Published in final edited form as:
Curr Opin Immunol. 2011 April ; 23(2): 265–271. doi:10.1016/j.coi.2011.01.002.

Epidemiologic perspective on immune-surveillance in cancer

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Abstract

Common "themes" in epidemiology related to cancer risk beg a comprehensive mechanistic explanation. As people age, risk for cancer increases. Obesity and smoking increase the risk for many types of cancer. History of febrile childhood diseases lowers the risk for melanomas, leukemias, non-Hodgkin's lymphoma (NHL) and ovarian cancer. Increasing number of ovulatory cycles uninterrupted by pregnancies correlate positively with breast, endometrial and ovarian cancer risk while pregnancies and breastfeeding lower the risk for these cancers as well as cancers of the colon, lung, pancreas and NHL. Chronic inflammatory events such endometriosis or mucosal exposure to talc increase the risk for several types of cancer. Mechanisms so far considered are site specific and do not explain multiple associations. We propose that most of these events affect cancer immunosurveillance by changing the balance between an effective immune response and immune tolerance of an emerging cancer. We review recently published data that suggest that immune mechanisms underlie most of the observed epidemiologic associations with cancer risk.

Introduction

Cancer is a threat to the survival of an organism and needs to be recognized early and reckoned with. The immune system has been invoked many times as a likely mechanism for keeping cancer under control but experimental techniques and animal models that could unambiguously show and test its role in cancer control were not available. Eventually, however, numerous molecules on human cancer cells or in animal models of cancer were discovered capable of triggering immunity (tumor associated antigens) and serving as targets of an immune response for tumor destruction. Immunosurveillance as a natural defense mechanism is now widely accepted but the definition has been broadened to include many different interactions between the immune system and cancer, including cancer elimination, long-lasting equilibrium, tumor escape and tumor promotion [1–3].

Because even the best and the newest mouse models cannot fully replicate human disease, and because of significant differences between the human and the mouse immune systems, the life-long protective or promoting effects of immunity on cancer and the factors that determine and modulate anti-cancer immunity need to be studied in humans. Since the

experimental studies performed in animals generally cannot be duplicated in humans, “natural experiments” are necessary in which past experiences of individual with and without cancer are compared or cohorts of persons with and without particular exposures are followed for the occurrence of cancer. These types of studies have revealed a number of common themes in cancer epidemiology. Risks for many types of cancer increase with aging, smoking, and obesity. History of febrile childhood infections, on the other hand, may actually lower the risk for certain adult cancers including ovarian cancer and non-Hodgkin’s lymphoma (NHL). In women, pregnancies and breastfeeding lower the risk for breast, endometrial, and ovarian cancers as well as cancers in “non-reproductive” organs such as colon, lung, and pancreas and NHL. Conversely, chronic inflammatory diseases like endometriosis or an increasing number of ovulatory cycles that have not been interrupted by pregnancies, breastfeeding, and oral contraceptive use correlate with increased breast, endometrial, and ovarian cancer risk. Proposed mechanisms that might govern these associations are often site specific and do not explain multiple associations. In this review we will present accumulating evidence that most events that epidemiologists have associated with a higher or a lower cancer risk affect the immune system and thus effective versus ineffective immunosurveillance may be the unifying mechanisms underlying all these different associations.

Immunosenescence: immune mechanism behind epidemiological associations between age and cancer

About 60% of all cancers occur in people age 65 or older [4]. With the obvious exception of childhood cancer, age specific incidence (i.e. number of cancer cases in a particular age group divided by the population in that age group) increases with age. Epidemiologically, this phenomenon can be demonstrated by plotting log of incidence against log of age and demonstrating a straight line with a positive slope [5]. Some cancers for which this linear pattern is most evident include prostate, ovary, colorectal, pancreas, bladder, stomach, lung, and uterine endometrium. One explanation for the increase in incidence of cancer with age is simply the latency period required for damage to occur and cancer to develop. More specifically this might involve the time necessary for accumulation of carcinogen-induced genetic mutations including those in oncogenes and tumor suppressor genes [6*]. The increase in cancer incidence with age has also been viewed as a maladaptive response to replicative senescence due to telomere shortening [7]. However, among the possible explanations, deterioration of the innate and the adaptive immune response with aging, referred to as immunosenescene, must also be considered.

