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ALLERGIES: THEIR ROLE IN CANCER PREVENTION

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ABSTRACT

The nature of the biological relationships between cancers and allergies has intrigued researchers and health care providers for five decades. Three hypotheses have been proposed: antigenic stimulation predicts positive associations between cancers and allergies (i.e., allergy sufferers are more likely to get cancer), whereas immunosurveillance and prophylaxis predict inverse associations (i.e., allergy sufferers are less likely to get cancer). Immunosurveillance predicts inverse associations for cancers of

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all tissues and organ systems, and prophylaxis predicts inverse associations specifically for cancers of tissues and organ systems that interface with the external environment. To comparatively evaluate these hypotheses, we comprehensively reviewed the literature on cancer and allergies. We located 148 papers published from 1955 through 2006 that reported results of 463 studies of relationships between patients' histories of 11 specific allergies and cancers of 19 tissues and organ systems, and 183 studies of patients' histories of multiple allergies in relation to various types/sites of cancers. Analyses of these studies revealed that (1) frequencies of positive, inverse, and null allergy-cancer associations differed considerably among cancers of different tissues and organ systems; (2) more than twice as many studies reported inverse allergy-cancer associations as reported positive associations; (3) inverse associations were particularly common for cancers of the mouth and throat, brain glia, colon and rectum, pancreas, skin, and cervix but (4) particularly rare for cancers of the breast, prostate, and brain meninges, and for myeloma, non-Hodgkin's lymphoma, and myelocytic leukemia; (5) lung cancer was positively associated with asthma but inversely associated with other allergies; (6) inverse associations with allergies were more than twice as common for cancers of nine tissues and organ systems that interface with the external environment compared to cancers of nine tissues and organ systems that do not interface with the external environment; and (7) eczema, hives, and allergies to animal dander and food were most frequently inversely associated with cancers of tissues that interface with the external environment. Taken together, these results are more consistent with the prophylaxis hypothesis than the two alternatives. IgE is a widespread and ancient immunoglobulin isotype in mammals, occurring among all known marsupials, monotremes, and eutherians. The IgE system and its associated allergy symptoms may serve a common protective function: the rapid expulsion of pathogens, dangerous natural toxins, and other carcinogenic antigens before they can trigger malignant neoplasia in exposed tissues.

INTRODUCTION

ACROSS THE WORLD, cancers and allergies cause physical suffering, financial hardship, morbidity, and mortality. However, that would seem to be the extent of their similarities. Physiologically, allergies involve IgE-mediated hypersensitivity to environmental antigens, and cancers involve unrestrained cell growth. Symptomatically, allergies cause coughing, sneezing, tearing, itching, and diarrhea, whereas the sequelae of cancers include pain, fatigue, and organ dysfunction. In terms of morbidity, allergies are twice as prevalent; in the United States, 40–50% of the population currently tests positive for allergies, but only 4% suffers from cancers (Arbes et al. 2005; Ries et al. 2005). However, in terms of mortality, the reverse is true: death rates from cancers (>500,000 people per year) vastly exceed those from allergies (<10,000 people per year). The estimated costs of cancers and allergies to the public health care system are enormous, currently exceeding \$210 billion per year and \$7 billion per year, respectively (AAFA 2007; Meropol and Schulman 2007).

Despite these differences, the possibility

that there are biological relationships between allergies and cancers has intrigued researchers and health care providers for five decades (see Vena et al. 1985). Although about 150 primary papers exploring these potential relationships have been published, no consensus has emerged. Many studies have reported inverse associations—i.e., that people diagnosed with cancers of certain types or sites were less likely to have had histories of allergies than comparison groups of noncancer patients. However, many other studies reported positive associations, and still others found no relationships at all.

To explain the positive associations, McWhorter (1988) proposed the “antigenic stimulation” hypothesis (reiterated by Bourguet and Logue 1993; Hedderson et al. 2003; Castaing et al. 2005), which states that allergies cause chronic inflammation and stimulation of cell growth, which, in turn, increase the likelihood of mutations of actively-dividing stem cells and malignant proliferation of aberrant clones. Indeed, the link between chronic inflammation and cancer occurrence is well-established (Balkwill et al. 2005). Under the antigenic stimulation hypothesis,

allergy symptoms directly increase risks of developing cancers in any tissue or organ system (Figure 1a).

Two hypotheses have been proposed to explain the inverse associations between cancers and allergy histories (Figure 1a). The first is the “immunosurveillance” hypothesis (Burnet 1957; reiterated by Mackay 1966; Golub and Green 1991; Eriksson et al. 1995; Markiewicz and Gajewski 1999; Castaing et al. 2005), which asserts that people whose immune systems effectively prevent cancer by detecting and eradicating autogenic, premalignant cells before tumors develop also

have immune systems that are adept at recognizing and destroying toxins, heterospecific cells (e.g., pollen, mold, helminths), and other foreign particles. Under this hypothesis, allergy symptoms are side effects of hyperimmunity and efficient immunosurveillance. That is, the allergy symptoms themselves do not directly affect the occurrence of cancers; therefore, inverse allergy-cancer associations indicate correlations—not causation.

The second explanation for inverse associations between cancers and allergy histories is the “prophylaxis” hypothesis (Profet 1991; reiterated by Ewald 1994; Nesse and

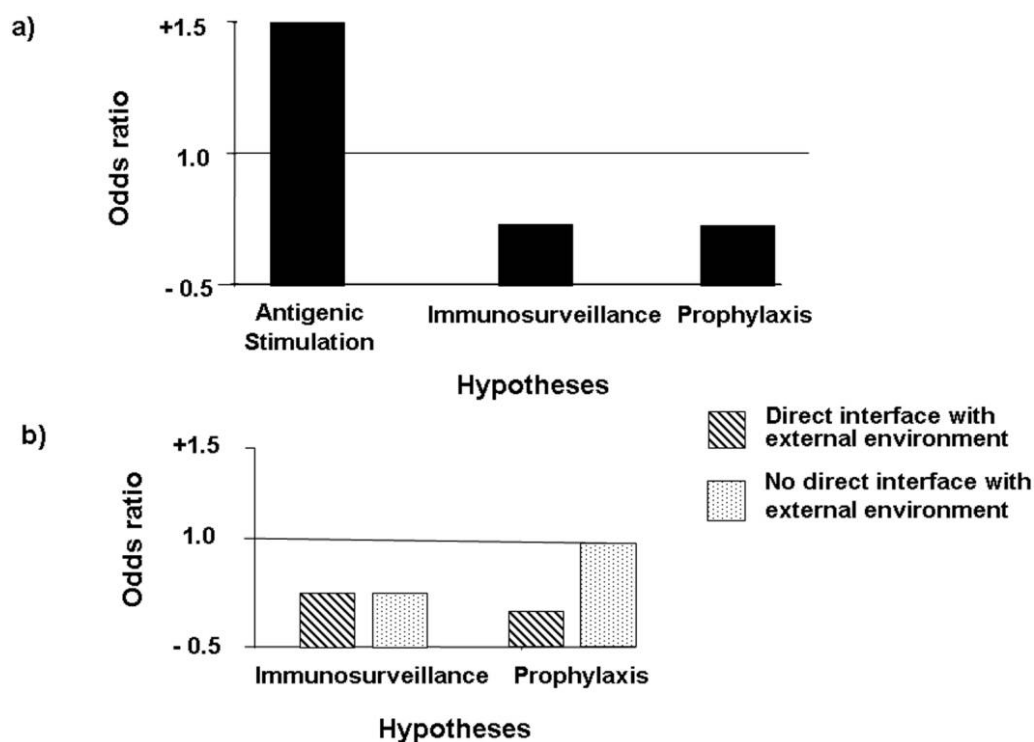


FIGURE 1. PREDICTIONS OF THE THREE ALLERGY-CANCER HYPOTHESES

(a) Predicted relationships between individuals' histories of allergy symptoms and occurrences of cancers under the antigenic stimulation, immunosurveillance, and prophylaxis hypotheses. (b) Predicted relationships, under the immunosurveillance and prophylaxis hypotheses, between individuals' histories of allergy symptoms and occurrences of cancers of tissues or organ systems that do and do not interface directly with the external environment, assuming that variations in allergy symptoms result more from differences in the physiological abilities of individuals to mount allergic responses than from differences in exposure to carcinogenic antigens. The prophylaxis hypothesis predicts that inverse allergy-cancer associations should be more prevalent among tissues or organ systems that are directly exposed to chemical and biological insults from the external environment.

