play a role in the process of tumorigenesis and progression of gastric carcinoma. However, whether H. pylori infection increases susceptibilities to other cancers is not fully understood. Several studies have been devoted to the relationship between H. pylori infection and laryngeal cancer risk and have yielded conflicting results. In this study, we aimed to evaluate the possible association of H. pylori infection with laryngeal cancer risk. METHODS: The associated literature was acquired through deliberate searching and selected based on the established inclusion criteria for publications. Extracted data were further analyzed by a systematic meta-analysis. RESULTS: A total of 15 papers were identified. Of these, five case-control studies were selected. Laryngeal cancer risk for H. pylori infection was 2.03-fold (95% CI=1.28-3.23) (Z=3.00, p<0.01) compared with the controls. CONCLUSIONS: The pooled data suggest infection with H. pylori as a possible risk factor for laryngeal cancer.

Zumkeller, N., H. Brenner, et al. (2007). "Helicobacter pylori infection, interleukin-1 gene polymorphisms and the risk of colorectal cancer: evidence from a case-control study in Germany." Eur J Cancer **43**(8): 1283-9.

Helicobacter pylori infection is a strong risk factor for gastric cancer. A positive association with colorectal cancer has also been suggested, but available evidence remains inconclusive. In this population-based case-control study we investigated the association between H. pylori seroprevalence and colorectal adenocarcinoma under consideration of pro-inflammatory gene polymorphisms (384 incident cancer patients, 467 matched control subjects). Overall, the H. pylori seroprevalence was higher among cases (51%) than among controls (44%), and a positive association between H. pylori seroprevalence and colorectal adenocarcinoma risk was found, that persisted after adjustment for known potential

confounders, including measures of socioeconomic status (odds ratio (OR)=1.41; 95% confidence intervals (CI), 1.06-1.87). Presence of specific H. pylori cytotoxin-associated gene A (CagA) antibodies did not significantly affect the observed risk. Additionally, a pro-inflammatory genotype did not increase the colorectal cancer risk associated with H. pylori infection. H. pylori positive subjects carrying the pro-inflammatory genotypes even had a lower risk.

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1/6/2011