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Cancer Detection and Prevention 30 (2006) 83–93

Cancer Detection and Prevention

www.elsevier.com/locate/cdp

Review

Acute infections as a means of cancer prevention: Opposing effects to chronic infections?

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Accepted 9 November 2005

Abstract

Purpose: Epidemiological studies have found an inverse association between acute infections and cancer development. In this paper, we review the evidence examining this potentially antagonistic relationship. *Methods*: In addition to a review of the historical literature, we examined the recent epidemiological evidence on the relationship between acute infections and subsequent cancer development in adult life. We also discuss the impact of chronic infections on tumor development and the influence of the immune system in this process. *Results*: Exposures to febrile infectious childhood diseases were associated with subsequently reduced risks for melanoma, ovary, and multiple cancers combined, significant in the latter two groups. Epidemiological studies on common acute infections in adults and subsequent cancer development found these infections to be associated with reduced risks for meningioma, glioma, melanoma and multiple cancers combined, significantly for the latter three groups. Overall, risk reduction increased with the frequency of infections, with febrile infections affording the greatest protection. In contrast to acute infections, chronic infections can be viewed as resulting from a failed immune response and an increasing number have been associated with an elevated cancer risk. *Conclusion*: Infections may play a paradoxical role in cancer development with chronic infections often being tumorigenic and acute infections being antagonistic to cancer.

Keywords: Fever; Cancer prevention; Infection; Leukocytes; Spontaneous regression

1. Introduction

A key vision of the World Health Organization has been to create ‘‘a world in which all people at risk are protected against vaccine-preventable diseases’’ [1]. An admirable goal in light of the considerable morbidity and mortality infectious diseases continue to inflict throughout the world. Yet, at the same time one cannot help but wonder whether the infectious diseases that have plagued humanity for millennia could somehow incur more intangible benefits. For example, the old adage ‘‘what does not kill me makes me stronger’’ may in some sense be applied to the influence of acute infectious disease on cancer development. In a 1929 review on the topic, Pearl commented ‘‘that there is an antagonism between cancer and infectious diseases . . . is a medical judgment which has existed from remote times’’ [2]. In this paper, we review past and present evidence for an antagonistic relationship between acute infectious disease and cancer, and its relevance to cancer prevention. We also explore the paradoxical role chronic infections may play in cancer development.

Acute infections may be defined as those that generally have a rapid onset and last for a relatively short period of time [3]. These infections are often associated with an ‘‘acute phase reaction’’—an early local inflammatory reaction, consisting of fever (a cytokine-mediated rise in core temperature), an increased synthesis in the liver of acute phase reactants, as well as a host of other immunologic, endocrinologic, neurologic and physiologic changes [4]. Chronic infections may be defined as afebrile infections lasting many years, which may have limited or no disease symptoms [3].

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0361-090X/$30.00
doi:10.1016/j.cdp.2005.11.001

Moreover, chronic infections may be regarded as a consequence of a failed or misguided immune response. Infections do not always fit into these two distinct categories. For example, a chronic infection at its outset may trigger an acute phase reaction, it may have recurrent acute phases, and may develop progressively more severe symptoms over time. Additionally, a pathogen that causes an acute infection in one individual may cause a chronic infection in another. For simplicity, we refer to infections as being either acute or chronic; however, in terms of their influence on cancer, we argue that the development of the acute phase reaction is an important determinate in cancer prevention.

2. Materials and methods

We have previously reviewed reports of spontaneous cancer regression and its frequent association with acute infections, and febrile infections in particular [5–7]. This led us to the hypothesis that if acute infections could induce cancer regression, then frequent acute infections within a population may also be able to reduce cancer incidence. Thus, the aim of the present study was to examine the epidemiologic evidence (case–control and cohort studies) investigating the association between acute infections and subsequent cancer development in adults. Papers that reported original research were identified by an electronic database search in PubMed (up to 2005) and EMBASE (1980–2005). Relevant papers were identified using the following keywords: neoplasms, infection, fever, epidemiologic studies, case–control studies, and cohort studies. Furthermore, we hand searched the bibliographies of these epidemiological studies and related review articles for additional publications on the subject. The odds ratios (OR) or relative risks (RR) and associated *p*-values or 95% confidence intervals (95% CI) from papers published since 1960 were summarized in structured tables to allow for comparison and discussion of findings.

As a background to these recent studies, we examined the historical literature on the association between infections and cancer development, as well as, reports of spontaneous tumor regression occurring in cancer patients with concomitant infections. The historical literature reviewed included textbooks on cancer written previous to 1950, historical articles found in the bibliographies of papers relevant to the topic reviewed, and from a search of *Index Medicus* during the period 1879–1926. Finally to contrast the data on acute infections, we review of the influence of chronic infections on cancer development.

3. Historical perspectives on infection and cancer

3.1. Acute infections and spontaneous cancer regression

Some of the evidence supporting the concept that acute infectious disease may be antagonistic to cancer relates to the repeated observations of spontaneous cancer regression in patients with coincident infections [5]. An early example is the report by Dupuytren [8] in 1829 of a woman with an extensive carcinoma of the breast who had refused surgery. Eighteen months later she was bedridden, cachectic and almost moribund. At this time, the patient became feverish with vomiting. Her now extensive tumor became inflamed and gangrenous. Three incisions were made into the tumor to evacuate a large quantity of viscous fluid. Within eight days the tumor had regressed by one-third. By the 4th week, the disease was no longer evident. Interestingly, the great frequency of such observations led to the development of active immunotherapy treatments for cancer in the 18th and 19th centuries [5]. Sometimes septic dressings would be applied to ulcerated tumors or the surgical incision would be left open to facilitate infection or often suppurating sores would be intentionally established [6].

The most conclusive evidence, however, that acute infections may counter tumor growth comes from the work of William Coley, whose career spanned from 1891 to 1936. At the turn of the century Coley, a surgeon, developed a killed bacterial vaccine for cancer consisting of the gram positive *Streptococcus pyogenes* and gram negative *Serratia marcescens*. His initially encouraging results in inducing tumor regression with repeated inoculations [9] was followed by similar successes reported by contemporaries who experimented with his vaccine [10–12]. It is documented that Coley's method of treatment could induce the complete regression of extensive metastatic disease [12]. Although there was considerable variation from one individual to the next, after many hundreds of cases, Coley confirmed his impressions that mimicking a *repetitive* acute febrile response was the key factor necessary to provoke and maintain tumor regression [6]. His treatment gradually fell out of favor following his death in 1936. By that time, radiation and increasingly chemotherapy had become mainstays of treatment for cancer and required less time, effort, and individualization than Coley's vaccine.

3.2. Acute infections in cancer prevention

If overt cancer can regress in association with acute infections, why not occult cancers and precancerous lesions? In fact, the impression that infections may *prevent* cancer arose from the often repeated observation that individuals who developed cancer generally had unexceptional medical histories. For example, Didot commented in 1852 that if one studies the prior health of cancer patients, one notes since the time of Hippocrates their previous health has been good until the onset of cancer [13]. In 1854, the physician Laurence stated, ''as a rule, it will be found that cancerous patients have otherwise been remarkably free of disease'' [14]. A similar perspective was later provided by the French physician, Lambotte, in 1896 [15]. He suggested that antecedent erysipelas (i.e. *S. pyogenes*) and other suppurative diseases rarely occurred in the cancer patient and that