Williams 1994). This hypothesis, which takes a Darwinian perspective, proposes that allergy symptoms themselves evolved by natural selection to serve a useful purpose: the expulsion of toxins, pathogens, and foreign particles before they, and any contained or adhering mutagens, can initiate carcinogenesis. In addition, allergy symptoms may serve as personal "warning signals" that indicate to an individual the array of environmental substances that he or she would do well to avoid contacting (breathing, eating, or drinking). Under the prophylaxis hypothesis, allergy symptoms reduce the occurrence of cancers directly, by quickly ridding exposed tissues of mutagenic toxins, microorganisms, and environmental contaminants, and by encouraging avoidance of those antigens in the future. Thus, inverse allergy-cancer associations indicate causal relationships—not just correlations.

Assuming that variations in allergy symptoms result more from differences in the physiological abilities of individuals to mount allergic responses than from differences in exposure to carcinogenic antigens, both the immunosurveillance and prophylaxis hypotheses predict inverse allergy-cancer associations (Ewald 1994). However, these hypotheses make a further, contrasting prediction (Figure 1b). If allergy symptoms function as prophylactics, they should be associated especially with reduced occurrence of cancers of tissues and organ systems that are directly exposed to chemical and biological insults from the external environment and from which carcinogenic antigens can readily be expelled, whereas if allergies are indicative of effective immunosurveillance, then they should be inversely associated with reduced occurrence of cancers of all types and sites.

To comparatively evaluate the likelihood of the antigenic stimulation, immunosurveillance, and prophylaxis hypotheses, we comprehensively reviewed the literature, and quantified which allergies have been associated positively and inversely with specific types and sites of cancers and for which no association has been observed. Although

some of our results were consistent with more than one of the three hypotheses, when all the information was considered, a front-runner clearly emerged: the prophylaxis hypothesis. We will consider the possible implications of this outcome for allergy sufferers, clinicians, and future research in the "Discussion" section of this paper.

METHODS

We sought primary papers on allergy-cancer relationships using electronic databases (primarily Medline and Web of Science) and recent reviews (especially Santillan et al. 2003; Gandini et al. 2005; Tennis et al. 2005; Wang and Diepgen 2005; Schoemaker et al. 2006; Turner et al. 2006; Merrill et al. 2007). Key words used in our database searches included either "allergy," "allergies," "atopy," "IgE," or the name of one of the nine most common allergies (i.e., dust mites, animal fur, asthma, hay fever, hives, eczema, food, insects, and drugs) (Arbes et al. 2005), plus the word "cancer" or the name of one of six common malignancies that do not include cancer (i.e., leukemia, glioma, meningioma, lymphoma, myeloma, and Hodgkin's).

We located 148 relevant publications, dating from 1955 through 2006. Many of these papers reported results of several independent studies, typically presenting data on relationships of each of several types of allergies to one or more types or sites of cancers, and then combining the results to assess relationships between allergies and cancer occurrence in general. Our database is presented in Appendix 1 (available online at *The Quarterly Review of Biology* homepage, www.journals.uchicago.edu/QRB) and Table 1. It contains 646 studies, as follows: 412 studies of associations between one of 11 types of allergies and cancers of one of 19 specific tissues or organ systems, 51 studies of cancers of unspecified types/sites or multiple cancers combined in relation to specific types of allergies, 156 studies of allergies of unspecified types or multiple types combined in relation to various types/sites of cancers, and 27 studies of multiple or unspecified types of both allergies and cancers.

TABLE 1
Allergy-cancer relationships according to cancer site/type

Cancer type	Specific allergies			Multiple allergies combined		
	Inverse	Positive	Neutral	Inverse	Positive	Neutral
Glioma	19(12)	0	5	9(7)	0	0
Meningioma	3(0)	0	6	1(1)	0	4
Non-Hodgkin's lymphoma	14(9)	12(6)	25	3(2)	4(2)	7
Hodgkin's disease	3(1)	1(1)	4	2(2)	1(0)	4
Acute myelocytic leukemia	6(3)	7(3)	8	3(2)	1(0)	2
Acute lymphocytic leukemia	16(10)	6(1)	12	5(3)	2(1)	1
Myeloma	6(1)	3(3)	14	2(1)	3(2)	9
Lung (excluding asthma)	8(5)	1(0)	6	10(7)	1(0)	5
Lung (asthma only)	4(3)	18(13)	6			
Oral/Throat	11(7)	1(0)	5	6(3)	0(0)	0
Pancreas	32(12)	8(2)	12	6(4)	2(0)	2
Gastrointestinal	6(3)	2(0)	6	4(3)	1(0)	1
Bladder	4(1)	4(3)	1	5(3)	1(1)	0
Colorectal	15(4)	3(1)	5	8(4)	1(0)	3
Prostate	4(1)	7(3)	9	1(0)	3(1)	4
Ovary	5(2)	1(0)	6	2(0)	0	2
Uterine/Cervical	9(4)	3(0)	5	3(2)	2(1)	3
Breast	3(3)	4(0)	16	4(3)	4(1)	5
Skin	6(2)	1(0)	4	4(2)	1(1)	1
Subtotals	174	82	155	77	27	53
Proportions	0.42	0.21	0.37	0.49	0.17	0.34
Cancers of multiple or unspecified types/sites	18(15)	10(5)	23	10(10)	4(4)	12
Totals	192	92	178	88	31	65
Proportions	0.42	0.20	0.38	0.48	0.17	0.35
Significant relationships	98	41	-	59	14	-
and proportions	0.71	0.29	-	0.80	0.20	-

Numbers of independent studies documented in 148 papers published from 1955 through 2006 that reported inverse, positive, and neutral relationships between patients' histories of specific allergy symptoms, as well as allergies in general (unspecified types or multiple types combined), and cancers of 19 tissues or organ systems. A positive relationship means that cancer of the specified tissue or organ system occurred more frequently among individuals with a history of the allergy listed than among comparison groups of nonallergy patients, an inverse relationship means that cancer of that type/site occurred less frequently among individuals with a history of the allergy listed than among comparison groups, and a neutral relationship means that cancer of that type/site was equally common among individuals both with and without a history of the allergy listed. For each cancer site or type, total numbers of studies reporting significant relationships appear in parentheses and are discussed further in the text. Complete references to all studies are provided in Appendix 1 (available online at *The Quarterly Review of Biology* homepage, www.journals.uchicago.edu/QRB).

The epidemiological details of the majority of allergy-cancer studies have been summarized multiple times in recent reviews (e.g., Wang and Diepgen 2005; Turner et al. 2006; Merrill et al. 2007); therefore, they will not be reiterated here. Briefly, the majority of studies (>80%) were retrospective, case-control analyses of the frequencies with which patients who had been diagnosed with cancer of a specific tissue or organ system, or cancers of unspecified types/sites or multiple types/sites combined, had histories of a specific

type of allergy or multiple allergies combined (cases) compared with allergy histories of a matched comparison group of noncancer patients (controls). Most of the remaining studies were cohort analyses in which patients with one or more allergies were followed for multiple years. The incidence of cancers in the cohort was compared with that in a specified comparison group or population. Finally, in a minority of studies (<5%), the frequency of occurrence of cancer of a specific type/site in a group of individuals with a history of one

or more allergies, or the frequency of occurrence of allergies in a group of patients with cancer of a particular site/type, were compared with average frequencies of the occurrence of that type/site of cancer or allergy, respectively, in the nation's population. Patients' histories of allergies most often (>80% of studies) were based on physicians' physical examinations or self-reports to health care professionals, although, in some studies, skin-prick tests (e.g., Eriksson et al. 1995; Gergen et al. 2000; Talbot-Smith et al. 2003) or IgE reactivity were used (Wiemels et al. 2004; Wang et al. 2006).

The authors of the majority of studies we reviewed tested their results for statistical significance, and we kept significant and nonsignificant studies separate in our analyses. For the small minority of studies in which statistical results were not presented, significance was inferred using a conservative approach. That is, a significant positive relationship was inferred when the relative risk (*RR*) or odds ratio (*OR*) for the occurrence of the type/site of cancer among individuals with a history of the allergy or allergies under consideration was >1.2 and when the 95% confidence interval (*CI*) did not include 1.0, and a significant inverse relationship was inferred when the *RR* or *OR* for the occurrence of the type/site of cancer among individuals with a history of the allergy or allergies under consideration was <0.8 and the 95% *CI* did not include 1.0. To minimize pseudoreplication, we analyzed the 463 studies of specific allergies and specific cancers or multiple cancers combined separately from the 183 studies of unspecified allergies or multiple allergies combined (Table 1). Studies of thyroid and testicular cancer could not be included in our analyses because of small sample sizes ($N \leq 10$ studies) (Appendix 1).

