

The association of atopic diseases with breast, prostate, and colorectal cancers: a meta-analysis

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Abstract There is a long-standing interest in finding whether allergic disorders cause or prevent cancer. We meta-analyzed associations of allergies with prostate, breast, and colorectal cancers. We searched MEDLINE, EMBASE, and *Web of Science* between 1966 and 2008 and eligible reference lists. A total of 16 observational studies were included. Meta-analyses revealed no evidence that asthma, hay fever, or ‘any allergy’ are associated with cancers of the breast (relative risk, RR = 0.93, 95% CI: 0.73–1.19 for asthma; 1.04, 0.94–1.16 for hay fever; 1.01, 0.94–1.08 for any allergy); prostate (RR = 0.93, 95% CI: 0.76–1.15 for asthma; 0.96, 0.87–1.05 for hay fever; 1.01, 0.87–1.17 for any allergy); or colorectum (RR = 0.95, 95% CI: 0.77–1.16 for asthma; 0.95, 0.86–1.05 for hay fever; 0.94, 0.85–1.04 for any allergy). There was a positive association of atopy (assessed by allergen-specific IgE or skin prick testing) with prostate cancer (RR = 1.43, 95% CI: 1.08–1.91), but not breast (1.18, 0.90–1.55) or colorectal (1.32, 0.69–2.53) cancers. There is little epidemiological support for the immune surveillance theory or antigenic stimulation theory in breast or colorectal carcinogenesis. The findings for prostate cancer warrant further investigation.

Keywords Atopy · Asthma · Allergy · Prostate cancer · Breast cancer · Colorectal cancer

Introduction

There is a long-standing interest in finding whether people with allergic disorders, such as hay fever, asthma, and eczema, have an increased or decreased risk of developing cancer [1–5]. Early papers largely reported inverse associations between a history of allergy or asthma and all-cancer risk [1, 3], but others found little evidence of any association [4, 5]. A number of methodological issues limit the usefulness of these initial studies, including small sample sizes and little or no control for confounders [6]. A narrative review based on the MEDLINE bibliographic database between 1986 and 2004 concluded that, although results were inconsistent, the evidence largely suggested an inverse association between atopy and non-lung cancer risk, especially for pancreatic cancer, childhood leukemia, and brain tumors [7]. A more recent narrative review suggested, however, that several cancers were positively associated with allergies, including bladder and prostate cancer, lymphoma, and myeloma [8]. A case-control study in 2006 observed a 20, 29, and 35% increased risk of breast, prostate, and lung cancer, respectively, associated with specific immunoglobulin E (IgE) positivity (an objective measure of atopy), but the confidence intervals (CI) were wide and all consistent with no association for any of these cancers [9].

The association of atopy with cancer is of interest, because hypersensitivity reactions initiated by immunologic mechanisms have long been hypothesized to influence carcinogenesis, and there could be therapeutic implications since animal models suggest that antihistamines may be carcinogenic [10]. However, two contradictory theories have been proposed: (1) the immune surveillance theory, which suggests that allergic conditions could reduce cancer risk by enhancing the immune system’s ability to recognize and destroy foreign cells, including those that are

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malignant; (2) the antigenic stimulation theory that argues allergy is accompanied by repeated tissue inflammation, damage, and repair, which increases cancer risk [11].

Systematic reviews with meta-analyses are a valuable way to display the body of the published literature, to highlight the extent of heterogeneity in effect estimates, and to explore reasons for heterogeneity. Three meta-analyses have been performed for the association of atopy with cancer: one investigating asthma and lung cancer risk among never smokers (an overall positive association was observed) [12]; another, asthma and all-cancer incidence or fatality (overall null association) [13]; and the other, atopy and brain tumors (overall inverse association) [14]. As associations appear to be site-specific [8], we conducted a systematic review with meta-analysis and meta-regression of the association of asthma, allergy, and atopy with risks of the epithelial cancers, breast, prostate, and colorectum.

Methods

We searched Web of Science, EMBASE, and MEDLINE bibliographic databases from 1966 to January 2008 using a combined text word and MESH/subject heading (for MEDLINE and EMBASE, respectively) search strategy, using terms for asthma, allergy, atopy, breast cancer, prostate cancer, and colorectal cancer (see “Appendix”). The electronic search was restricted to studies written in English, carried out in human subjects and the reference lists of all studies that fulfilled the inclusion criteria were also manually searched (search completed by Vojtechova, medical student). Eligible studies were those that reported on the association of asthma, any type of atopy, or allergy with incident or fatal colorectal, breast, or prostate cancers. The studies had to have reported quantitative effect estimates, expressed as an odds ratio, relative risk ratio, standardized mortality ratio, or standardized incidence ratio. We excluded abstracts that were never subsequently published as full papers and studies on animals. Vojtechova extracted the data on two separate occasions to ensure the consistency of the data extraction and the data were checked for accuracy by Martin, professor of clinical epidemiology.

Statistical analysis

As it is conceivable that any associations of cancer with atopic disorders could depend on the exposure-duration or the population studied, effect estimates from the individual studies were pooled using random-effects models (although results from fixed-effects models are shown for completeness). Random-effects models are appropriate in this instance because there was little evidence of publication bias. We pooled the effect estimates from the maximally

adjusted models presented in each paper. The Egger regression asymmetry test was conducted to examine the relationship between sample size and observed cancer risk by exposure category; this is a test for publication and other sources of small study bias [15, 16]. We calculated the I^2 value as a quantitative measure of the degree of inconsistency across studies, which is not dependent on the number of studies [17]. An I^2 value of 0% indicates no observed heterogeneity, and larger percentages show increasing heterogeneity.

In the studies that presented only subgroup analyses (e.g., results stratified by age-groups, severity of atopy [18], or separate results for rectal and colonic cancers [18–21]), we combined the subgroups statistically where possible, using fixed-effects models (e.g., to obtain an all-ages group, all atopy category, or a colorectal cancer group). Few studies provided sex-specific estimates for colorectal cancer; where sex-specific estimates are provided these are shown separately on the Forest plot.

Methodological quality was assessed according to four a priori selected study components that might have affected the strength of the associations: (1) study design (retrospective case–control vs. cohort/nested case–control); (2) method of cancer confirmation (reported histological confirmation or identified in a national/regional cancer registry vs. other); (3) male versus female sex (colorectal cancer); (4) and length of time diagnosed with allergy/asthma/atopy prior to the cancer diagnosis. We entered these selected study characteristics as indicator variables in separate meta-regression analyses [22] to assess their impact on between-study variation (heterogeneity). Meta-regression analysis offers a conservative test of the effect of certain exposures on outcome, assessed at study level [22]. We also compared pooled effect estimates generated from study-specific regression models that were minimally adjusted (crude, or adjusted for sex, age or calendar year only) compared with those that were adjusted for one or more other potential confounding factors (for e.g., smoking status, a measure of socioeconomic status, alcohol intake, or body mass index). If not already provided, crude odds ratios were computed from the raw data presented in tables [9, 23–25]. We did an influence analysis (in which the meta-analysis is re-estimated omitting each study in turn) to assess the effect of each individual study on the pooled relative risks [26].

All statistical analyses were carried out using Stata statistical software (version 10.0. College Station, TX: Stata, 2007).