Among the many changes to innate immunity with advancing age, for example, are decreased chemotaxis in neutrophils, decreased phagocytosis in monocytes and macrophages, and decreased cytotoxicity of NK cells. Among the changes in adaptive immunity are a decrease in numbers of naïve CD4+ T cells and increase in memory CD8+ T cells, as well as a decrease in their telomere length and IL-2 production [6,8*]. The newest findings regarding immunosenescence show that this age-related change in immune responsiveness might be linked to chronic presence of viruses such as cytomegalovirus (CMV), varicella zoster virus (VZV) and Epstein-Barr virus (EBV). While the reduced output of naïve T cells from the thymus in old age is likely responsible for the inability of individuals to generate strong T cell immunity against new antigens, clonal expansion of T cells specific for persistent viruses overwhelms the T cell pool and compromises expansion of memory T cells specific for previously encountered antigens. Seropositivity for one or more of these viruses is a risk factor for immune senescence. Interestingly, this risk may be genetically controlled. A study of individuals with familial longevity, who have a 30% reduced standardized mortality rate compared to matched controls, do not show CMV-associated age-driven immune alterations that are the hallmarks of immune senescence

[9***]. They also show a much lower pro-inflammatory status as measured by C-reactive protein levels in the serum. A viral cause of immunosenescence could also limit expansion and function of effector and memory T cells for tumor associated antigens resulting in higher cancer risk. On the other hand, in Individuals genetically less prone to immunosenescence, tumor-specific immune responses would be expected to be highly effective and most strongly associated with reduced cancer risk.

Chronic inflammation: immune mechanism behind epidemiological associations between obesity and cancer

Obesity is associated with approximately 14% of cancer deaths in men and 20% of cancer deaths in women [10]. Risk for colorectal, esophageal, gallbladder, renal, pancreas cancers, myeloma, and NHL is increased with body mass in both men and women. In obese women, risk for postmenopausal breast cancer and endometrial cancers is increased, while in men, obesity is associated with a more aggressive form of prostate cancer [11]. Multiple site-specific mechanisms have been proposed. For example, obesity may predispose to reflux, which could explain the connection with esophageal cancer; obesity-associated hypertension could promote kidney cancer; elevated levels of insulin and insulin-like growth factor might explain the link with colorectal and possibly pancreatic cancer; and conversion of estrogen precursors into active estrogen in fatty tissue to explain breast and endometrial cancer risk.

Recently, however, evidence has been obtained in both animals and humans, that obesity affects immunity, which could offer a more unified explanation for the above associations. Obese individuals are more susceptible to and suffer more serious complications from infection, suggesting a compromised immune system. It is also newly appreciated that adipose tissue is an active endocrine organ that secretes adipokines including leptin, which may contribute to chronic systemic inflammation and IL-6 production. This particular immune microenvironment has been found to be especially relevant to the association between obesity and increased risk of myeloma and NHL. Leptin can also have direct negative effects on activating immune-competent cells [12**]. It is furthermore known that obesity is associated with infiltration of adipocytes into bone marrow and thymus, which can compromise their function as primary lymphoid organs [13**]. Obesity in mice increases mortality after influenza infection, in part due to impaired antigen specific CD8 T-cell responses [13] but also due to the reduced ability of the thymus to produce naïve T cells, known as acceleration of thymic aging [14***]. This impairs the individual's ability to respond to new viruses and also to a developing cancer. More importantly, mouse models of diet-induced obesity show that T cell memory responses are compromised as shown in the example of cross-reactive immunity against influenza [15**]. Memory T cells from obese mice had greater than 50% lower INF-gamma response than control mice and were much less likely to control repeat infection. Pro-inflammatory cytokines, IL-6 and TNF, associated with chronic inflammation and immune suppression, are copiously produced. Obesity thus may negatively affect the ability of tumor-specific T cells to be activated in response to a growing tumor and to control its progression.