Comparatively evaluating the three alternative hypotheses required comparing the directions and strengths of associations between cancers of various tissues or organ systems and individuals' histories of allergies. In turn, this raised the question of

which studies to include. There are two approaches to addressing this issue for heterogeneous data sets like ours. As we will explain, neither is perfect—each has its strengths and weaknesses.

The first approach is known as “total evidence”—i.e., analysis of an unpartitioned body of evidence (Kluge 1989). It is now used commonly in phylogenetic inference analyses, which involve simultaneously considering molecular, morphological, and biogeographic information (Grant and Kluge 2003; Bininda-Emonds 2004). The strengths of the total evidence approach are that (1) all the information is considered, and (2) the information is “unweighted.” However, in regard to allergy-cancer studies, these also are its weaknesses, because factors such as sample sizes, control of confounding variables, selection of comparison groups, and outcome assessments differ from study to study. The key assumption of the total evidence approach is that whatever deficiencies and biases may exist in individual studies, they are not more likely to mistakenly create positive associations than negative associations (or vice versa) for cancer of one tissue or organ system than for cancers of other tissues or organ systems. Like noise in a signal, deficiencies in individual studies may increase variance and mask overall associations that actually exist, but they should not systematically generate differences between cancers of different types/sites or create overall patterns that do not in fact occur.

The alternative analytical approach is called “quality analysis,” and it entails selectively combining, excluding, or differentially weighting evidence. This approach “purport[s] to distinguish good, reliable, accurate data from bad, misleading, erroneous data” (Grant and Kluge 2003:379). In regard to the epidemiological literature, this approach involves emphasizing results of certain studies while deemphasizing or ignoring others in drawing conclusions. The strength of quality analysis is that it places the greatest weight on studies that, in each reviewer's opinion, are the most scientifically valid. However, this is also its weakness because there are no universally agreed-upon standards of “quality” (e.g.,

What is an adequate method for determining allergy status? How many cases are required? What controls are necessary and sufficient? How many and what types of potentially confounding variables must be controlled for? How does one evaluate outcome assessments such as incidence or mortality?). Differences among reviewers in criteria for assessing quality result in different studies being included and excluded, or weighted differently, and, in consequence, different conclusions often are reached. For example, Wang and Diepgen (2005) recently concluded that “despite the mixed results, the emerging picture from most of the currently available epidemiological data indicate that atopic disease is associated with a reduced risk for cancer” (p. 1098), whereas the very next year, Turner et al., using different quality criteria, concluded that “overall, the studies conducted to date provide little clear evidence that allergies are associated with cancer overall” (2006:3124).

Grant and Kluge (2003) and Kluge (2004) compared several alternative approaches for analyzing heterogeneous data sets, including total evidence and quality analysis. Kluge (2004) summarized the results succinctly: “While maximizing explanatory power continues to justify a total evidence analysis of equally weighted evidence, no unassailable alternative founded on truth, reliability or validity has yet to be articulated” (p. 206). We therefore adopted the total evidence approach to compare and contrast outcomes predicted by the antigenic stimulation, immunosurveillance, and prophylaxis hypotheses.

RESULTS

Among the 463 studies of cancer occurrence in relation to patients' histories of specific allergies, 192 (0.42, proportionally) reported inverse associations, 93 (0.20) reported positive associations, and 178 (0.38) found no associations (Table 1, Figure 2). These results differ significantly from random expectation—i.e., the expected outcome if allergy history and cancer occurrence were independent of one another ($\chi^2 = 21.0$, $df = 2$, $P < 0.0001$). Significance

resulted from both an excess of inverse allergy-cancer associations (+0.11 deviation from expectation) and a deficit of positive associations (-0.25 deviation from expectation). Considering only the 139 studies that reported statistically significant associations, 98 (0.71) were inverse and 41 (0.29) were positive, once again resulting in a highly significant deviation from randomness ($\chi^2 = 11.4$, $df = 1$, $P < 0.0007$, with Yates's χ^2 correction for continuity).

Among the 183 studies of cancers of individual sites/types in relation to allergies in general (unspecified types or multiple types combined), 88 (0.48) reported inverse associations, 31 (0.17) reported positive associations, and 66 (0.36) found no associations (Table 1, Figure 2). These results were significantly nonrandom ($\chi^2 = 16.5$, $df = 2$, $P < 0.0003$), again owing to both an excess of inverse allergy-cancer associations (+0.18 deviation from expectation) and a deficit of positive associations (-0.36 deviation from expectation). Considering only the studies that reported statistically significant associations, 60 (0.81) were inverse and 14 (0.19) were positive ($\chi^2 = 15.1$, $df = 1$, $P < 0.0001$, with Yates's χ^2 correction for continuity).

The foregoing analyses help to distinguish the antigenic stimulation hypothesis from immunosurveillance and prophylaxis (see Figure 1), but they are too broad-brush to be useful in distinguishing between the latter two hypotheses. Rather, the focus must be on cancers of individual tissues and organ systems. Indeed, we found that associations between patients' histories of individual allergies differed considerably among cancers of different types/sites (Table 1, Figure 3). Comparisons of the frequencies of these relationships revealed an intriguing pattern: specific allergies were inversely related to cancers of seven tissues or organ systems that interface with the external environment significantly more often than to cancers of nine tissues or organ systems that do not directly interface with the external environment ($Z = 2.6$, $P < 0.009$) (Figure 3, left). Specifically, inverse associations were considerably more common for

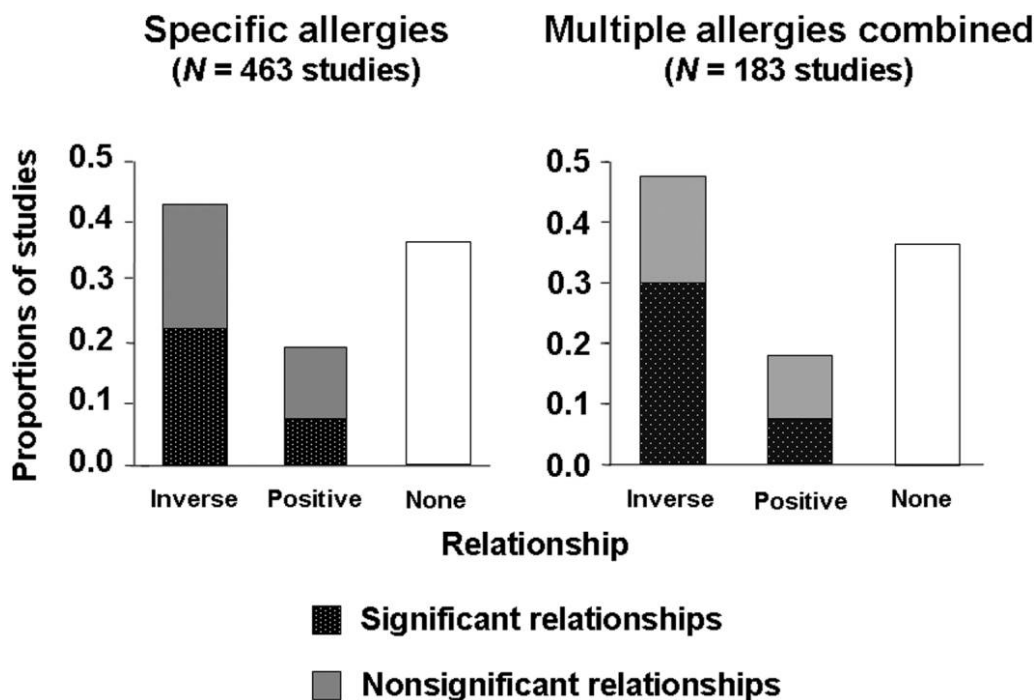


FIGURE 2. CANCER-ALLERGY RELATIONSHIPS

Proportions of studies featured in 148 papers published from 1955–2006 that reported inverse, positive, or no associations between cancers of any tissue or organ system and patients' histories of specific allergies (left) and allergies in general (unspecified types or multiple types combined) (right). Proportions of studies documenting significant positive and inverse relationships are indicated. Results of statistical tests for differences in these distributions are discussed in the text. References to all studies are provided in Appendix 1 (available online at *The Quarterly Review of Biology* homepage, www.journals.uchicago.edu/QRB).

cancers of the mouth and throat, colon and rectum, skin, uterus and cervix, lungs, bladder, and gastrointestinal tract than for cancers of the ovaries, meninges, prostate, and breast, as well as for myeloma, Hodgkin's disease, lymphocytic leukemia, myelocytic leukemia, and non-Hodgkin's lymphoma. Inverse associations also were reported significantly more frequently in studies of allergies in general (unspecified types or multiple types combined) relative to cancers of the seven tissues or organ systems that interface with the external environment compared to cancers of the nine tissues or organ systems that do not interface with the external environment ($Z = 3.0$, $P < 0.003$) (Figure 3, right). Glioma, pancreatic cancer, and lung cancer were not included in this initial analysis for reasons that we will discuss below.