Results

The electronic searches yielded 4,844 references. After title and abstract review, 4,824 publications were excluded and

20 papers were selected as potentially relevant; the full papers were retrieved for more detailed assessment (Fig. 1). We retrieved additional seven papers from a manual search of the references lists of included papers and of previous reviews (total = 27).

We excluded a total of 11 studies for the following reasons: one study that investigated associations of drug allergy with colorectal cancer [27] was excluded because drug allergy may have different pathophysiological implications compared with chronic allergies, such as asthma, hay fever, and eczema; one letter based on only a total of 10 prostate cancer cases [28], that did not appear to have subsequently been published as a full paper; one case-control study that was subject to clear selection bias because the mean ages differed by 17 years, comparing the control (mean 38 years) versus cancer (56 years) groups, as a result of controls being chosen from medical school students, teachers, and healthy relatives and friends of the authors [29]; three papers were narrative reviews [6–8]; one meta-

analysis of all-cancer incidence/mortality up to October 2002 [13]; one study reported on all-cause mortality alone [1]; three reported cancer incidence or mortality overall, but not by the sites included in this study [30–32].

Overall, 16 studies provided an estimate of the association of atopy, allergy, hay fever, or asthma with breast, prostate, or colorectal cancer and were included in the meta-analysis [4, 5, 9, 18–21, 23–25, 33–38]. These 16 studies included a total of 7,890 prostate, 10,736 breast, and 15,451 colorectal cancers.

In total, eight of the included papers were prospective cohort and eight were case-control studies (Table 1). The exposure categories that were measured were: (1) asthma only; (2) hay fever (rhinitis) only; (3) atopy (assessed by allergen-specific IgE measurement or by skin prick testing or, in one study, a history of type I hypersensitivity reactions [36]); and (4) ‘any allergy’ (atopy and/or asthma, hay fever, or ‘other allergies’ [defined by self-reported questionnaires, interviews or by reports of a previous doctor

Fig. 1 Quorum flow diagram showing the number of studies included in and excluded from the meta-analysis

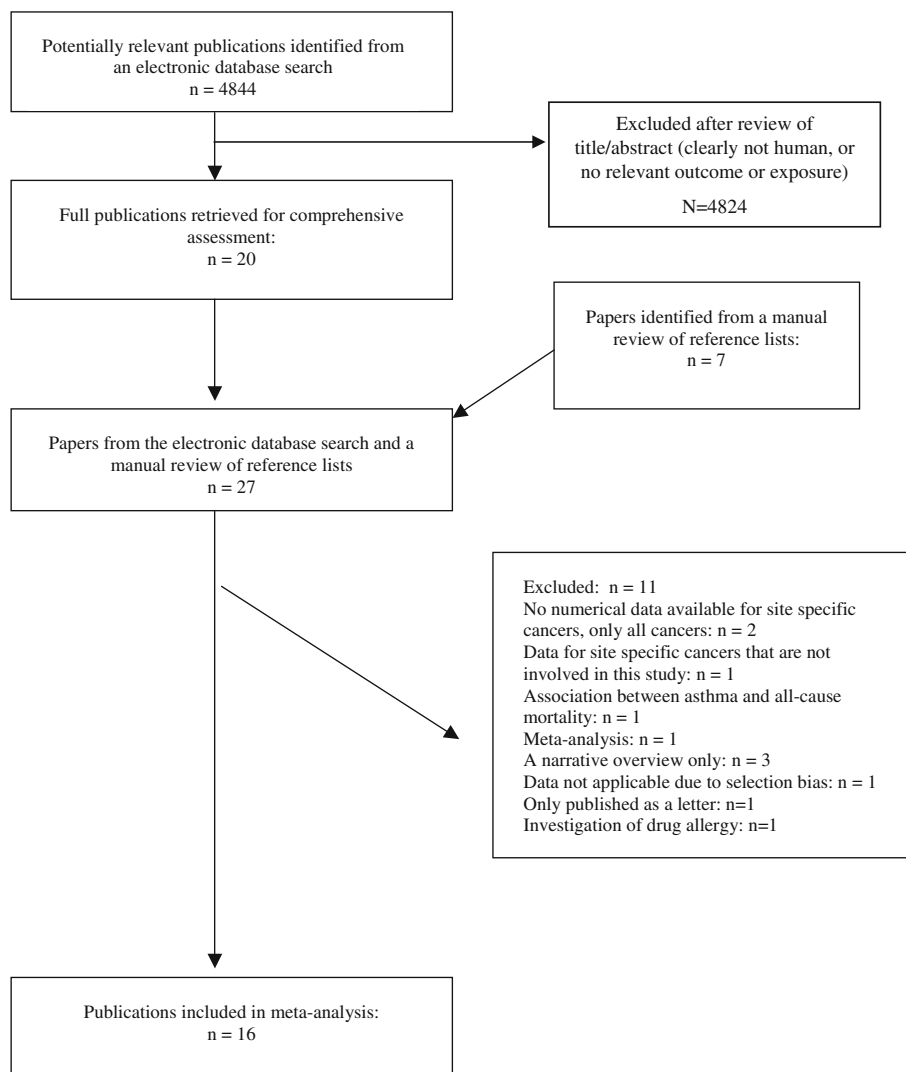


Table 1 Characteristics of included studies

First author (year published)	Country	Total participants (total number of <i>all</i> cancers in cohort study or numbers of cases and controls)	Age at exposure assessment (years)	Exposure assessment	Exposures	Cancer outcomes (number)	Cancer identification	Controlled for smoking and/or a measure of socioeconomic status
<i>Prospective or nested case-control studies</i>								
McWhorter 1988 [35]	USA	6,108 (341)	25–74	Questionnaire on physician diagnosed allergy ^a	Any allergy	Breast (34), prostate (34), colorectal (45)	Hospital and nursing home records; death certificates	Smoking
Mills 1992 [20]	USA	34,198 (1,094)	Not available	Questionnaire on medical history	Asthma, hay fever, any allergy	Breast (215), colon (138), rectum (58), prostate (180)	Hospital records and cancer registries	Smoking
Kallen 1993 [21]	Sweden	64,346 (4,520)	Not available	Hospital discharge registry	Asthma	Breast (385), prostate (671), colon (389), rectum (188)	National cancer and death registries	No
Vesterinen 1993 [19]	Finland	77,952 (3,842)	35–84	Data from Finnish registers	Asthma	Breast (429), prostate (256), colon (220), rectum (187)	Finnish cancer registry	No
Eriksson 1995 [18]	Sweden	6,593 (87)	Median age 31; age range 16–80	Skin prick tests; clinical diagnoses at allergy clinic	Asthma, hay fever (rhinitis) ^b , atopy ^c	Breast (12) ^d , prostate (1), colon (3), rectum (4)	Swedish national tumor registry	No
Talbot-Smith 2002 [34]	Western Australia	3,308 (343)	Mean age men 50.7 Mean age women 50.0	Self-reported physician diagnosed allergy; skin prick testing	Asthma, hay fever, atopy	Breast (65), prostate (86), colorectal (67)	Linkage to death registrations and West Australian cancer registry	Smoking
Turner 2005 [23]	Canada	1,102,247 (81,114)	30 and older	Self-reported physician diagnosed allergy	Asthma, hay fever, any allergy	Breast (5,250), prostate (5,674), colorectal (9,341)	National death index	Smoking and education
Gonzalez-Perez 2005 [33]	Spain	5,263 cancers; 20,000 controls	20–79	Automated general practitioner records	Asthma	Breast (802), prostate (407), colorectal (436)	Automated general practitioner records	Smoking
<i>Case-control</i>								
McKee 1967 [5]	USA	104 cancers; 299 controls	Not provided	Standardized questionnaire interview	Any allergy	Breast (31)	Tissue diagnosis of prostate cancer	No
Shapiro 1971 [4]	USA	605 cancers; 3,310 controls	30–79	Standardized nurse interview	Any allergy	Breast (136)	Discharge diagnosis	No