Immune mechanisms modulating cancer risk from smoking

Smoking is the leading cause of cancer and deaths from cancer. From a comprehensive review by the Centers for Disease Control and Prevention (CDCP), there is consistent evidence that smoking increases the risk for cancers of the lung, esophagus, larynx, mouth, throat, kidney, bladder, pancreas, stomach, and uterine cervix, as well as acute myeloid leukemia [16]. Additional epidemiologic evidence suggests that smoking (or smokeless tobacco) may also increase the risk for colorectal cancer [17], NHL [18] and highly malignant prostate cancer [19]. The important link between smoking and these cancers is, in

large part due to inhalation and absorption of carcinogens present in tobacco smoke, including arsenic, benzene, benzo(alpha)pyrene, cadmium, ethlylene oxide, vinyl chloride, toluene, and many others that can accumulate in various body fluids. However, not everyone who smokes develops cancer and additional mechanisms of risk modulation, including immune mechanisms, have been studied. Smoking exerts multiple boosting as well as suppressive effects on immunity. Smoking is known to augment production of numerous pro-inflammatory cytokines such as TNF-alpha, IL-1, IL-6, IL-8, and GM-CSF and to decrease anti-inflammatory cytokines, like IL-10. Smoking also leads to elevated IgE concentrations and activates proinflammatory macrophages and dendritic cells [20*]. Cigarette smoking also suppresses DC maturation within the lymph nodes in the lung, as demonstrated by reduced cell surface expression of MHC class II and the costimulatory molecules CD80 and CD86. As a result, DCs from cigarette smoke-exposed animals have a diminished capacity to activate antigen-specific T cells in vitro consistent with a reduced antigen-specific T cell proliferation in vivo in smoke-exposed mice. Smoke-induced defects in DC function leading to impaired T cell function could similarly inhibit tumor immunosurveillance. Curiously, the pharmaco-active agent in tobacco smoke, nicotine, is thought to have anti-inflammatory properties, perhaps by inhibiting the production of pro-inflammatory cytokines [21]. These contrasting mechanisms may be reflected in inconsistencies in some of the epidemiologic observations. Both smoking and ulcerative colitis may increase the risk for colorectal cancer but smoking may decrease the risk for ulcerative colitis. Smoking may increase the risk for uterine cervical cancer but decrease the risk for cancer of the uterine endometrium [22]. A better understanding of the effects of smoking on the immune system may help to identify mechanisms that both explain the generally increased risk for cancer that occurs with smoking as well as the rarer protective effects on certain other cancers or conditions.

Childhood illnesses and cancer immunosurveillance

The role of childhood infections in childhood cancers has been examined in epidemiologic studies looking for cancer clusters among children. A study in England identified several higher than expected clusters and concluded that measles might have occurred 2–3 years before the onset of leukemia in close pairs of affected children [23]. On the other hand, another study found that larger sibship size, greater household crowding, and occurrence of childhood infections lowered the risk for childhood acute lymphoblastic leukemia [24]. Another study confirmed that smaller family size and delayed childhood infections increased risk for NHL [25]. The authors attributed this to the difference among the children in the balance of their Type 1(Th1) versus Type 2(Th2) immunity. Exposure to more infections earlier in life appears to favor Type 1 immunity while fewer and delayed infections favor Type 2 immunity. Type 1 immunity is associated with tumor rejection and would correlate well with reduced cancer risk while type 2 immunity supports tumor progression and thus would be associated with increased cancer risk in children.

More intriguing are studies that suggest that childhood infections might lower the risk for cancer in adulthood. A case-control study of stomach, colorectal, breast and ovarian cancer found lower risk for these cancers associated with childhood chicken pox and pertussis infections as well as with more frequent episodes of cold and influenza in adulthood [26]. Better studied is the link between childhood mumps and lower adult risk for ovarian cancer [27–29]. History of childhood mumps and measles has also been linked to a lower risk for NHL [30]. An interpretation proposed for these inverse associations with infections was that immune surveillance might be enhanced by prior contact with component proteins of pathogens that possess homology with peptide sequences of cellular antigens found in cancer precursor lesions (cross-reactive immunity) [31]. We favor an alternative hypothesis. We have obtained evidence that cancer immunosurveillance resulting in cancer risk

reduction is not mediated through cross-reactive pathogen specific immunity but rather through immunity specific to cellular proteins that are altered in their level of expression or posttranslational modification due to infections and other acute inflammatory events and then undergo similar alterations during malignant transformation. In the most recent study we analyzed serum stored from individuals going through an active mumps infection and found a higher level of antibodies against a well-known tumor antigen MUC1, a normal epithelial cell surface antigen that is altered in adenocarcinomas [32***]. There is no immunity against normal forms of MUC1 in healthy individuals but patients with cancer generate antibodies and T cell responses to the cancer form of this molecule [33,34]. MUC1 is expressed on normal salivary glands and it appears that mumps parotitis affecting the salivary glands leads to presentation to the immune system of the abnormal form of MUC1 (similar to tumor-like MUC1), eliciting anti-MUC1 immunity and immune memory. MUC1-specific immune memory can be reactivated in response to abnormal MUC1 expression on emerging MUC1+ ovarian premalignant lesion or cancer and participate in its elimination or the control of its progression.