It is interesting to note that probabilities

of cancer occurrence decreased with increasing numbers of different allergies per patient for pancreatic (Holly et al. 2003) and ovarian cancer (Mills et al. 1992), leukemia (Severson et al. 1989), and cancers in general (Petroianu et al. 1995). Wiemels et al. (2002) and Wigertz et al. (2007) reported that glioma risk also decreased with increasing numbers of allergies, whereas Schoemaker et al. (2006) did not observe this effect. However, in Schoemaker et al.'s study, glioma was reduced so significantly in patients with a history of just one allergy, and the sample size of multiple allergy sufferers who contracted glioma was so small, that, according to the authors, it would have been difficult to detect any further risk reductions statistically.

Allergies were related differently to the two major types of brain cancers, glioma

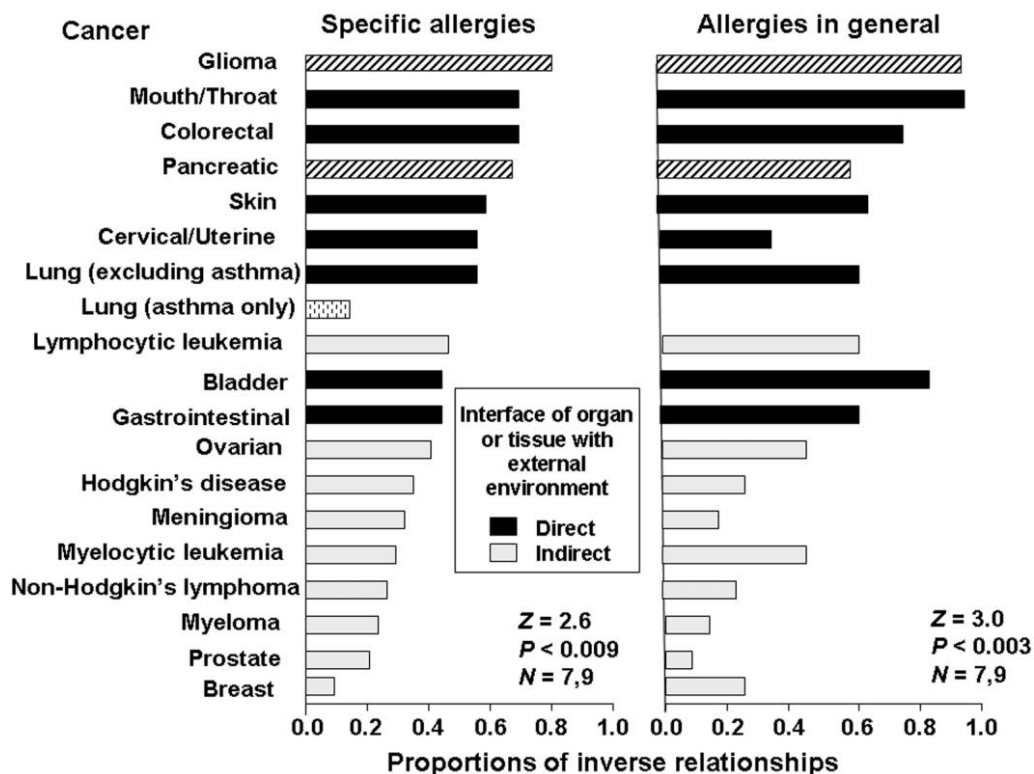


FIGURE 3. PROPORTIONS OF STUDIES THAT REPORTED INVERSE RELATIONSHIPS TO CANCERS

Proportions of studies of specific allergies (left) and allergies in general (unspecified types or multiple types combined) (right) that reported inverse associations with various cancers, separated according to whether the afflicted tissues and organ systems directly interface with the external environment (filled bars, $N = 7$) or do not directly interface with the external environment (open bars, $N = 9$). Results of Wilcoxon-Mann-Whitney tests of the null hypothesis, which states that there is no difference in relationships between tissues that directly interface and do not directly interface with the external environment, are indicated. Sample sizes (numbers of studies) are given in Appendix 1 (available online at *The Quarterly Review of Biology* homepage, www.journals.uchicago.edu/QRB) and in Table 1. Glioma and pancreatic cancer are highlighted with slashes and were not included in this initial statistical analysis because the internal tissues that they affect can interface directly with the external environment (see text). Relationships of lung cancer to asthma and to other allergies are separated for reasons discussed in the text.

and meningioma (Figure 3, Table 1). Inverse associations with specific allergies were reported in 19 of 24 studies of glioma (12 of which were significant), but in only 3 of 9 studies of meningioma (none significant) ($P < 0.005$, Fisher's exact test). Inverse associations with allergies in general were reported in 9 of 9 studies (7 significant) of glioma, but in only 1 of 5 studies (1 significant) of meningioma ($P < 0.002$, Fisher's exact test). No studies reported

positive relationships between brain cancers and allergies.

The different relationships of allergies to glioma and meningioma require further consideration, especially because of the likelihood that there are differences between the glia and meninges in degree of environmental exposure. Recently it was discovered that ultra-fine airborne particles (Oberdörster et al. 2004; Elder et al. 2006), viruses (Iwasaki et al. 2004), and

drugs (Bergström et al. 2002; Graff and Pollack 2005) that are deposited on the nasal mucosa of laboratory mammals are rapidly translocated across the blood-brain barrier, via the olfactory nerve and the nasal epithelium (Graff and Pollack 2005; Kanayama et al. 2005). Although this mechanism is not yet fully understood, it is clear that airborne toxins and pathogens potentially have a direct conduit to neural stem cells and glial progenitor cells that lie near the olfactory bulb in the lateral ventricles of the brain (Sanai et al. 2005). This may help explain why glioma risk—but not meningioma risk—is associated with occupations such as farming and firefighting that involve frequent exposure to particulate pollutants (e.g., smoke, lead, and pesticides) (Zheng et al. 2001; Ohgaki and Kleihues 2005). The implication is that the proliferative, neuroectodermal glial stem cells (De Groot et al. 1992; Pilkington 2005) are exposed more directly to environmental insults (e.g., toxins and pathogens) than the more sequestered and non-proliferative meningeal cells.

The relationship of lung cancer to asthma and to other allergies also requires special consideration. Asthma is an unusual disorder. Whereas most allergies are accompanied by increases in secretion and clearance of mucous (e.g., via sneezing, tearing, coughing, or diarrhea), both allergic and nonallergic asthma are constrictive airway disorders whose symptoms compromise lung function and make breathing difficult (Reed 2006). Essentially, asthma obstructs clearance of pulmonary mucous, blocking any potentially prophylactic benefit of allergic expulsion of carcinogenic particulates. Under the prophylaxis hypothesis, lung cancer should, therefore, be more prevalent among asthmatics but less prevalent among people with allergies that enhance expulsion of lung mucous. Consequently, we considered the relationship between asthma and lung cancer separately from associations of other allergies with lung cancer.

Among 28 studies of lung cancer in relation to allergic and nonallergic asthma (studies rarely differentiated between the two types), 18 reported positive associa-

tions (13 significant), 4 reported inverse associations (3 significant), and 6 reported no associations (Table 1), whereas among 15 studies of specific allergies other than asthma, only 1 reported a positive association (not significant), 8 reported inverse associations (5 significant), and 6 reported no associations. This difference between asthmatic and allergic associations with lung cancer was highly significant ($\chi^2 = 13.8$, $df = 2$, $P < 0.001$) (Figure 4). The data indicate that lung cancer risk was increased among asthmatics (in accordance with Brown et al. 2005; Santillan et al. 2003; Wang and Diepgen 2005; Turner et al. 2006), but was decreased in association with other allergies (in accordance with McDuffie et al. 1988; Castaing et al. 2005).