Table 1 continued

First author (year published)	Country	Total participants (total number of <i>all</i> cancers in cohort study or numbers of cases and controls)	Age at exposure assessment (years)	Exposure assessment	Exposures	Cancer outcomes (number)	Cancer identification	Controlled for smoking and/or a measure of socioeconomic status
Vena 1985 [25]	USA	13,663 cancers; 4,039 controls	Not provided	Self-completed questionnaire (demographics) and interview (medical history)	Asthma, hay fever	Breast (1,835), prostate (263), colon (579), rectum (652)	Admissions with cancer	Smoking ^e
Kune 1988 [38]	Australia	714 cancers; 727 controls	Mean 65	Interview questionnaire on past illnesses	Asthma	Colorectal (714)	Histologically confirmed cancers at study centers	No
Ghadirian 1998 [37]	Canada	414 cancers; 429 controls	35–79	Questionnaire interview on medical history	Asthma	Breast (414)	Hospital admission data	Income
Negri 1999 [24]	Italy	1,953 cancers; 4,154 controls	Median age 62 (cases) and 58 (controls), age range 23–74	Self-completed questionnaire on past medical diagnoses	Any allergy	Colon (1,225), rectum (728), colorectal (1,953)	Histologically confirmed cancers at study centers	Smoking and education
Hedderston 2003 [36]	USA	747 cancers; 958 controls	21–45	Interview questionnaire on physician diagnosed allergy	Atopy, any allergy	Breast (747)	SEER cancer registry	Smoking and education
Wang 2006 [9]	Germany	1,376 cancers; 4,271 controls	50–74	IgE measurement; questionnaire on physician diagnosed allergy	Asthma, hay fever, atopy, any allergy	Breast (381), prostate (318), colorectal (477)	Histologically confirmed cancers at study centers	Smoking and education

SEER Surveillance, Epidemiology and End Results cancer registry

^a Diagnosis of allergy restricted to more than 5 years before the initial interview

^b There were no prostate cancers with hay fever (rhinitis)

^c To define atopy we combined subjects with a definite or intermediate skin prick test

^d Based on Table 4 of paper [18], number of observed cancers in atopic and intermediate categories

^e Age- and smoking-adjusted data were only provided as point estimates and threshold *p* values, so were not used in the meta-analysis

diagnosis]). The study by Vena et al. provided sufficient data to calculate crude odds ratios and 95% CI but the age- and smoking-adjusted data were only provided as point estimates and threshold p values, hence were not used in the meta-analysis [25].

Individual studies had notable aspects to their study design that may produce clinical heterogeneity. The case-control study on allergies and breast cancer by Hedderson et al. included only women aged 45 years and younger [36]. Three studies compared observed cancer incidence rates in cohorts of patients with asthma [19, 21] or allergy [18] against expected numbers estimated from population-based cancer registries and their effect estimates were standardized incidence or mortality ratios. In a sensitivity analysis, we assessed the impact of excluding these studies from the pooled effect estimates.

Most studies reported that cancers were histologically confirmed or were identified from national/regional cancer registries, which we assumed verified the cancers pathologically. Six papers based their cancer diagnoses on different sources: cancers recorded on an automated general practice database [33]; a linked national death register [23]; review of hospital and nursing home records and death certificates [35]; and admission/discharge diagnoses [4, 25, 37]. Only two studies [24, 36] attempted to assess the duration of allergy in relation to cancer, by stratifying results by age at onset of allergy.

Breast cancer

The association of asthma with breast cancer was investigated in 10 studies [9, 18–21, 23, 25, 33, 34, 37]. The pooled relative risk across these 10 studies was 0.93 (95% CI: 0.73–1.19; $I^2 = 91\%$), indicating little evidence of any association, but with considerable heterogeneity (Fig. 2a). Exclusion of the Kallen study had the largest impact on the observed heterogeneity, reducing the I^2 value to 4%, with a pooled relative risk across the nine remaining studies of 0.98 (95% CI: 0.91–1.06) in both random-effect models and fixed-effect models. There was no difference in the effect estimate for asthma and breast cancer risk when seven prospective cohort/nested case-control studies were analyzed separately from three retrospective case-control studies (p for difference in effect estimates from a meta-regression analysis = 1.0). There was no difference in the effect estimate for asthma and breast cancer risk when seven studies with histological confirmation of cancer were analyzed separately from three studies without histological confirmation (p for difference = 0.5). There was no evidence of publication bias (Egger $p = 0.4$).

In a meta-analysis of six studies investigating the association of hay fever with breast cancer [9, 18, 20, 23, 25, 34], the pooled relative risk was 1.04 (95% CI: 0.94–1.16;

$I^2 = 7\%$) (Fig. 2b). For atopy (four studies [9, 18, 34, 36]), the pooled relative risk was 1.18 (95% CI: 0.90–1.55; $I^2 = 43\%$), and for any allergy (seven studies [4, 5, 9, 20, 23, 35, 36]), the pooled relative risk was 1.01 (95% CI: 0.94–1.08; $I^2 = 0\%$) (Fig. 2c, d).

Prostate cancer

The association of asthma with prostate cancer was investigated in eight studies [9, 19–21, 23, 25, 33, 34]. The pooled relative risk was 0.93 (95% CI: 0.76–1.15; $I^2 = 84\%$) (Fig. 3a). Exclusion of the Kallen study had the largest impact on the observed heterogeneity, reducing the I^2 value to 50%, with a pooled relative risk across the seven remaining studies of 0.99 (95% CI = 0.84–1.17). In a stratified analysis of the association of asthma with prostate cancer risk, the pooled relative risk for six prospective cohorts/nested case-control studies was similar to the two retrospective case-control studies (p for difference in effect estimates from a meta-regression analysis = 0.7). There was no difference in the effect estimate whether or not cancers were histologically confirmed (p for difference = 0.4). There was no evidence of publication bias ($p = 0.4$).

There was no evidence that prostate cancer was associated with hay fever in five studies [9, 20, 23, 25, 34] (pooled relative risk = 0.96; 95% CI: 0.87–1.05; $I^2 = 0\%$) (Fig. 3b), or allergy in four studies [9, 20, 23, 35] (pooled relative risk = 1.01; 95% CI: 0.87–1.17; $I^2 = 23\%$) (Fig. 3d). There was evidence of an increased risk of prostate cancer in association with atopy in three studies [9, 18, 34] (pooled relative risk = 1.43; 95% CI: 1.08–1.91; $I^2 = 0\%$) (Fig. 3c).

