

Infectious Agents

Introduction

Chronic microbial, parasitic, or viral infections are thought to contribute to the carcinogenic pathway of many different cancers. These include gastric cancer and gastric lymphoma (*Helicobacter pylori*), cervical cancer (human papillomavirus), non-Hodgkin's and Hodgkin's lymphoma (Epstein-Barr virus), T-cell leukemia/lymphoma (human T-cell leukemia virus--HTLV-I virus), Kaposi's sarcoma (human herpesvirus-8), bladder cancer (*Schistosomiasis haematobium*), cholangiocarcinoma of the liver (liver flukes), and liver cancer (hepatitis B and C viruses). Infectious agents may account for nearly 18 percent of the global cancer burden, with *H. pylori*, HPV, and hepatitis viruses each contributing about 5 percent.¹

Breast cancer incidence varies both geographically and by birth cohort, variations that also parallel differences in the extent of individual exposure to infections and microbes. People in western, industrialized countries where breast cancer rates are highest, experience substantially less exposure to infection than those in developing nations, where breast cancer rates are lower. Populations in industrialized societies have lower rates of gastrointestinal infections and substantially less exposure to parasites; they also receive routine vaccination against a multitude of viral illnesses. With industrialization, exposure to many microbes once considered a part of the natural human ecosystem has been altered by urbanization, public health infrastructure changes such as indoor plumbing and advanced sewage treatment systems, and widespread personal and domestic

use of antibiotic pharmaceuticals, antiseptics, and detergents. As an example, *H. pylori* infection (still the most common chronic infection in the world and once almost universally acquired in early childhood) is rapidly disappearing from western societies, a trend that has been accompanied by dramatic reductions in gastric cancer rates over the past century.² Yet there has been little research of these global epidemiologic transitions as they might relate to observed breast cancer patterns.

Most work to date examining infections and breast cancer has focused on possible etiological roles of specific microbes, as well as infectious complications of breast cancer treatment. However, emerging evidence suggests that infectious agents could potentially alter breast cancer risk through three other pathways:

- 1) by potentiating other risk factors, such as chemical exposures;
- 2) by altering the timing of sexual maturation during childhood and/or by altering the levels of circulating sex hormones; or
- 3) by influencing particular immune responses to breast cancer that alter its initiation, progression, metastasis, or response to treatment.

Exposure Definition

This review focuses on environmental exposures to pathogenic microbes, including viruses, bacteria, and parasites, as well as benign/commensal microbes (e.g. intestinal microflora), as they might relate to breast cancer incidence, etiology, and outcome.

Biologic Plausibility

Infectious agents may play a contributory role in breast cancer if they work in combination with other causative agents, such as chemical carcinogens. In an example of this contributory role with another type of cancer, a nested case-control study of non-Hodgkin's lymphoma and serum organochlorine residues revealed a synergistic relationship between PCB exposures and Epstein-Barr virus infection with regard to lymphoma risk.³ A possible interactive role for chemical agents and Epstein-Barr--or any other infectious pathogen--with regard to breast cancer has not yet been explored.

Infectious agents in childhood may serve to lower breast cancer risk if they delay the onset of sexual maturation and, in particular, menarche. As age of menarche decreases, overall risk of breast cancer increases.⁴ Conversely, for each year menarche is delayed, the risk of breast cancer declines by 5–20 percent.⁵ The presence of chronic disease is associated with later onset of puberty and is believed to influence the endocrine regulation of that part of the hypothalamus that governs pubertal onset.⁶ Most recently, a study of Bangladeshi women who migrated to the United Kingdom found that those who migrated as infants and young children reached puberty earlier and had significantly higher levels of circulating progesterone than women who migrated at a later age or than those who stayed in Bangladesh. Poor sanitation and higher exposure to infectious agents were posited as possible explanations for the slower sexual maturation of Bangladeshi women who grew up there.⁷