Finally, pancreatic cancer merits further consideration. Because the pancreas lies outside the digestive tract, we initially considered it an organ that does not interface with the external environment. However, the juxtaposition of the pancreas and the duodenum, which conjoin at the ampulla of Vater, potentially exposes the pancreas to reflux of intestinal contents. Indeed,

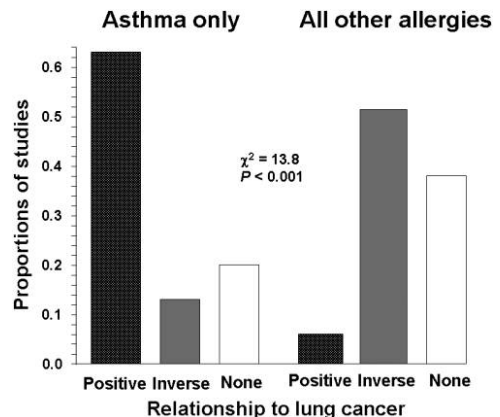


FIGURE 4. RELATIONSHIPS OF ASTHMA AND ALLERGIES TO LUNG CANCER

Lung cancer risk relative to patients' histories of asthma (allergic and nonallergic; $N = 28$ studies, left) and allergies other than asthma ($N = 15$, right). The hypothesis that there is no difference between asthma and other allergies in distributions of positive, inverse, and null relationships was tested with chi-square.

dysfunction of the sphincter of Oddi and associated duodenal reflux are well-known causes of bacterial infections of the pancreas (Sung et al. 1992) and idiopathic recurrent pancreatitis (Toouli and Craig 2000; Woods et al. 2005). Moreover, pancreatic cancer has been linked to diet, especially diets that are high in fats (Ghadirian et al. 1991; Nkondjock et al. 2005) and processed or overcooked red meats (Anderson et al. 2005; Nöthlings et al. 2005; Larsson et al. 2006), as well as to occupational and environmental exposure to certain pesticides and fertilizers, manufacturing paints and pigments, heavy metals, and soldering residues (Kriegel et al. 2006). Adenocarcinoma of the head of the pancreas, which is the portion of the organ that lies closest to the duodenum, is far more common than adenocarcinoma of the pancreatic body or tail (Sener et al. 1999). This implies that the pancreas can sometimes be acted on directly by substances from the external environment because of its close contact with the gut. If so, then allergies may be associated with reduced risk of pancreatic cancer (Figure 3), because, should the sphincter of Oddi malfunction, copious mucous secretion would reduce the reflux of duodenal contents through the ampulla of Vater.

In light of these considerations, we recalculated the relationships between histories of specific allergies and occurrences of cancers of various types/sites (Figure 5). Inverse associations were significantly more frequent for cancers of the nine tissues or organ systems that we now see can interface with the external environment (i.e., glia, mouth and throat, colon and rectum, pancreas, skin, uterus and cervix, lungs [excluding asthma]), bladder, and gastrointestinal tract), compared with cancers of the nine tissues or organ systems that do not interface with the external environment ($Z = 3.4$, $P < 0.0007$) (Figure 5, left). Similarly, more than two-thirds of studies of cancers of the nine tissues or organ systems that can interface with the external environment reported inverse associations with allergies in general (unspecified types or multiple types combined), versus less than one-

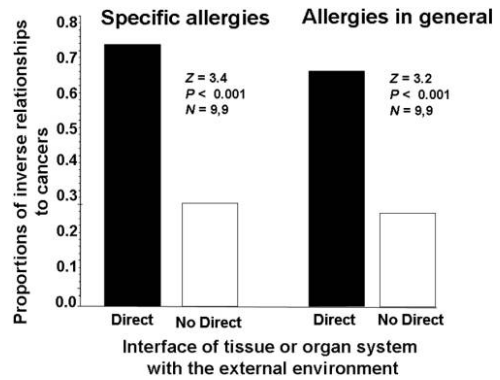


FIGURE 5. ALLERGY-CANCER RELATIONSHIPS AND EXPOSURE TO ENVIRONMENTAL INSULTS

Proportions of studies of cancers of nine tissues and organ systems that can directly interface with the external environment (filled bars) and nine tissues and organ systems that do not directly interface with the external environment (open bars) that reported inverse relationships with patients' histories of specific allergies (left) and allergies in general (unspecified types or multiple types combined) (right). Results of Wilcoxon-Mann-Whitney tests of the hypothesis that there is no difference in each pair of distributions are indicated. Sample sizes are given in Appendix 1 (available online at *The Quarterly Review of Biology* homepage, www.journals.uchicago.edu/QRB) and Table 1.

third of studies of cancers of the nine tissues or organ system that do not interface with the external environment ($Z = 3.2$, $P < 0.00$) (Figure 5, right). Finally, among the 109 studies that reported positive associations with allergies (Table 1), 77 (0.71) were cancers of the nine tissues or organ systems that do not interface with the external environment, but only 32 (0.29) were cancers of the nine tissues or organ systems that can interface with the external environment.

Among studies of eight common types of allergies, inverse associations with cancers of tissues that can directly interface with the external environment were reported most frequently for eczema and hives and for allergies to animal dander and food (Figure 6, Table 2). By contrast, these allergies were rarely inversely associated with cancers of tissues that do not directly interface with the external environment. Among

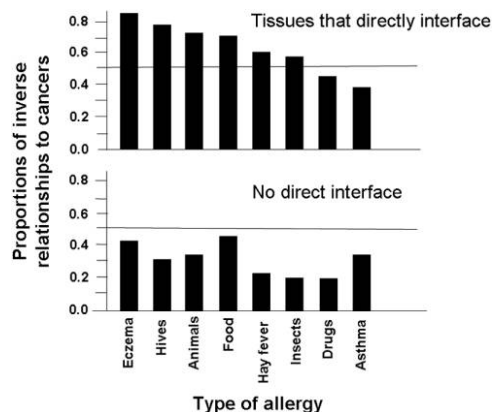


FIGURE 6. RELATIONSHIPS OF COMMON ALLERGIES TO CANCERS

Proportions of studies of eight specific types of allergies that reported inverse relationships with cancers of tissues or organ systems that can directly interface with the external environment (above) and tissues or organ systems that do not directly interface with the external environment (below). Sample sizes for each allergy are given in Table 2.

160 studies of the same eight allergies in relation to cancers of the nine tissues or organ systems that can interface with the external environment, 86 (0.54) reported inverse associations (43 significant), 33 (0.20) reported positive associations (21 significant), and 41 (0.26) reported no associations,

whereas among 149 studies of these same allergies in relation to cancers of tissues or organ systems that do not interface with the external environment, only 48 (0.32) reported inverse associations (21 significant), 30 (0.20) reported positive associations (15 significant), and 71 (0.48) reported no associations. Once again, differences in the distributions of inverse, positive, and null associations with allergies for cancers of tissues that do and do not interface with the external environment were highly significant ($\chi^2 = 18.6$, $df = 2$, $P < 0.0001$).

DISCUSSION

We utilized information from all studies published over the course of 51 years (1955–2006) to evaluate three alternative hypotheses that have been proposed to explain relationships between allergies and cancers. Our main results were that (1) frequencies of positive, inverse, and null allergy-cancer associations differed considerably among cancers of different tissues and organ systems; (2) more than twice as many studies reported inverse allergy-cancer associations as reported positive associations; (3) inverse associations were frequently reported for cancers of the glia, mouth and throat, colon and rectum, pancreas, and skin, but (4) infrequently for cancers of the breast and prostate, myeloma,

TABLE 2
Allergy-cancer relationships according to allergy type

Allergy type	Inverse	Positive	Neutral
Animal dander	4(2) [0.57]	1(0) [0.14]	2[0.29]
Eczema	29(13) [0.54]	9(5) [0.16]	16[0.30]
Food	9(6) [0.53]	3(2) [0.18]	5[0.29]
Hives	20(11) [0.50]	10(8) [0.25]	10[0.25]
Dust mites	4(2) [0.44]	1(1) [0.12]	4[0.44]
Insects	10(2) [0.43]	5(0) [0.22]	8[0.35]
Hay fever	38(24) [0.40]	12(1) [0.13]	44[0.47]
Chemicals	2(1) [0.40]	3(0) [0.60]	0[0.00]
Drugs	12(3) [0.37]	7(3) [0.21]	14[0.42]
Asthma	57(29) [0.35]	39(22) [0.24]	67[0.41]
Plants	6(4) [0.35]	3(0) [0.18]	8[0.47]
Total	191[0.42]	93[0.20]	178[0.38]

Total numbers of studies that reported inverse, positive, and neutral relationships between patients' histories of 11 specific allergies and cancers in general (all types/sites combined). Numbers of significant studies appear in parentheses, and proportions of studies appear in brackets. Definitions are as in Table 1, and references are in Appendix 1 (available online at *The Quarterly Review of Biology* homepage, www.journals.uchicago.edu/QRB).

lymphoma, leukemia, and meningioma; and (5) regarding lung cancer, asthma was associated with increased risk, whereas other allergies were associated with decreased risk. These five conclusions are in agreement with those of numerous previous reviewers (e.g., Gandini et al. 2003; Santillan et al. 2003; Wang and Diepgen 2005; Schoemaker et al. 2006; Wang et al. 2006; Merrill et al. 2007).