Other studies supporting similar mechanisms relate to the role of immunity against cyclin B1, previously identified by us [35,36] and others [37*][38] as a tumor antigen. In healthy cells, cyclin B1 serves as a cell cycle regulatory molecule expressed in small amounts in the nucleus of dividing cells as they transition from G2 to M phase of the cell cycle. In cancer cells and in premalignant lesions [36], cyclin B1 is constitutively overexpressed in the cell cytoplasm where it can be processed by proteasomes and presented as numerous peptides in the MHC molecules of the tumor cells. It can also be released in large amounts as soluble protein to be taken up by nearby antigen presenting cells and cross-presented to T cells and/or recognized directly by B cells. What we [39**] and others [38**] have found is that many healthy individuals, as young as 20 years of age and as old as 80, have T cell memory responses for cyclin B1, as well as different levels of anti-cyclin B1 IgG. We have also shown in a mouse model of a spontaneous tumor development that vaccination against cyclin B1 and induction of specific humoral and cellular immunity protects from spontaneous cancer later in life [39]. Specific events that can elicit cyclin B1 immunity in people have not yet been defined, but published reports of changes in cellular proteins brought on during an acute infection with varicella zoster virus (chicken-pox) [40] or human cytomegalovirus (HCMV) [41*], suggest a likely scenario. Both publications show that infection of target cells (in these studies fibroblasts were used) with either VZV or HCMV results in unscheduled overexpression of cyclin B1 in the cytoplasm, very similar to what is seen in transformed cells. Furthermore, cyclin B1 was found to phosphorylate varicella-zoster virus protein IE62 and to be incorporated into new virions [42*]. As virions spill from infected lysed cells to go on and infect other cells, they are picked up by dendritic cells and other antigen presenting cells. Activated antigen presenting cells process the virions and present to the immune system not only the viral proteins but also encapsulated cyclin B1. This generates immune T cell memory for both the pathogen and the cyclin B1 that is expected to protect against future exposures to the same pathogen but also against other pathogens or other events that might cause abnormal overexpression of cyclin B1.

It is unfortunate that history of childhood infections was not a frequent topic of epidemiologic studies of cancer, especially prior to 1975 before childhood diseases came to be widely vaccinated against. With near universal vaccination for childhood illnesses in industrialized societies, prospective studies that would collect blood, serum and other tissue samples for immune and molecular analysis will be impossible to perform. However, tracking cancer occurrence in the post vaccination era is going to be just as important. Indeed there has been a dramatic increase in NHL since 1975 in this country that has not been explained [43]. While it is impossible to return to the pre-vaccination era, incidence data should be carefully monitored to identify those cancers that may be most affected by

the absence of childhood infections and experimental studies designed to explain the basis for protective effects including immunosurveillance of abnormally expressed cellular antigens.

Reproductive events, cancer risk and immunosurveillance

Pregnancies and breastfeeding are known to reduce the risk for breast, ovarian, and endometrial cancer [44–47]. Oral contraceptives (OC) also substantially reduce the risk of ovarian and endometrial cancer but an effect on breast cancer is less clear [48–50]. Explanations are, again, site-specific and include terminal differentiation of breast tissue with pregnancy and breastfeeding for breast cancer; protection from the harmful effects of ovulation for ovarian cancer; and protection by progesterone exposure for endometrial cancer. However, it has also been hypothesized that pregnancy reduces the risk for breast cancer by exposure of fetal antigens and development of maternal immunity and immune memory against these antigens, which might subsequently be expressed on breast cancers as oncofetal antigens serving as targets for breast cancer cell elimination by the immune effector mechanisms [51]. We have provided additional evidence in support of the hypothesis that these events reduce cancer risk by causing abnormal expression of various cellular proteins and promoting establishment of immune memory that can be reactivated by the expression of these molecules on cancer cells [52,53**].