Mechanisms of action by which infectious agents might cause cancer include: 1) direct carcinogenesis through DNA damage; 2) induction of chronic inflammation or rapid cell proliferation; 3) suppression of immune responses against cancer; and/or 4) immune stimulation of cancer growth factors. In the case of infectious agents, virulence factors, host genetic polymorphisms, concomitant infections, and lifestyle can also play important roles. For breast cancer, there is some evidence that inflammation may contribute to the alterations in estrogen metabolism that are involved in carcinogenesis or growth. Provocative evidence of an association with inflammation derives from animal studies showing that NSAIDs inhibit mammary carcinogenesis, as well as case-control and prospective epidemiologic studies generally reporting that long-term users of anti-inflammatory medications have markedly lowered risk (> 20 percent) of breast cancer,⁸⁻¹⁰ especially for hormone-receptor positive types.⁹⁻¹²

Criteria for establishing a cause-effect relationship between a microbe and cancer are evolving along with technology.^{13, 14} At present, useful criteria include: consistency of association; molecular evidence of oncogenicity (consistent observation of genomic particles within a host cell line, or of translocational correlates enabling cell proliferation and immortalization); and isolation of functional mechanisms of the agent that are responsible for perpetuating the malignant phenotype. Not all discoveries follow a consistent path to these conclusions or subscribe to a common physiologic model. Some agents, such as DNA-containing tumor viruses, are latent infections. Some, like hepatitis viruses and *H. pylori*, are chronic active infections that induce

tumorigenesis. Interdisciplinary approaches— involving basic laboratory, animal models, as well as population-based epidemiology and clinical trials—are increasingly needed to understand causal relationships.

Critical Review of the Literature

Most work to date examining infections and breast cancer has focused on possible etiologic roles of specific infections, as well as infectious complications of breast cancer treatment.

However, it is possible that a wide spectrum of single or cumulative microbial exposures influence particular immune responses to breast cancer, affecting its initiation, progression, metastasis, and response to treatment.

Incidence/Etiology

Epstein-Barr Virus

Epstein-Barr virus (EBV) is a persistent herpesvirus known to transform lymphocytes in vitro. In addition, B-cell lymphoproliferation is observed in patients with immunosuppression.¹⁵ EBV is considered a Group I carcinogen by IARC and has been implicated in the etiologies of several cancers, including Burkitt's lymphoma, non Hodgkin's and Hodgkin's lymphomas, other lymphoma subtypes, and nasopharyngeal carcinoma.^{16, 17} Studies have also been conducted to explore possible associations of breast cancer with EBV.

EBV seropositivity is nearly universal by late adulthood, although ages of primary infection may differ among populations in patterns that also correlate with economic development. One

analysis of U.S. SEER registry data reported a two- to five-fold increase in rates of breast cancer associated with older age at diagnosis of infectious mononucleosis or tonsillectomy.¹⁸ A study of women under age 40 did not observe case-control differences in seropositivity to EBV or another herpesvirus, cytomegalovirus (CMV), but did note higher CMV antibodies in breast cancer cases than controls, independent of other factors, suggesting an association with later age at primary CMV infection.¹⁹ In support of a role of infectious mononucleosis in breast cancer etiology, authors have cited circumstantial associations between breast cancer and Hodgkin's disease, a lymphoma associated with history of infectious mononucleosis, including strong correlations of incidence rates internationally,¹⁸ and, in a Connecticut registry series, similarities in birth-cohort-specific incidence patterns.²⁰ However, an elevated rate of breast cancer was not detected in women with hospital-treated infectious mononucleosis in a Scandinavian cohort.²¹ In addition, other explanations for international correlations, such as ethnic differences, have been posed,²² and in a large population-based prospective study of individuals with confirmed infectious mononucleosis, the standardized incidence ratio was 1.01 (0.92–1.23), suggesting no excess rates of breast cancer were detected.²³

Epstein-Barr viral proteins have been variably detected in breast cancers. However, use of immunohistochemical techniques for detection of the viral antigen, EBNA1, may be confounded by cross-reactivity with other common proteins.^{24, 25} These studies have concluded that there is little evidence to support the consistent involvement of EBV.²⁵ Thus, despite the presence of EBV viral

material in some breast tumor cells, there is no evidence to date that EBV plays any etiologic role in the carcinogenesis of breast cancer.