Colorectal cancer

There was no evidence that colorectal cancer was associated with asthma in 10 studies [9, 18–21, 23, 25, 33, 34, 38] (pooled relative risk = 0.95; 95% CI: 0.77–1.16; $I^2 = 86\%$) (Fig. 4a). Exclusion of the Kallen study had the largest impact on the observed heterogeneity, reducing the I^2 value to 34% and with a pooled relative risk across the seven remaining studies of 1.05 (95% CI = 0.94–1.19).

There was no evidence that colorectal cancer was associated with hay fever in six studies [9, 18, 20, 23, 25, 34] (pooled relative risk = 0.95; 95% CI: 0.86–1.05; $I^2 = 0\%$); atopy in three studies [9, 18, 34] (pooled relative risk = 1.32; 95% CI: 0.69–2.53; $I^2 = 51\%$), or any allergy in five studies [9, 20, 23, 24, 35] (pooled relative risk = 0.94; 95% CI: 0.85–1.04; $I^2 = 13\%$) (Fig. 4b, d). There was no difference in the effect estimate by study design ($p = 0.9$), sex ($p = 0.3$) (sex-specific estimates are provided separately in the Forest plots for colorectal

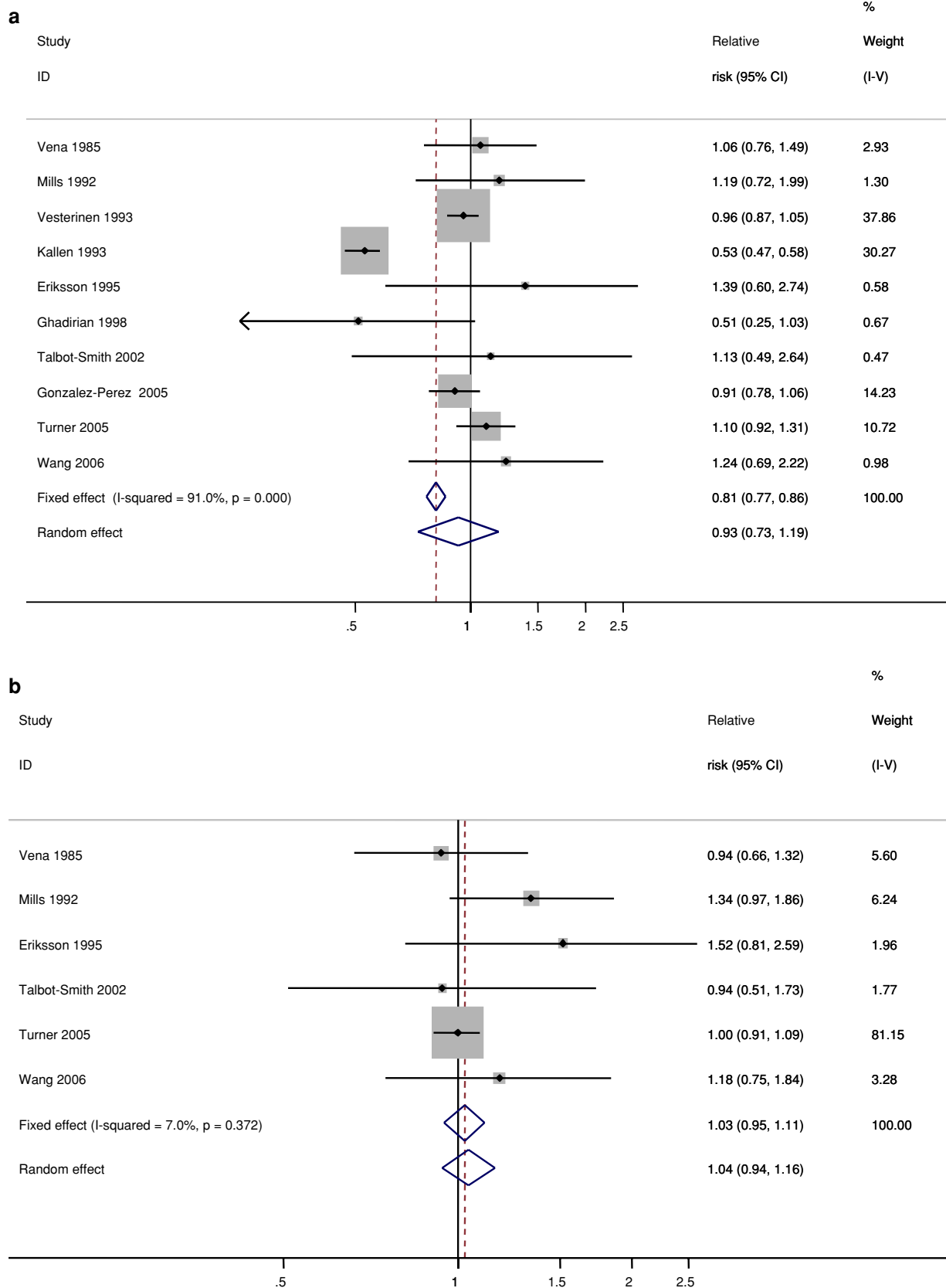


Fig. 2 Forest plot of the association of breast cancer with asthma (**a**), hay fever (**b**), atopy (**c**), and any allergy (**d**). Squares indicate the study-specific effect estimate, with the size proportional to the inverse

of the variance, with horizontal lines showing 95% CI. The dashed vertical line and diamonds (95% CI) are the pooled estimates based on random- or fixed-effects meta-analysis models, as indicated