Conversely, absence of pregnancies, breastfeeding, or OC use leads to an increasing number of ovulatory cycles, which predicts greater risk for ovarian cancer [54] and also correlates directly with endometrial and breast cancer risk [55,56]. It has not been examined for the other cancers noted to be decreased by pregnancies, but it is quite likely that increasing ovulatory cycles would correlate with increased risk for pancreas and colon cancer as well as NHL. We have shown in two separate data sets that a greater number of ovulatory cycles is associated with a lower level of anti-MUC1 antibodies [53*], which could be expected from earlier observations that “incessant ovulation” creates a chronic inflammatory microenvironment that is known to be tumor-promoting [57,58] and would be expected to suppress adaptive immunity. Endometriosis, the occurrence of endometrial tissue outside the uterus, is another chronic inflammatory event that increases the risk not only for ovarian cancer but also for breast cancer and NHL [59].

Although not a “reproductive event,” use of talc powders in the genital area rounds out the triumvirate of chronic exposures together with incessant ovulation and endometriosis that increase the risk of ovarian cancer [60] and endometrial cancer [61]. Talc may lead to chronic irritation and thus inflammation of mucous membranes that could affect generation of effective immunity (e.g. lower or no anti-MUC1 antibody) and may also track to pelvic lymph nodes and affect antigen processing [62]. This raises the possibility that talc use may also be a factor in other pelvic cancers in women including cervix, bladder, or kidney, by interfering with induction of an effective immune response.

Conclusion

We have reviewed the most recent studies that implicate the immune response as a unifying and non-site specific determinant (both positive and negative) of cancer risk. Antibodies and T cells to numerous abnormally expressed self molecules on tumor cells (tumor associated antigens) have been detected in cancer patients and some have been associated with better prognosis [63,64***]. The most abundant data exist on the humoral immune responses against tumor-associated antigens (TAA). A recent detailed review of 145 studies of over 100 TAAs revealed that the most frequently analyzed antigens include p53, MUC1, NY-ESO-1, c-myc, survivin, p62, cyclin B1, and Her2/neu [64]. [65–72]. The common

assumption has been that this immunity was generated in response to the developing tumor. However, the more we learn about the immunosuppressive nature of the tumor microenvironment, the less likely it is that the tumor itself can provide a strong immunogenic signal for effective priming of the immune system against tumor associated antigens. Animal models show that even in the very early stages of tumor development, including some advanced premalignant lesions; the tumor microenvironment is characterized by the presence of innate immune cells and inflammatory cytokines that are capable of promoting tumor growth. It is much more likely that a nascent tumor triggers memory T cells and antibodies through the expression of abnormal self-antigens the immune system previously encountered on infected or otherwise diseased non-malignant tissues. These responses can quickly expand at the site of the premalignant lesion or early tumor leading to its elimination or control of its growth and malignant progression.

The most important outcome of the work we reviewed is that it not only unites two different scientific disciplines, epidemiology and immunology, but it also brings closer the historically separate branches of immunology: immunology of infectious diseases and immunology of cancer. Collectively, the papers we highlight suggest that the immune system learns very early (and primarily through fighting off infections) what molecules characterize diseased cells and tissues and commits to immune memory responses to foreign antigens belonging to the specific infectious agents as well responses to abnormal self antigens expressed by infected damaged or dying cells. This memory is triggered and likely boosted through exposure to future infections with the same or unrelated pathogens. Many infections may not be clinically diagnosed since infected cells can be eliminated early in infection through an anamnestic immune response directed against abnormal cellular antigens, without waiting for the immunity to the new pathogen to develop. If every new infection had to be handled solely through the generation of adaptive immunity (T cells and specific antibodies) against individual specific pathogens, extensive pathology would result due to a large number of infected cells in the absence of protective preexisting immunity. One would also expect establishment of a chronic infection accompanied by chronic inflammation, which can exert a suppressive effect on adaptive immunity or result in immune tolerance.

The obvious utility of these and future studies of this kind will be the opportunity to define many more targets of successful immune surveillance and to establish immunophenotyping of individuals as an additional and we believe critical risk assessment tool. Furthermore, if a protective immune memory has not been generated through natural exposures to pathogens, or previous exposures have resulted in tolerance, it may be possible to induce these responses later in life with appropriately designed vaccines.

Acknowledgments

The authors gratefully acknowledge NCI support for their collaborative studies under the RO1CA054419 (D.W.C.) with added support from P50CA105009 (D.W.C) and PO1073743 (O.J.F.).

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