Mouse Mammary Tumor Virus (MMTV) Analog

MMTV is a mouse betaretrovirus. MMTV was first identified in the 1920s, when it was found that a breast cancer-causing agent was passed through milk from mouse mother to mouse daughter.²⁶ This transmissible agent caused almost 100 percent of the mouse daughters to develop breast cancer. However, when the newborn daughters of mice from a strain with a high rate of breast cancer were nursed by foster mothers from a strain that had a low rate of breast cancer, the virus was not transmitted and the daughters did not develop breast cancer. Milk is the only clearly established mode of transmission of infectious MMTV in mice.

Interest in the idea that human breast cancer could also be caused by a virus was renewed when MMTV-like sequences were detected using polymerase chain reaction methods in more than 30 percent of human breast cancer samples in at least two clinical series.^{27, 28} However, subsequent studies using more advanced technologies found some of these sequences were of human origin, that the sequences were found in surrounding tissues and not tumor cells, or that the observations otherwise could not be replicated. Serologic studies to identify antibodies to an MMTV-like virus were initially plagued by similar methodological difficulties and yielded uneven results.²⁹ With more advanced techniques, a considerable proportion of sporadic breast cancer samples have been observed to contain an

MMTV-like env+ gene sequence.³⁰ Using cDNA microarray to compare two sublines of the MCF-7 breast cancer cell line, one team reported differential expression of interferon, TNF-alpha, and TGF-b, cytokines associated with the inflammatory phenotype.³¹

However, there is little corroborating epidemiological support for a milk-borne, MMTV-like-induced breast cancer in humans. Population-based case-control studies have not shown increased incidence of breast cancer in daughters who were nursed by mothers who later developed breast cancer, compared with daughters who were not breast-fed.^{32, 33} These studies do not support evidence of a transmissible agent in breast milk.³³

Recently it has also been suggested that the MMTV could be transmitted directly from mice to humans. This zoonotic mode of infection was proposed because geographic areas of high breast cancer incidence (Western Europe and North and South America) overlap with the distribution of the *Mus domesticus* species of house mouse.³⁴ Recent National Cancer Institute assessments of MMTV antibody prevalence utilizing state-of-the-art methods and examining multiple strains of MMTV support very low population prevalence (no greater than 3 percent) of MMTV antibodies in representative women with breast cancer.³⁵ Thus, support for MMTV or for MMTV-like viruses causing human breast cancer is weak or confined to experimental systems at the present time.

Bovine Leukemia Virus (BLV)

BLV is an oncogenic bovine retrovirus that causes a B cell leukemia/lymphoma in 1–5 percent of all infected cattle. The tax subunit of the pXBL genetic region is responsible for malignant transformation^{36,37} and may be relatively conserved in evolution.³⁸ As BLV is present in infected cows' milk and breast tissue, it was hypothesized that it could be transmitted to humans via dairy products and other cattle-based foods. In one serologic survey, 74 percent of 257 human serum samples were reactive to the BLV p24 capsid protein.³⁹ However, numerous surveys have failed to find a link between contaminated milk products and human leukemias, including the related human lymphoma, HTLV-1.^{40,41} With respect to breast cancer, assays of human breast tissue have yielded variable detection of BLV genes and gene products. In a case-control comparison, breast cancer cases were significantly more likely to have evidence of BLV genes in their unaffected breast tissue (Odds Ratio = 5.4; 95% CI = 2.42–11.9) than healthy women, after adjustment for age, but not after adjusting for other breast cancer risk factors.⁴² Work is ongoing to further isolate the location of BLV material in breast tumor cells, but the variable detection of BLV antibodies and genetic material do not support a major role of BLV in breast carcinogenesis in humans. While evidence linking adult dairy consumption with breast cancer risk is inconsistent (see I.B.7. Hormones in Food for a discussion of these studies), studies are ongoing to examine early-life exposure to dairy products.⁴³