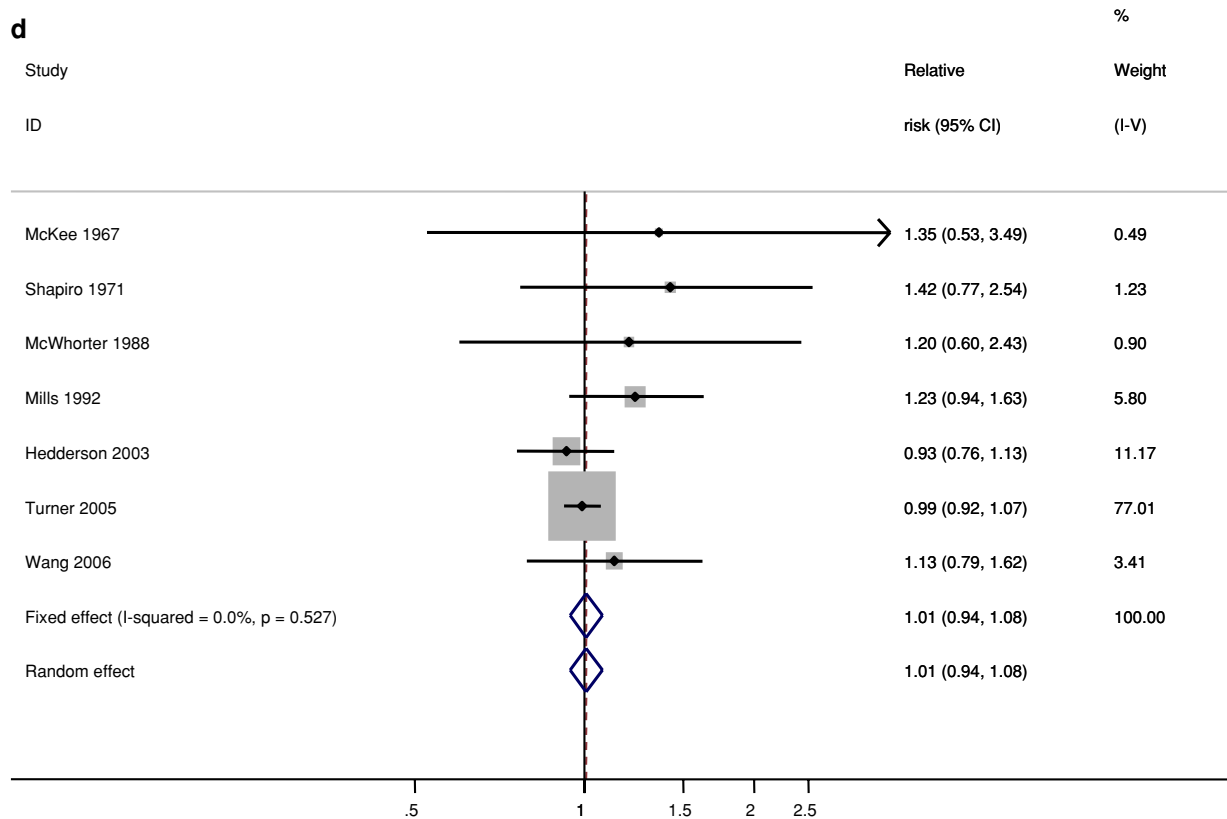
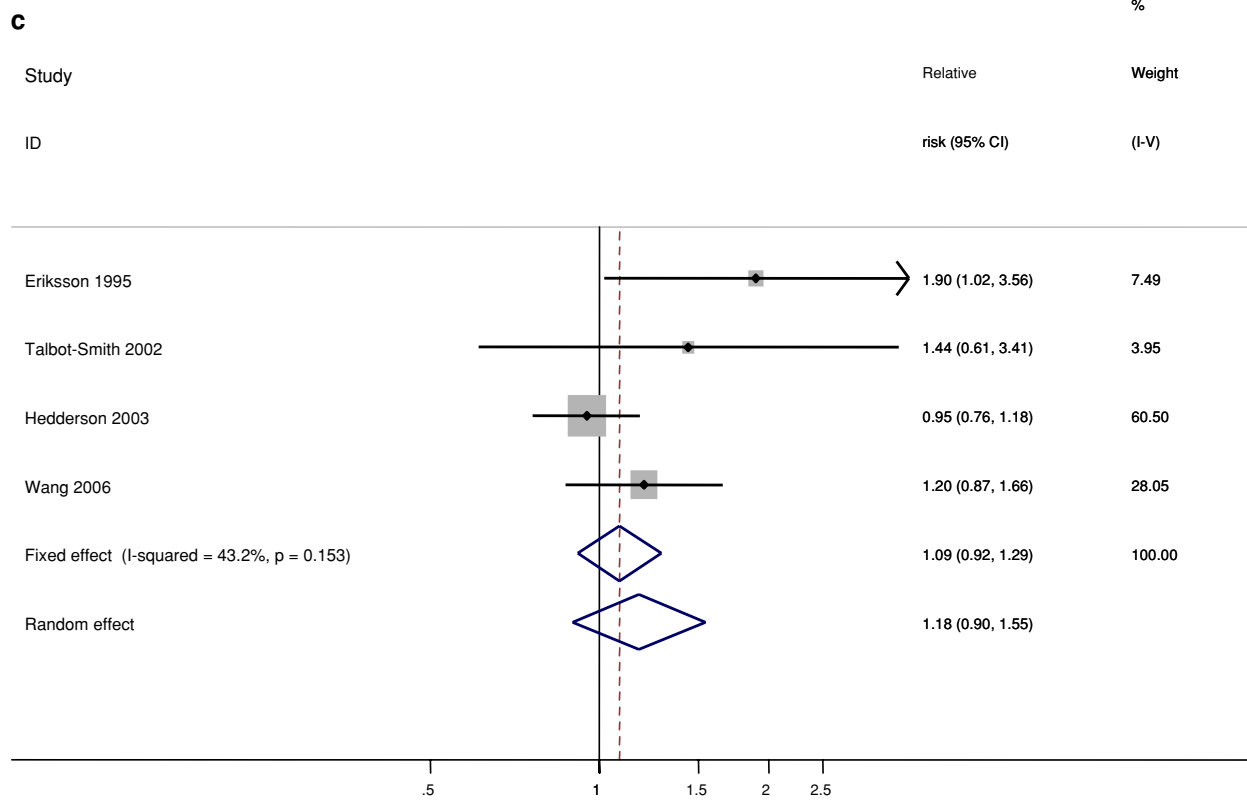