In addition, our analyses yielded two novel insights: (1) inverse relationships with allergy histories were considerably more frequent for cancers of nine tissues and organ systems that can interface with the external environment (e.g., glia, mouth and throat, colon and rectum, pancreas, skin, uterus and cervix, lungs [excluding asthma]), bladder, and gastrointestinal tract) than for cancers of nine tissues or organ systems that do not interface with the external environment (e.g., ovary, meninges, prostate, and breast as well as myeloma, Hodgkin's disease, lymphocytic leukemia, myelocytic leukemia, and non-Hodgkin's lymphoma), and (2) inverse relationships to cancers were more frequent for eczema, hives, hay fever, and animal and food allergies than for drug allergies or asthma.

These results enable us to comparatively evaluate the three alternative allergy-cancer hypotheses. First, the antigenic stimulation hypothesis predicts that because allergies cause chronic inflammation and stimulation of cell growth, the preponderance of associations between patients' histories of allergies and occurrences of cancers of all types/sites should be positive (Figure 1a). However, inverse allergy-cancer associations were reported more than twice as often as positive relationships (Figure 2, Table 1), and the directions of allergy-cancer associations were highly tissue- and organ-specific (Figures 3 and 5). Lung cancer risk was positively associated with asthma (Figure 4; in accordance with Castaing et al. 2005), but it was inversely associated with other allergies (in accordance with Santillan et al. 2003). These results were not predicted under the antigenic stimulation hypothesis.

Inverse allergy-cancer associations are expected to predominate under both the immunosurveillance and prophylaxis hypotheses (Figure 1a), assuming that variations in

allergy symptoms result more from differences in the physiological abilities of individuals to mount allergic responses than from differences in exposure to carcinogenic antigens (Ewald 1994). According to the immunosurveillance hypothesis, inverse associations should characterize cancers of all tissues and organ systems (Figure 1b). These associations result fortuitously, not causally: a hyperactive immune system that effectively targets and destroys aberrant (pre-malignant) cells, thereby arresting carcinogenesis, also readily attacks foreign antigens, resulting in allergy symptoms as unselected side effects.

In contrast, according to the prophylaxis hypothesis, inverse allergy-cancer associations should vary according to the degree that each tissue and organ system is exposed to chemical and biological insults from the external environment (Figure 1b). Such inverse associations are causal, not fortuitous. The prophylaxis hypothesis proposes that allergy symptoms function to rapidly expel toxins, micro- and macro-organisms, and environmental particles, some of which carry or contain carcinogens. Allergy symptoms also may serve as personal surveillance systems that indicate to individuals which environmental chemicals and particles they would do well to avoid contacting (i.e., breathing, eating, or drinking). People who heed their own body's warning signals will reduce their exposure to those pathogens, toxins, and potential carcinogens.

The following results of our analyses are in accord with prophylaxis, but not immunosurveillance: (1) the organ and tissue specificity of allergy-cancer relationships (Figure 3), (2) the interorgan variability in frequencies of inverse allergy-cancer associations (Table 1, Figure 3), (3) the relatively high frequency of inverse associations with allergies among cancers of tissues and organ systems that can be directly exposed to the external environment as compared to the predominance of null associations with allergies for cancers of tissues or organ systems that are not directly exposed (Figure 5), (4) the predominance of inverse associations between allergies and glioma but not meningioma

(Figure 3), (5) the increased risk of lung cancer among asthmatics compared with the decreased risk among people with other allergies (Figure 4), and (6) the greater prevalence of inverse relationships among allergies associated with exposed body surfaces (Table 2, Figure 6).

The prophylaxis hypothesis requires that environmental substances that cause allergic responses are either carcinogenic themselves or capable of absorbing carcinogens. There is considerable evidence supporting this. Infections by parasitic helminths (e.g., *Schistosoma mansoni*) trigger IgE production, and these worms are the leading cause of bladder cancer in northern Africa (Zacharia and Sherman 2003). Contact allergens in plants such as poison oak and ivy (urushiol), as well as scorpionweed (quinones), cleave DNA in vitro (Wasser et al. 1990; Aregullin and Rodriguez 2000). Similar to the ultra-fine particulates contained in the wood and cooking fire smoke of ancient environments, those found in the diesel exhaust and tobacco smoke of modern environments trigger IgE production and allergy symptoms and contain multiple carcinogens (Diaz-Sanchez et al. 1994, 2006; Nikasinovic et al. 2004). Even seemingly harmless pollen grains can adsorb mutagenic chemicals such as heavy metals, nitrate, sulphur, PCBs, phenols, heterocyclic amines, and pesticides (e.g., McDuffie et al. 2001; Traidl-Hoffmann et al. 2003; Salam et al. 2004).

Some readers may remain skeptical of our data supporting the prophylaxis hypothesis because 123 of the studies that we surveyed reported positive associations between allergies and cancers (Table 1). However, among these, a minority were cancers of the nine tissues or organ systems that can interface with the external environment (32 studies = 0.26). Moreover, as Ewald noted, "Some people may have strong allergic responses and a high risk of cancer because they are exposed to high levels of cancer-causing compounds" (1994:32). In other words, if variations in allergy symptoms at least sometimes result more from differences in antigen exposures than from inter-individual differences in physiological capacities to mount allergic responses, then, even

if the prophylaxis hypothesis is correct, positive associations may still occur because people who are heavily exposed to carcinogenic allergens suffer both more cancers and more allergies. For example, both IgE production and allergy symptoms are triggered by exposure to known carcinogens including cigarette smoke (Jensen et al. 1992; Diaz-Sanchez et al. 2006), diesel exhaust (Diaz-Sanchez et al. 1994; Nikasinovic et al. 2004), dioxin (Oikawa et al. 2002), and polycyclic aromatic hydrocarbons (Miller et al. 2004). We suspect that many of the positive allergy-cancer relationships in our database, especially those involving tissues and organ systems that interface with the external environment, were studies conducted in areas where carcinogenic allergens were prevalent. If so, they should not count as evidence against the prophylaxis hypothesis. Unfortunately, we cannot rigorously evaluate this conjecture, because, although many studies controlled for smoking, none took into account possible differences between "cases" and "controls" in exposure to whatever carcinogenic pollutants existed in the areas where the studies were conducted.

Another potential reason for skepticism about the prophylaxis hypothesis on the part of the reader is that we used the "total evidence" approach, which places equal weight on each original study rather than emphasizing studies that exceeded certain thresholds of "quality." We addressed this issue at length earlier, in the "Methods" section of this review. Certainly, some of the allergy-cancer studies we surveyed had larger sample sizes, better control of confounding variables, and different outcome assessments than others. However, there are no well-supported, universally agreed-upon quality standards for deciding whether to include or exclude studies from allergy-cancer meta-analyses. Of course, conclusions about whether and how various allergies and cancers are related depend critically on which studies are included, and, when reviewers adopt different criteria, different conclusions result. The total evidence approach assumes that whatever deficiencies or biases may have existed in individual studies, they are no more likely to falsely create positive associations than negative associations (or vice versa) for cancer of

one tissue or organ system than for cancers of other types/sites. Although deficiencies in individual studies could increase variance and mask overall associations that actually exist, there is no reason to suppose that they would systematically generate differences in the directions or strengths of associations between cancers of tissues and organ systems that are directly exposed to the external environment versus those that are not directly exposed (Figure 3, Table 1) if those differences did not in fact occur. Moreover, our total evidence approach yielded five quantitative conclusions that were similar to the qualitative conclusions of previous reviewers of the same literature but who adopted the quality analysis approach for including and excluding studies—as well as two novel conclusions about issues not addressed by previous reviewers.

If the prophylaxis hypothesis is indeed correct, three corollary predictions follow. First, owing to the proposed protective effects of allergies, people who express symptoms should exhibit lower concentrations of environmental carcinogens in their bodies than people living in the same area who do not express allergy symptoms. Information to test this prediction is sparse. Interestingly, however, Van den Heuvel et al. (2002) reported that, among 200 Flemish adolescents, there were significant inverse relationships between levels of specific IgEs to cat dander, dust mites, birch pollen, and grass pollen and blood concentrations of polyhalogenated aromatic hydrocarbons, particularly dioxin-like compounds. Inverse relationships between levels of IgEs to dust mites, cat dander, and birch pollen and concentrations of polychlorinated biphenyls in blood were also found, but these relationships were not significant. Van den Heuvel et al. argued that exposure to chemical pollutants had suppressed their subjects' allergic responses. Perhaps so, but there is an alternative explanation that reverses cause and effect—i.e., perhaps it was the subjects' high IgE levels and allergy symptoms that were responsible for the reduced levels of dangerous chemicals in their blood.