Human Immunodeficiency Virus (HIV)

HIV is a widespread human retrovirus that destroys specific lymphocytes, T-helper cells. At least two studies have reported lower rates of breast cancer outcomes in women with HIV infection: a European cohort (RR = 0.43; 95% CI = 0.24–0.73),⁴⁴ and a large population-based series in the U.S. (Standardized Incidence Ratio 0.69; 95% CI = 0.62–0.77).⁴⁵ The lowest risks were found in those with greatest immunosuppression (women 4–27 months after AIDS diagnosis RR = 0.5; 95% CI = 0.3–0.8).⁴⁶ Notably, reduced risk in AIDS patients appears to be largely independent of reproductive history, such as lower parity. Furthermore, the introduction of highly active AIDS therapies appears to be attenuating this breast cancer deficit. Possible explanations for reduced breast cancer outcomes in the setting of T-cell mediated immunodeficiency may include down-regulation of hormone metabolism or other inflammatory processes, impairment of cell proliferation by the virus, or differential ascertainment bias.

Sexual Activity/Sexually Transmitted Diseases

Many factors or co-factors potentially associated with breast cancer are also related to sexual history, including reproductive history, lifestyle, and hormone production. In adulthood, a theoretical correlate of microbial exposure is sexual activity, particularly with multiple partners. Among white women in Seattle, an increasing number of male sex partners was associated with decreased breast cancer risk in a dose-response fashion (15 or more partners vs. 1 partner OR = 0.6; 95% CI = 0.3–1.0), after adjustment for

reproductive characteristics, alcohol use, education, and religion, but not for contraceptive practices like condom use.⁴⁷ To the extent that marital status correlates with more frequent sexual activity (albeit with fewer partners), similar interpretations can be made from several other studies: lower breast cancer rates have been reported among married nulliparous women compared to unmarried women;⁴⁸ among postmenopausal women married multiple times compared to those married once, after adjusting for parity and other factors;^{47, 49} and in Islamic countries--where extramarital sexual activity has been uncommon among women--among ever-married women compared to never-married women, after consideration of nulliparity, age and other confounders.^{50, 51}

Perhaps the best example of a sexually-transmitted cancer is the human papilloma virus (HPV). Considered a true human tumor virus, genotypes 16 and 18 are consistently associated with cervical cancers. HPV genes E6 and E7 have the ability to immortalize breast cell lines, as well as human target cells in vitro.⁵² Several reports have detected high-risk HPV genotypes in breast carcinoma samples, although variation in laboratory methods, as well as the ubiquity of different papilloma infections in humans, make the specificity of these findings difficult to establish.^{53, 54} HPV DNA has been detected in ductal cancer specimens, including histologic features consistent with HPV, but no correlations with tumor grade or p53 expression have been observed.^{52, 55} It has been speculated that the virus, which requires cell surface contact, may be transmitted to the breast by autoinoculation during sex, or even bathing and

showering. However, evidence of an oncogenic role for HPV in the breast remains circumstantial.

To our knowledge, no epidemiologic studies have addressed associations of breast cancer with history of common sexually-transmitted diseases other than HIV (see above). Other sexually-transmitted infections, including Chlamydia trachomatis and syphilis, have been inversely associated with prostate cancer, but have not been studied for breast cancer.