Fig. 2 continued

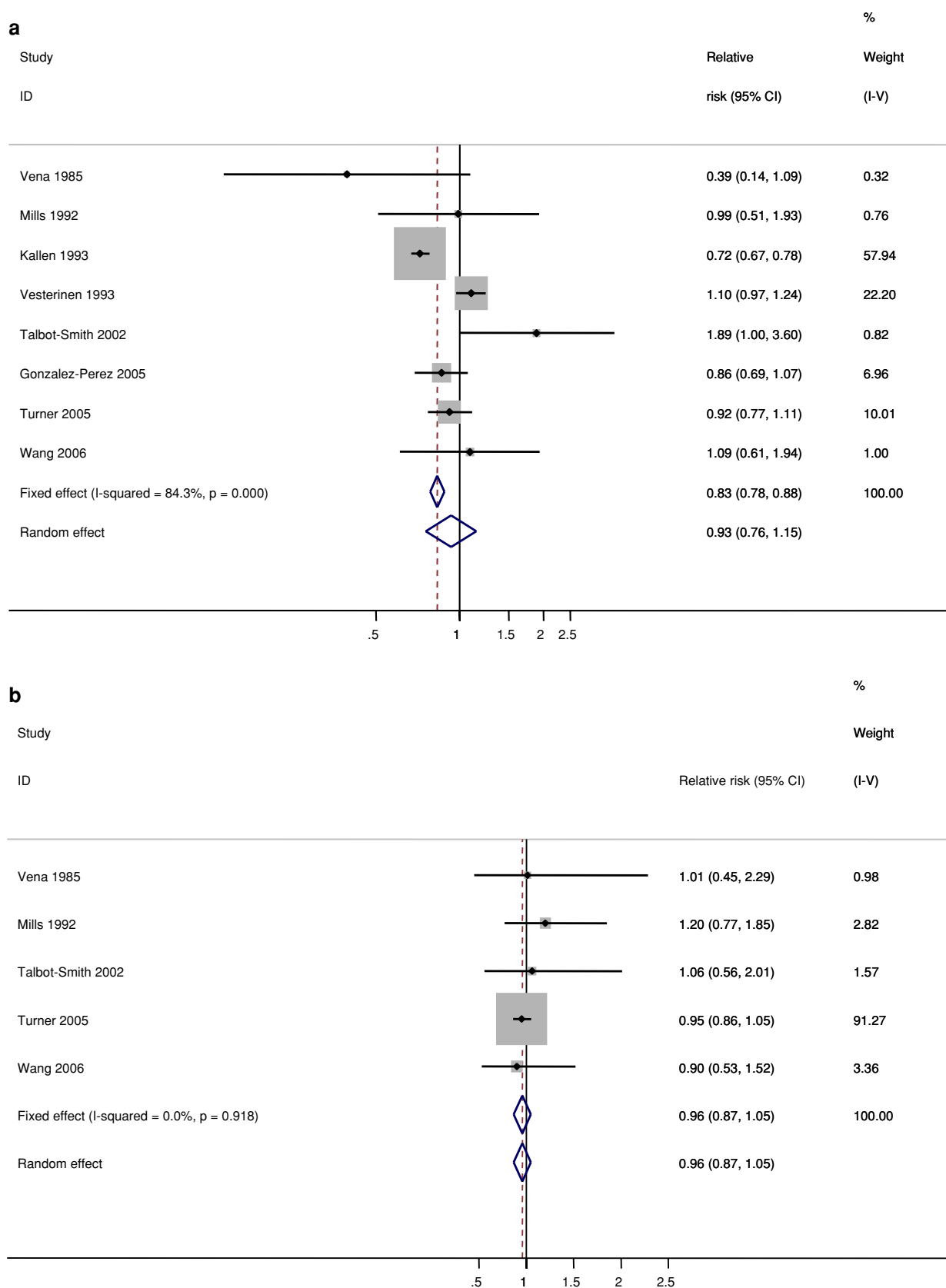


Fig. 3 Forest plot of the association of prostate cancer with asthma (**a**), hay fever (**b**), atopy (**c**), and any allergy (**d**). Squares indicate the study-specific effect estimate, with the size proportional to the inverse

of the variance, with horizontal lines showing 95% CIs. The dashed vertical line and diamonds (95% CI) are the pooled estimates based on random- or fixed-effects meta-analysis models, as indicated

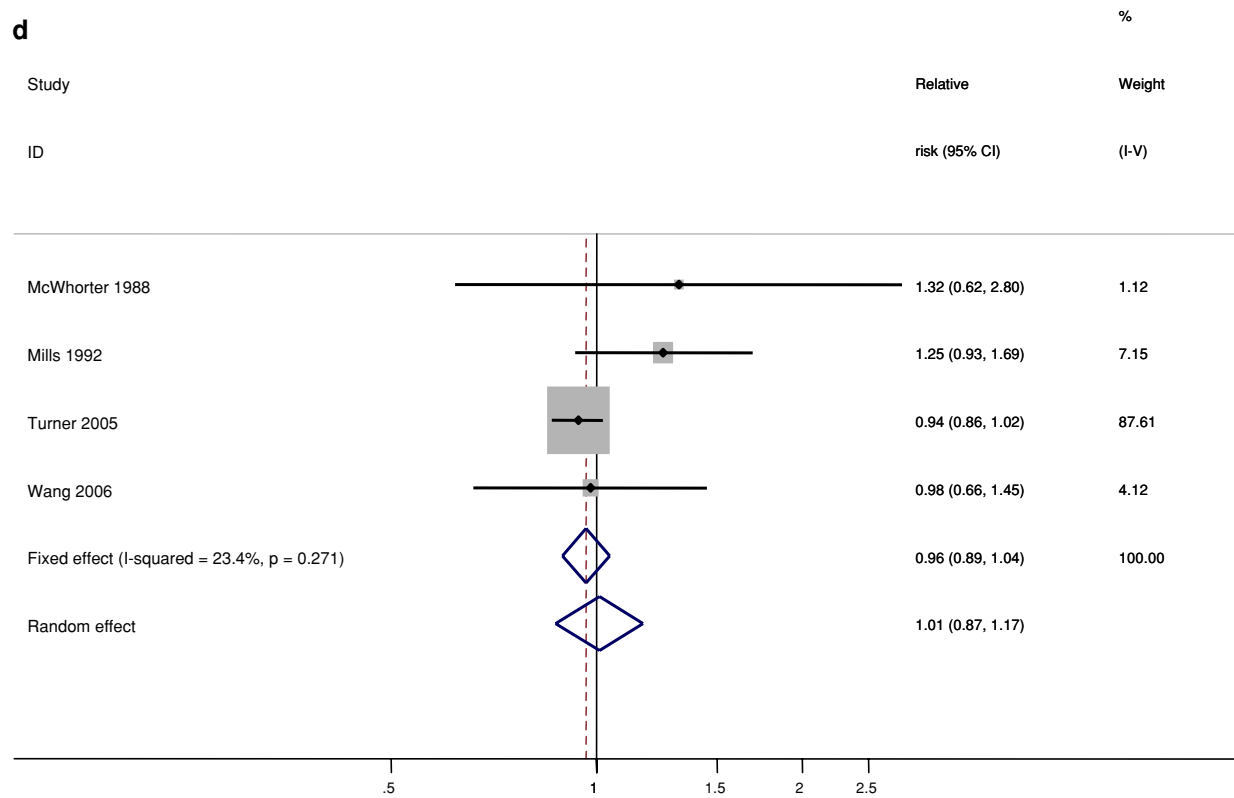
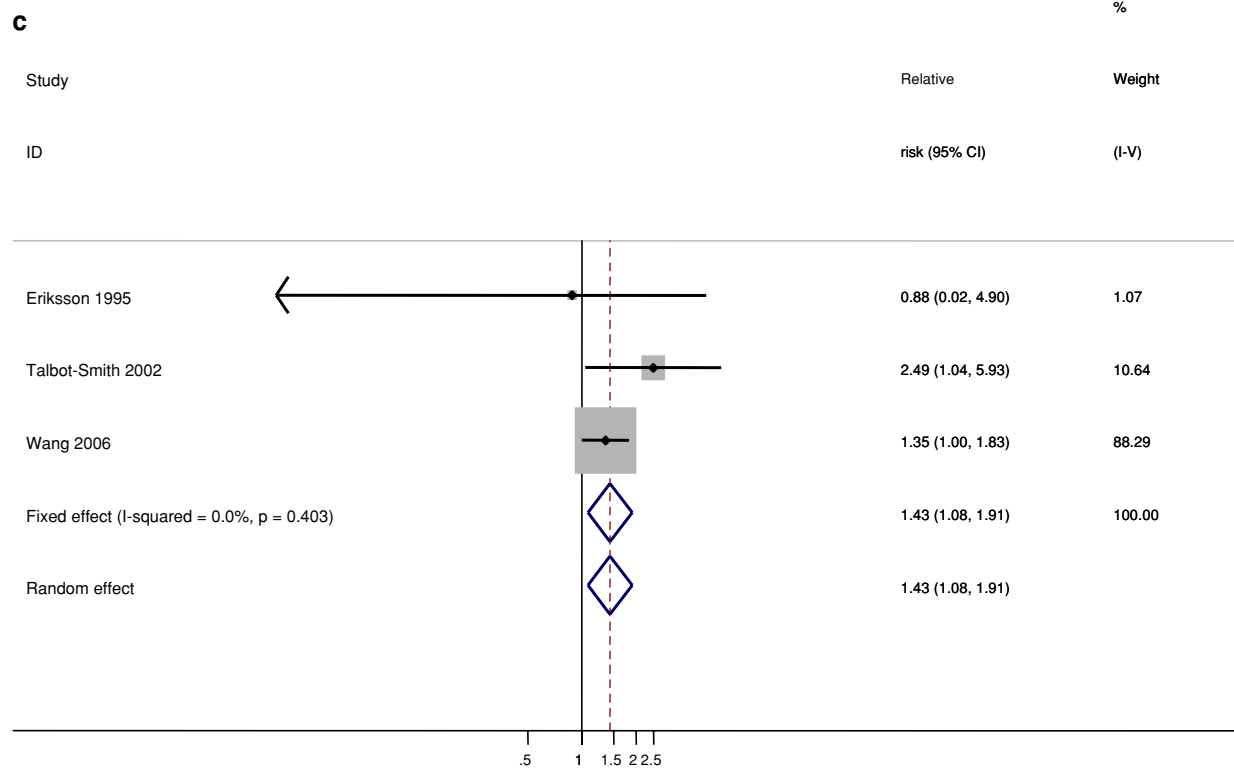