In a second relevant study, Noakes et al.

(2006) collected blood samples from 31 randomly selected women in an area of Western Australia where “allergic disease” was epidemic. Samples were analyzed for concentrations of cytokines and persistent organic pollutants (POP), such as organochlorine insecticides and polychlorinated biphenyls. Noakes et al. reported inverse correlations between blood concentrations of three interleukins (allergy-associated cytokines) as well as dichloroethylene (DDE). They concluded that “POP exposure/tissue levels . . . [have] declined over a period when allergic disease has continued to increase” (Noakes et al. 2006: 1309). Once again, we suggest that the subjects' high cytokine levels and allergy symptoms may have been responsible for reductions in levels of blood POPs.

Finally, it is well-known that inverse correlations exist between allergy symptoms and heavy infections of *Helicobacter pylori* (Chen and Blaser 2007), schistosomes, and hookworms (Yazdanbakhsh et al. 2002), all of which are carcinogenic (Zacharia and Sherman 2003; Wang et al. 2007). Yazdanbakhsh et al. suggested that “heavy helminth infections protect against allergy” (2002:492), but this statement may again reverse cause and effect. That is, we hypothesize that individuals' allergic responses serve to protect them from infections by pathogens and parasites that could result in cancers. Individuals who are unable to mount sufficient allergic responses are therefore more susceptible to parasite infections.

Alternatively, it is possible that *H. pylori* and parasitic worms have evolved the capacity to handicap their hosts physiologically because of the benefits of impairing hosts' abilities to mount allergic defensive responses. For example, worms possess immunomodulatory molecules that prevent mast-cell degranulation and inflammation (Yazdanbakhsh et al. 2002). This implies that inverse parasite-allergy relationships may actually be the outcome of a long co-evolutionary history, with some parasites currently being slightly ahead, effectively thwarting the allergic responses that would have expelled them from the victim's body. If so, then inverse parasite-allergy relationships are more appropriately viewed as out-

comes of parasitic manipulation than parasitic "protection."

A second corollary prediction of the prophylaxis hypothesis is that individuals with conditions that prevent rapid expulsion of toxins and potential carcinogen-carrying particles should be at greater risk of developing cancers. In this context, asthma is particularly interesting. Whereas most allergies are accompanied by increases in the rate of secretion and clearance of mucous (e.g., via sneezing, tearing, coughing, or diarrhea), both allergic and nonallergic asthma symptoms obstruct clearance of pulmonary mucous (Kalinin et al. 1991; Reed 2006). Under the prophylaxis hypothesis, occurrences of certain cancers, especially lung cancer, are expected to be more prevalent among asthmatics because of bronchioconstriction and reduced ability to expel environmental toxins and ultra-fine particles carrying carcinogens. By contrast, lung cancer should be less prevalent among people with allergies that encourage expulsion of mucous, such as eczema and hay fever. Our results (Figure 4) are consistent with both predictions and in agreement with those of previous reviewers (Santillan et al. 2003; Castaing et al. 2005; Turner et al. 2005; Wang and Diepgen 2005). Furthermore, among eight allergies for which sufficient comparative data exist (Figure 6), asthma was the one that was least often inversely associated with cancers and most often positively associated with cancers (Table 2). We infer that the effects of asthma differ from those of allergies because asthma thwarts rather than enhances expulsion of environmental toxins and potentially carcinogenic particulate matter.

A third corollary prediction of the prophylaxis hypothesis is that artificial suppression of allergy symptoms (e.g., via desensitization or antihistamines) should result in greater vulnerability to certain cancers, especially those of tissues that interface with the external environment. Information on cancer occurrence and allergy symptom suppression is available only for breast cancer and glioma. Regarding the former, Selby et al. (1989), Kelly et al.

(1999), and Nadalin et al. (2003) all reported that antihistamine users had no increased risk of breast cancer, and Nadalin et al. additionally found no associations between risk and either the age at which antihistamine use began or the duration of use. Regarding glioma, Schoemaker et al. (2006) and Wigertz et al. (2007) reported that risk was reduced among patients with hay fever who used nasal sprays.

These studies offer no support for the third corollary of the prophylaxis hypothesis, but neither do they disconfirm it. Studies of breast cancer do not provide a strong test of the corollary because, among all cancers, breast cancer exhibits the lowest proportion of inverse associations (Figure 3) and the highest proportion of null associations with allergies (Table 1). In other words, since allergies have so little relationship to breast cancer occurrence, suppressing allergy symptoms is not expected to have a detectable effect.

Results of the two glioma studies are opposite to that predicted by this corollary. However, they also do not represent unambiguous tests of it, because the mechanisms underlying the seemingly protective effect of nasal sprays (especially vasoconstriction) may be impeding absorption of ultra-fine particles and chemical pollutants by the nasal epithelium, thus helping to prevent carcinogenic antigens from ever reaching the blood-brain barrier. If so, then nasal sprays may actually work like nasal allergies in providing prophylaxis against glioma.

In 2003, a product called Xolair (omalizumab), produced by Genetech, was approved by the U.S. Food and Drug Administration for treating asthma. Omalizumab is a monoclonal antibody that binds to the high-affinity Fc receptor of IgE and blocks all IgE-mediated allergy symptoms. Widespread use of omalizumab may not only relieve asthma but incidentally provide a critical test of the third corollary of the prophylaxis hypothesis. Interestingly, among the warnings in Xolair advertisements (e.g., Genetech 2008) is mention of increased malignant neoplasms and geohelminth infections that occurred in clinical trials. Malignancies were observed in 20 of 4127 (0.005) omalizumab

recipients versus 5 of 2236 (0.002) placebo controls, and parasitic worms were observed in 36 of 68 (0.53) omalizumab recipients versus 29 of 69 (0.42) placebo controls. Among the observed malignancies of the omalizumab recipients were 11 cases of skin cancer, as well as cases of colorectal, bladder, pancreatic, prostate, and breast cancer, and, among the geohelminths, roundworms, hookworms, whipworms, and threadworms were identified. In these trials, most patients were followed for no longer than one year, and the differences in malignancy and geohelminth occurrences between patients treated with omalizumab and placebo were not statistically significant. Studies to assess effects of longer-term exposure to omalizumab have been called for (e.g., Lanier 2006). Results of such studies also may help determine if the increased malignancy and parasite infestation rates among omalizumab users resulted, at least partly, from suppression of allergy symptoms as predicted by the prophylaxis hypothesis (i.e., because of failure to quickly expel macroparasites and potential carcinogens from exposed tissues), or whether some other physiological mechanism is involved.

IgE is a widespread and ancient immunoglobulin isotype in mammals. It occurs among all marsupials, monotremes, and eutherians that have been examined, and its origins are believed to date back more than 300 MYA (Vernersson et al. 2002, 2004). As Nesse and Williams (1994) pointed out, "It is perhaps conceivable that our IgE system is merely a remnant of a system that was useful for other species, but this is unlikely because systems of this complexity degenerate quickly if they are not maintained by natural selection and even more quickly if they cause any harm" (p. 159). Similar reasoning led Profet (1991) to suggest that IgE and associated allergy symptoms were favored by natural selection as mechanisms of protection from environmental toxins of plant, insect, and parasite origin and from dust and pollen with adhering toxins.

Many natural toxins are mutagenic or teratogenic, and parasitic helminths can cause cancer of the bladder, liver, and colon (Zacharia and Sherman 2003). In light of this, an inter-

esting question is whether or not the evolutionary origins of allergies lie specifically in cancer prevention. Barnes et al. (1999) thought not. They argued that "only recently in our human history has life expectancy been extended to a point at which cancer affects a large enough proportion of the population to the degree that a mechanism . . . would be selected that would protect us from cancer" (Barnes et al. 1999:228). It is true that in modern societies occurrence rates of most cancers accelerate at age 40 (Pompei and Wilson 2001; Edwards et al., 2002), and paleodemographers (e.g., Kennedy 2003) generally agree that lifespans of ancient humans typically were short (20-40 years), similar to those of modern hunter-gatherers. However, some cancers afflict children, and their occurrence obviously would select for mechanisms of protection. Moreover, 5-19% of individuals in modern traditional populations live past 50 years of age, as did their ancient counterparts (Kennedy 2003)—that is, they live to ages at which cancer prevention would still be advantageous, especially for postmenopausal women (Hawkes 2003; Lahdenperä et al. 2004). The widespread occurrence of tumor suppressor genes (especially p53) (Oren 2003; Presneau et al. 2003; Laptenko and Prives 2006) and molecular mechanisms that protect stem cells (Leroi et al. 2003), excise and repair damaged DNA, and induce apoptosis of malignant cells (Sancar et al. 2004) all attest to the potency of selection for cancer prevention adaptations over evolutionary history (Crespi and Summers 2005). Finally, it should be noted that the prophylaxis hypothesis does not hinge on whether or not allergies evolved in ancestral mammalian populations solely to protect against carcinogenesis. The important point is that allergies apparently can function in that context, by expelling the carcinogen-carrying particles (e.g., smoke from cooking fires, pollen) and environmental toxins that once permeated ancient environments and that still permeate, to an even greater extent, modern human environments.