Parasites

The inflammatory immune response is a key factor in the development of many cancers. Overexpression of cyclooxygenase (COX) -2, and the cytokine TNF-alpha, are found in a variety of breast tumors and associated with poor prognosis. Conversely, drugs to inhibit this cascade are targets for new chemotherapies.^{56, 57} Some parasite infections, in particular those caused by the geohelminths, induce a strong, even polarizing, non-inflammatory or Th2-type immune response to infection. In mouse models of gastric cancer, helminth infection has been associated with attenuation of Helicobacter-associated gastritis and metaplasia.⁵⁸ In high-risk cancer populations, serologic response to H. pylori infection may also vary with respect to helminth burdens.⁵⁹ Given the virtual disappearance of helminths from areas with the highest rates of breast cancer, and the fact that these chronic infections are profoundly immunomodulatory, one could hypothesize that systemic parasitic infections might also interact with risk of breast cancer. In the laboratory, Sheklakova⁶⁰ detected a directly inhibitory effect of Trypanosoma cruzi, a protozoan, on cultured breast cancer (MCF-7) cells in vitro. Schistosoma

haematobium, a water cestode found in Africa and Asia, is linked to increased risks of bladder cancer. In some Egyptian studies, it has been associated with increased risks of breast cancer in men.⁶¹ Although rates of helminth infection can be significantly higher in recent U.S. immigrants than in U.S.-born, to our knowledge, no epidemiologic studies have explored a comparison of breast cancer rates in this context.

Non-Specific Microbial Exposures: Probiotics and Persistent Gastrointestinal Infections

Intestinal bacteria may influence breast cancer development through effects on inflammatory responses or cytotoxic anti-tumor responses, or through their influence on metabolizing ingested hormones or phytoestrogens as well as endogenous estrogens. *Helicobacter pylori*, a pre-eminent cause of gastric cancers,⁶² induces a chronic Th1 inflammatory state in the gut. Strains containing the pathogenetic island (PAI) can, in combination with host genetic polymorphisms, dramatically multiply the risk of gastric cancer.⁶³

⁶⁴ In an animal model, irritable bowel disease (IBD)-resistant mice rapidly developed mammary tumors after *Helicobacter* infection, a "surreptitious" result that was subsequently tracked to TNF-alpha triggered effects of infection.⁶⁵ This animal model lends further support to the speculation of cross-talk between intestinal bacterial infections and extraintestinal immunoregulatory systems.

Probiotics are fermented foods and supplements, including beneficial bacteria like lactobacillus that presumably make intestinal microflora composition more beneficial. To the extent that

gut bacteria might be involved in the metabolism of protective phytoestrogens, studies have addressed relationships between probiotic consumption and serum levels of endogenous estrogens and phytoestrogens in post-menopausal women. These did not detect associations between probiotics and estrogen levels.⁶⁶ One breast cancer case-control study addressing consumption of fermented dairy products reported a negative association,⁶⁷ implying a protective effect. Although molecular technologies to describe intestinal microflora are newly developed, there is little other extant work to understand how characteristics of intestinal bacteria may regulate hormone levels or affect breast cancer risk.

Antibiotic use plays an important role in modifying intestinal microflora at both population and individual levels. In the industrialized world, for example, counterposing trends in incidence of esophageal and gastric cancers beginning in the last century parallel the disappearance of *H. pylori* infections, an infection that is susceptible to many common antibiotics.⁶⁸ See Section I, Chapter D for a discussion of antibiotics and breast cancer risk.

Other Non-Specific Microbial Exposures: "The Hygiene Hypothesis"

The "hygiene hypothesis" proposes that cumulative exposure to common infections and other microbes, particularly in early life, protects against the development of childhood asthma, allergy and other immune-mediated diseases.⁶⁹ This literature suggests that immune system development is adaptive, that is, influenced by cumulative exposures^{70,71} to a variety of microbes,

innocuous microbial by-products like endotoxin,^{72, 73} and perhaps even intestinal microflora.⁷⁴ From this, one can speculate that negative influences of insufficient microbial exposures in early life on immune system development may impact the ability of the immune system to fight off breast tumor cells in later life. By analogy, as rates of non-cardial stomach cancer have plummeted in the industrialized world, rates of upper stomach and esophageal diseases--such as GERD, Barrett's esophagus, and pancreatic cancers--have surged. One hypothesis is that loss of *H. pylori* from the gut microflora has disturbed a historically important niche of adaptive immune response to this chronic infection.