Fig. 3 continued

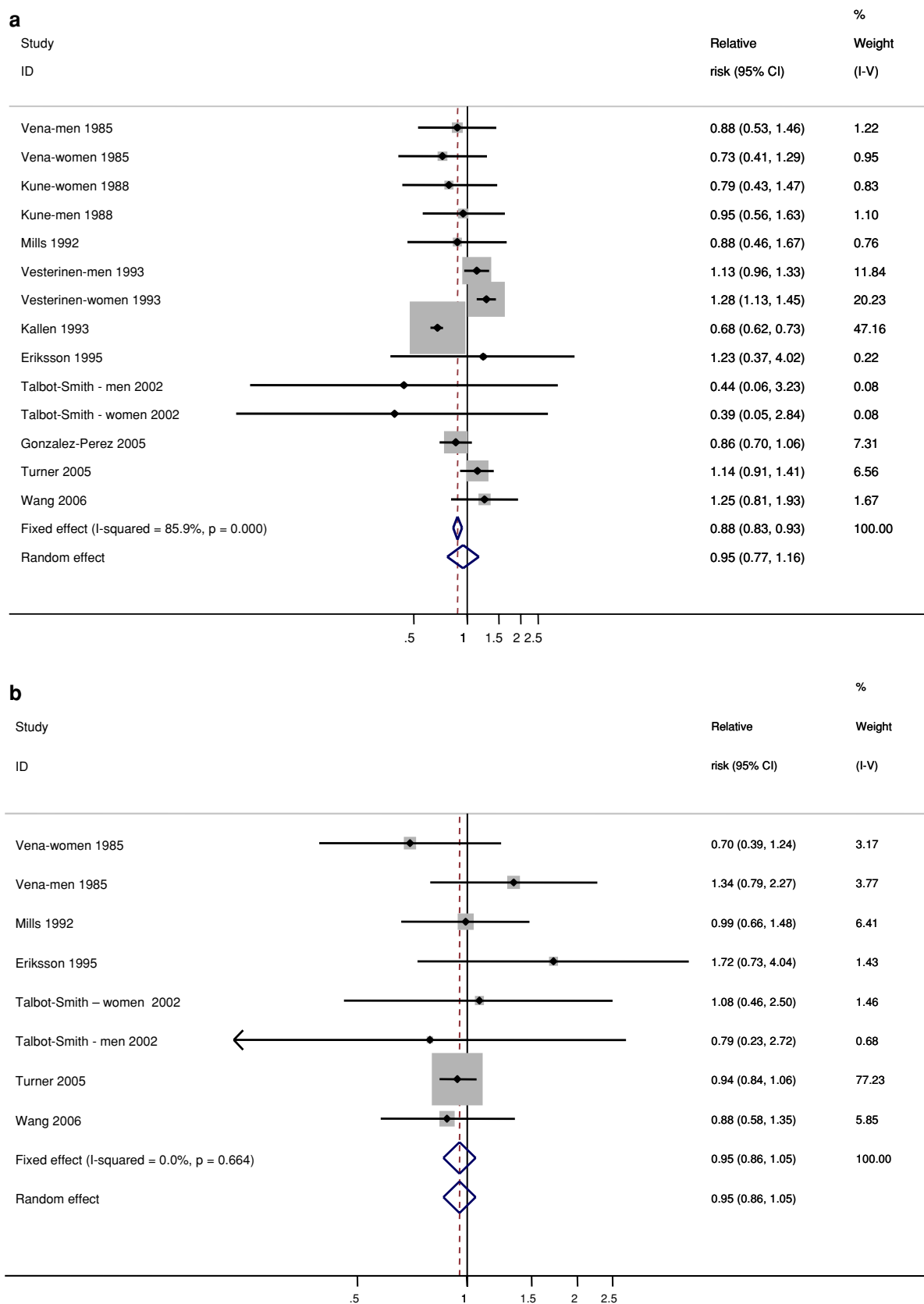


Fig. 4 Forest plot of the association of colorectal cancer with asthma (a), hay fever (b), atopy (c), and any allergy (d). Squares indicate the study-specific effect estimate, with the size proportional to the inverse

of the variance, with horizontal lines showing 95% CIs. The dashed vertical line and diamonds (95% CI) are the pooled estimates based on random- or fixed-effects meta-analysis models, as indicated