Rates of occurrence of many allergies are rising (e.g., atopic dermatitis, eczema, rhinitis, asthma, and food allergies), and the increases have been linked to three evolutionary novel aspects of modern environments: (1) chemical

pollutants and food additives (von Mutius 2000; McDuffie et al. 2001), (2) "hygienic" childhood environments (Strachan 1989; Kim and Drake-Lee 2003), and (3) improved transportation, increased migration, and the development of dense population centers, resulting in increased pathogen loads (Varner 2002). These explanations identify factors that result in hypertrophy of the T helper 2 (Th2) immune response, and, thus, lead to increased secretion of IgE and the expression of allergies (Wang et al. 2006).

The pollution explanation suggests that exposure to man-made chemicals in air, food, and water directly increases Th2 hypersensitivity. Indeed, IgE production and allergy symptoms are triggered by cigarette smoke (Jensen et al. 1992; Diaz-Sanchez et al. 2006), diesel exhaust particles (Diaz-Sanchez et al. 1994; Nikasinovic et al. 2004), pesticides and herbicides (McDuffie et al. 2001), and various industrial pollutants, including dioxin (Oikawa et al. 2002) and polycyclic aromatic hydrocarbons (Miller et al. 2004). The hygiene explanation suggests that proper development of the cells that regulate immune system function requires exposure to the mostly benign parasites and pathogens that have coexisted with humans over evolutionary history. In hygienic childhood environments, immunoregulation does not develop properly, resulting in hypertrophy of both Th2 and Th1 responses (Guarner et al. 2006). The industrialization explanation (Verner 2002) suggests that maintenance of a highly developed Th2 system is adaptive because it protects youngsters against infections, especially viral respiratory pathogens, which have increased in frequency and severity because of modern patterns of emigration and immigration and the development of dense population centers.

All three explanations for the recent rise in allergies in industrialized countries have received some support (Wjst 2004; Nicolaou et al. 2005; Inadera 2006; Penders et al. 2007), but they all treat the symptoms of allergies as unwanted side effects of Th2 hypersensitivity, and they are silent about whether the symptoms themselves are or ever were either useful or related to the occurrence of cancers. Thus, they do not help us distinguish between the antigenic stimulation, immunosur-

veillance, and prophylaxis hypotheses. The empirical evidence on environmental chemicals and childhood health also does not help to distinguish these hypotheses, as childhood infection rates are inversely related to inflammatory diseases (von Mutius 2001; Varner 2002; Kim and Drake-Lee 2003; Radon et al. 2004; Borchers et al. 2005; Kamradt et al. 2005) and to certain cancers in adulthood (Krieger et al. 2003; Vijn 2004), and exposure to toxic chemicals is directly related to both inflammatory diseases and cancers in adulthood (Inadera 2006). The recent rise in Th2 sensitivity and allergies in industrial societies, because of pollution, hygienic childhood environments, urbanization, or all three, has essentially set the stage for the studies we synthesized (Table 1; see also Appendix 1, available online at *The Quarterly Review of Biology* homepage, www.journals.uchicago.edu/QRB). In other words, it is only possible to detect allergy-cancer associations if allergies and cancers occur frequently enough to be studied quantitatively.

Allergy symptoms are annoying, sometimes debilitating, and, in the most extreme manifestations (anaphylaxis), deadly. However, this does not mean that normal allergy symptoms are necessarily maladaptive. Indeed, if they were, it would be difficult to explain why allergies are so widespread and ancient among mammals. From a Darwinian perspective, "The specialized mechanisms that collectively constitute the allergic response appear to manifest adaptive design in the precision, economy, efficiency, and complexity with which they achieve the goal of producing allergy [symptoms]" (Profet 1991: 25). The studies that we and our predecessors synthesized (e.g., Vena et al. 1985; Wang and Diepgen 2005; Turner et al. 2006; Merrill et al. 2007) are more consistent with predictions of the prophylaxis hypothesis than either the antigenic stimulation and or the immunosurveillance hypothesis. By rapidly ridding the body of natural toxins (fungal toxins, plant secondary compounds, insect venoms), parasitic worms, bacterial and fungal pathogens, particulate matter (pollen, smoke, dust) that may contain or have mutagenic substances adhering to its surfaces, and now industrial chemicals, allergy symp-

toms retard or prevent the initiation of certain types of carcinogenesis—especially malignancies of tissues or organ systems that are directly exposed to insults from the external environment. In addition, allergies may provide symptomatic warnings that something in the local environment is potentially dangerous to an individual. This, in turn, alerts the person to take evasive action that will minimize future exposure to the antigen, thus reducing risks of carcinogenesis.

We believe it is appropriate to view the Th2/IgE system and associated allergy symptoms as part of a hierarchical suite of physiological defense mechanisms. The first of these is the innate immune system, especially inflammation, phagocytosis, and the regular shedding of cells from the epithelial surfaces that are directly exposed to the environment. The shed cells and mucous carry away parasites, pathogens, toxins, and foreign particles before they can invade and initiate carcinogenesis. The second mechanism is the adaptive immune system, including both IgE-mediated allergy symptoms and mucosa-associated lymphatic tissues. Allergies can help rid exposed tissues of antigens and their associated toxins, thus preventing precancerous cell transformation (Lupulescu 1996; Pontén 2001), through symptoms that include increased mucous secretion and itching, followed by rapid expulsion via scratching, coughing, sneezing, tearing, and diarrhea. The mucosal immunity system consists of mucosa-associated, gut-associated, and nasal-associated lymphoid tissues (MALT, GALT, and NALT, respectively) (Williams 2003). These components function together to attack parasites, pathogens, and foreign substances that have managed to enter the body despite inflammation, continual cell shedding, and episodic allergic reactions to specific antigens. The mucosal system, which includes elements of both innate and adaptive immunity, destroys harmful pathogens directly via unique lymphocyte populations, creates barriers to penetration of infectious agents and immunogenic chemicals, and serves an immunoregulatory function by maintaining mucosal homeostasis (Tlaskalová-Hogenová et al. 2002). The final line of defense is the suite of genetic

and molecular mechanisms that reduce accumulation of deleterious mutations and proliferation of precancerous cell lineages (Leroi et al. 2003), repair damaged DNA (Sancar et al. 2004), and suppress tumor formation (Oren 2003; Presneau et al. 2003; Laptenko and Prives 2006).

The practical implications of the results presented in this paper await future research. However, people who are allergy-free certainly need not fear that they are therefore likely to develop cancer. There are many reasons why some individuals do not express allergy symptoms other than physiological inability to do so, the most likely of which are minimal exposure to ingested, inhaled, or absorbed parasites and pathogens, environmental toxins, and particulate pollutants, and reduced susceptibility to invasion by toxins, foreign cells, and environmental chemicals because of effective innate and mucosal immunity and detoxifying enzymes.

Readers who are afflicted with allergy symptoms may wonder whether chemical suppression is always an advisable solution. Our study does not provide an answer to this question. To address it, studies of the potential prophylactic and personal “warning system” benefits of allergies in different environments, among different age and sex groups, and at different life stages (e.g., during pregnancy, before adolescence) relative to the physiological, psychological, and financial costs of individuals’ symptoms are required. Results would help health care professionals and individual patients determine when it would be wise to heed the implied message of allergy symptoms (via reducing environmental exposure) and reap their protective benefits for exposed tissues, versus when medical intervention to suppress allergy symptoms is preferable.

We hope that our analyses and arguments will encourage such cost/benefit analyses. More importantly, we hope that our work will stimulate reconsideration—and renunciation—of the currently prevailing view (Hammarström and Smith 1987; Nicolaou et al. 2005; Jackson 2006; Steinke and Borish 2006) that allergies are merely disorders of

the immune system, which, therefore, can be suppressed with impunity.

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