While some studies have examined associations between breast cancer and some relevant markers of microbial exposure identified in the allergic disease literature, this inquiry has occurred as secondary analyses and has focused on single rather than cumulative measures of infection. Case-control studies to examine associations of post-menopausal breast cancer with markers relevant to the hygiene hypothesis are currently ongoing.

Mortality/Survival

The idea that infectious agents might be effective cancer treatments was first posed in the 1900s by William Coley, who observed that patients with advanced soft tissue sarcomas who went on to develop streptococcus infections sometimes experienced spontaneous regression of the tumors. He went on to develop "Coley's toxins" which were not uniformly produced, but nonetheless were tested broadly as a cancer remedy, mostly to no avail. Today, there is one FDA-approved

infectious-agent-based treatment for cancer, the Bacille-Calmette-Guerin (BCG) vaccine against *M. tuberculosis* for treatment of bladder cancer. Little is known about how infections occurring during the course of breast cancer treatment might influence propensity for recurrence or lengthen survival. To the extent that breast cancer differs from other tumors in its propensity for recurrence, and can recur up to 20 years after initial treatment, the idea of immunosurveillance of malignant breast cells is intriguing.

Discussion

Carcinogenesis is a complex process involving the contribution of many different factors. Rarely is a single factor implicated as both sufficient and necessary on this pathway. Nevertheless, the possibility that infectious agents might influence breast cancer development and outcome has not been well studied. Furthermore, genetic technologies needed to identify novel viral causes of breast cancer are constantly being developed and refined. Recognizing these, the National Action Plan on Breast Cancer (NAPBC) held in 1997 a workshop entitled "Viruses and Human Breast Cancer: Exploring the Links."⁷⁵ First, this workshop recommended conducting large epidemiologic studies of breast cancer and established viral antibodies or other biomarkers. They specified that such efforts should proceed even in the absence of a specific suspected causal entity, noting that HPV was determined to be the cause of cervical cancer only after persistent and diverse investigations over many years. They also recommended comprehensive viral characterization studies to identify and describe viral material in a variety of specimens relevant to

breast cancer (e.g., sera, blood, normal tissue, tumor tissue, breast milk), reasoning that identification of novel breast cancer viruses will come only from careful cross-checking of newly-identified sequences with those already published or reported.

In the ten years since the workshop was convened, searches for novel viral causes of breast cancer--including mouse mammary tumor virus, its possible human analogs, and bovine leukemia virus--have generally followed these recommendations. As yet, research has not identified consistent molecular evidence of viral involvement in carcinogenesis. Similarly, efforts to detect EBV in breast tumors have not yielded strong evidence of involvement. However, there may be progress in this area as technologies for identifying, sequencing, and communicating novel viral sequences in breast cancer-relevant biospecimens are improved. The inauguration in September 2006 of a new, open-access medical journal, *Infectious Agents and Cancer*, focusing entirely on viral and infectious causes of malignancy, should provide a welcome forum for improved communication of findings and research issues.

As indirect causes of breast cancer, chronic viral and parasitic infections, including aspects of age at infection (and/or vaccination), are promising candidates for future study, especially as the immunologic sequelae of these kinds of exposures--including chronic inflammation, and dysregulation of Th2 cytokines and regulatory T-cell functions--are increasingly understood to influence steroid hormone metabolism. Several small European studies and a recent large,

population-based U.S. study have consistently demonstrated that HIV infection is associated with lower rates of breast cancer occurrence, with risk that decreases as immunosuppression becomes more profound. Some evidence for a link of infectious agents and breast cancer also comes from studies illustrating the antithetical trends associated with NSAID and antibiotic use.¹¹ These findings additionally support an important regulatory role of immune factors on the expansion of nascent breast tumor cells, or on hormones or other determinants of breast tumor growth and spread. Other data hint at inverse associations with other sexually-transmitted microbes. Inverse associations with many of these infections, especially early age at or intense exposure, would be consistent with many aspects of the descriptive epidemiology of breast cancer, particularly the incidence variation with socioeconomic status, race/ethnicity, and immigration status.

Limitations

An important limitation for investigations into the effect of infectious agents on breast cancer is the need for a developmental model of cumulative, including concomitant, exposure. Chronic infections frequently co-exist within the same host, while diagnostic agents are designed to capture "one disease-one pathogen." Second, infections potentially related to breast cancer tend to be ubiquitous when they are prevalent at all. To this extent, the challenge is to establish specific, sentinel biomarkers that can be informative for birth cohort studies. One approach is to incorporate a definitive temporal marker, like *H. pylori* infection, that has a known secular

influence on the distribution of cancers over time. Third, studies considering the timing of infection, of vaccination for childhood diseases, or severity of infection have to rely on self-report or medical records. Especially in the setting of a life-defining event like breast cancer, recall of antecedent exposures can be difficult to validate. If complete medical records are needed, this can introduce bias into ascertainment systems. As was the case with *H. pylori* and stomach cancer, where induction periods or mechanisms are uncertain, nested case-control designs within large subscriber populations can be useful for matching pre-diagnostic biologic specimens to identify infectious exposures of interest.

Gaps in Knowledge

There are several gaps in our understanding that, if filled, might shed light on the potential role of microbes in influencing breast cancer occurrence and outcomes. These gaps stem largely from the absence of any epidemiologic studies designed specifically to examine associations of microbial exposures with breast cancer or its probable precursors (e.g. hormone levels or mammographic density). In particular, there is a paucity of literature addressing the associations of sexually transmitted diseases and parasitic infections in breast cancer development, despite biologic and epidemiologic consistencies. Also virtually unstudied is the relevance of the intestinal microflora to breast carcinogenesis, despite its known influence on the metabolism of endogenous and exogenous hormones, and emerging information on extraintestinal effects of gastrointestinal infections. Infectious causes of inflammatory breast cancer, a rare and virulent

breast cancer subtype characterized by vigorous inflammation of the tumor site, are suggested by the clinical features of the disease, but remain poorly understood. In addition, no studies have examined the influence of acute infections, which might influence the likelihood of breast cancer recurrence and/or survival time.

Conclusion and Future Directions

Infectious and immunologic conditions predisposing to or protecting against breast cancer are plausible but have not been well studied. In this effort, we have reviewed available evidence for only a few of the infectious agents that could be relevant to breast cancer development. Many common infectious agents, including *Helicobacter pylori* and all classes of parasites, have been rarely considered as they might associate with breast cancer risk.

As a first step, associations of relevant markers of infections and microbial exposure should be examined in a study population with adequate exposure variation. The diversity of the California population with respect to race/ethnicity, socioeconomic status, and immigration status would be important to ensuring appropriate heterogeneity. However, the very low prevalence of some of the infectious exposures of interest (e.g. parasites) might support an international or other multicenter study design. To the extent that serologic (e.g. antibodies) markers are available for exposures of interest, these studies should be designed to rely upon these measurements for exposure classification.

Future studies should pursue interactive links between infectious agents and environmental

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contaminants. Research should also examine the role of chronic infectious disease in altering pubertal timing and circulating hormone levels in ways that might lower breast cancer risk.

Although an infectious etiology for breast cancer remains elusive, the field of infectious disease oncology is only in its infancy. With the advent of translational medicine modalities in research, there is an historic opportunity to integrate basic science, immuno-epidemiology and clinical trial disciplines. New technologies, such as DNA and protein microarrays, have potential to identify molecular signatures and gene expression profiles associated with different cancers. The UC campuses have been in the vanguard of this movement, and are well equipped to assist in this challenge. The human immune system has co-evolved with infectious agents. The adaptive and homeostatic features of this extraordinary system enable the vast majority of hosts to escape the long-term consequences of infection, including cancer. Through our own cross-talk, the cross-talk of the host-pathogen ecosystem may be revealed.

The future of this branch of breast cancer research may well hold the clues to our past.

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