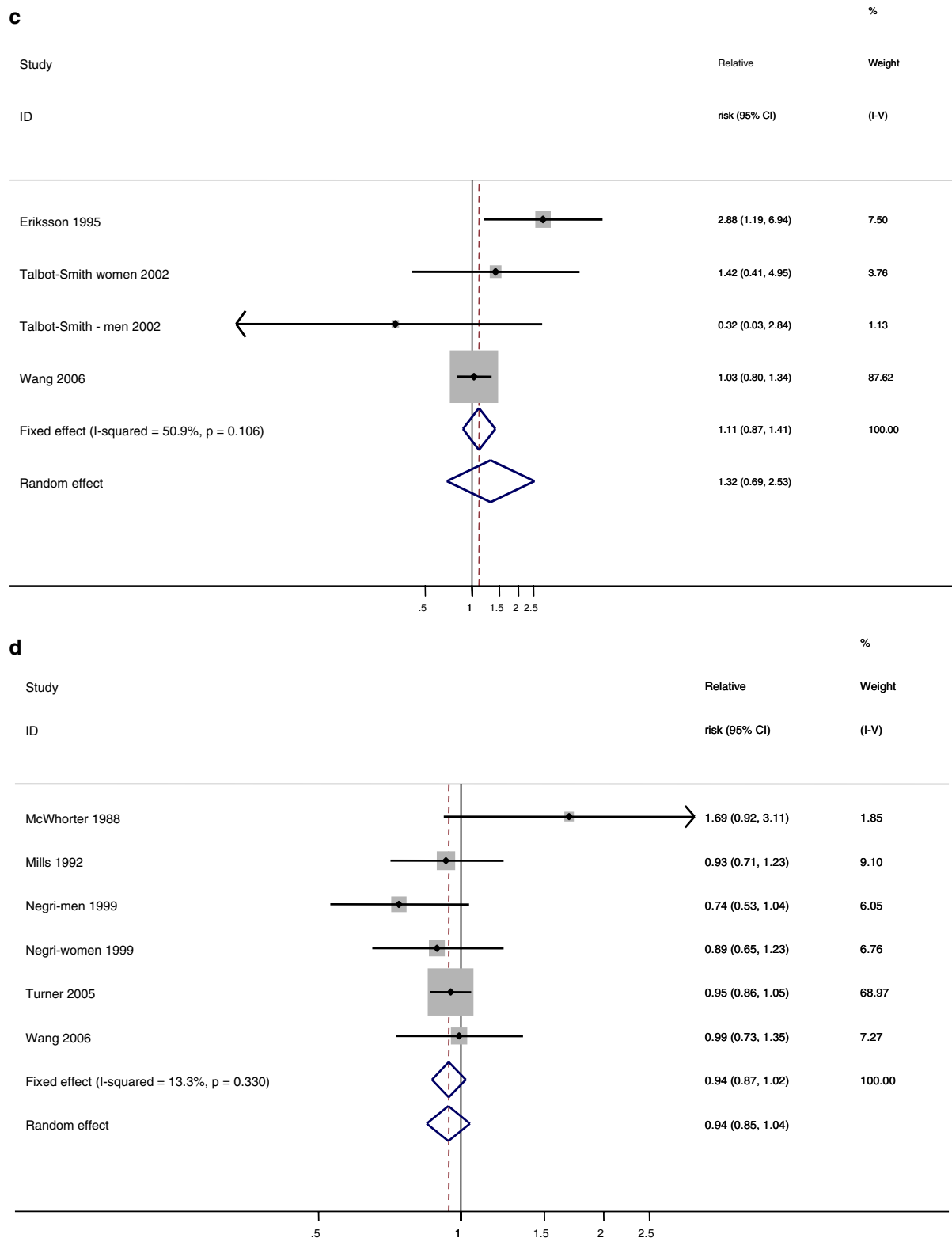


Fig. 4 continued

cancer), or whether or not cancers were histologically confirmed (p for difference = 0.9). There was no evidence of publication bias ($p = 0.5$).

Only four studies had data allowing comparison of both minimally adjusted and adjusted relative risks, so formal testing of differences across the different cancer sites and

exposures was not possible [9, 23, 24, 33]. However, effect estimates based on crude estimates were almost identical to those based on the maximally adjusted data.

Results were generally consistent when we repeated the analyses with fixed-effects models. A fixed-effects model suggested asthma was protective against breast cancer, but there was marked heterogeneity, suggesting that this model is inappropriate. The Kallen study [21] reported standardized incidence ratios comparing observed cancer incidence rates in a hospital asthma cohort versus expected rates from population data. Exclusion of this study resulted in similar pooled estimates from the fixed- and random-effects models, indicating no evidence of an association of asthma with breast cancer risk. Similar findings were found for asthma and both prostate and colorectal cancer risk, i.e., exclusion of the Kallen study resulted in similar findings of no associations from both the fixed-effects models and the random-effects models. Influence analysis confirmed that the Kallen study had a major impact on the pooled effect estimates for all three cancer sites, as described earlier.

Discussion

We found that the body of the current worldwide literature provides little evidence that allergic conditions are associated with breast or colorectal cancer, suggesting little epidemiological support for the immune surveillance theory or antigenic stimulation theory in the development of these cancers. The findings for prostate cancer were inconsistent, being null for a history of asthma, hay fever, or any allergy and indicating a 43% increased risk of prostate cancer with atopy. This finding warrants further investigation because it is based on only three studies, so may have arisen by chance or publication bias, but it may reflect the objective measurement of atopy by IgE or skin prick tests, in contrast to the self-reported histories of allergy, asthma, or hay fever (which are probably prone to a greater degree of measurement error than objective tests). These quantitative data contradict at least three non-systematic, narrative-based reviews that conclude that there is a protective association of allergy with colorectal cancer [6–8]; the results do broadly agree with the conclusions of these reviews of a possible increased risk of prostate cancer with allergy and little consistent evidence for an association with breast cancer. However, as far as we are aware, this study is the first to provide systematically retrieved pooled effect estimates for these cancer outcomes.

Other studies that investigated the role of immune processes in prostate carcinogenesis suggest an increase in prostate cancer risk among individuals with altered inflammatory and immunological pathways [39, 40]. A case-control study [39], based on 247 cases and 263

controls (cancer-free bone marrow and solid organ donors), showed that single nucleotide polymorphisms of the promoter region of cytokines with angiogenic properties [interleukin (IL)-8, IL-10 and vascular endothelial growth factor (VEGF)] were associated with an increased risk of prostate cancer. Zheng et al., in a study based on 200 familial prostate cancer cases and 200 controls (randomly selected from a Swedish population registry), found strong associations between genes in inflammatory pathways and an increased prostate cancer risk [40]. Several hypotheses have been proposed to explain the above associations: immune-mediated inflammation may promote carcinogenesis via induction of hyperplasia, release of reactive oxygen species and subsequent DNA mutation, promotion of vascularization or release of anti-inflammatory mediators, which suppress the tumor surveillance system [40].

The main limitations of the meta-analytical approach for inference based on the current evidence are as follows. Firstly, the number of studies was small, so investigation of some possible sources of clinical heterogeneity was not possible—it could be that associations vary by sex, or age of onset, severity or duration of allergy [24, 36]. Secondly, publication bias may distort the evidence base, but is generally a problem that tends to exaggerate the magnitude of associations, rather than to produce the largely null results that were observed in this analysis. We found no evidence of publication bias for any cancer site. Thirdly, the quality of inference from meta-analyses depends on the quality of the included studies. We assessed the methodological quality of component studies and explored sources of heterogeneity with meta-regression models. For example, there was little evidence that the pooled effect estimates differed when the meta-analyses were stratified by prospective or retrospective case-control status or whether cancers were histologically confirmed. Other sensitivity analyses suggested that the results were largely robust to model assumptions. Fourthly, the CIs in our meta-regression analyses were wide; therefore, small but possibly important differential sub-group effects may have been missed. Sub-group effects studied in individual reports include age of onset of cancer or age at diagnosis of allergy [24].

Measurement error in the assessment of exposure may be a concern, because the diagnosis of asthma, hay fever, and allergies was largely based on a self-report. Measurement error would be expected to attenuate associations towards the null. However, all studies required either a doctor's report of a previous diagnosis of the conditions of interest or obtained a history of asthma from hospital or general practice records. Furthermore, apart from the findings for prostate cancer, results for the atopy category were null, even though this category was largely based on measures that may be considered to be more objective:

serum IgE or skin prick tests. Confounding is a major problem in epidemiological studies, but for this to have produced the null results we observed would require a confounder that is masking a true association, for e.g., a protective influence on the cancer outcome that is positively associated with allergic exposure. It is difficult to imagine any such strong negative confounder that could have created the null associations we observed.

We conclude that there is little epidemiological support for the immune surveillance theory or antigenic stimulation theory in the development of breast or colorectal cancer. The findings for prostate cancer, however, warrant further investigation.

Appendix

See Table 2.

Table 2 MEDLINE search strategy

Exposure	Outcome
exp asthma/	(breast adj1 cancer\$.tw
exp allergy/	(breast adj1 neoplas\$.tw
exp atopy/	(colorectal adj1 cancer\$.tw
allerg\$.tw	(colorectal adj1 neoplas\$.tw
atopy.tw	(prosta\$ adj1 cancer\$.tw
asthma\$.tw	(prosta\$ adj1 neoplas\$.tw
asthma.m_titl	asthma\$.mp and cancer\$.ti
	cancer\$.ti
	exp neoplasms/
	exp prostate neoplasm/
	exp breast neoplasm/
	exp colorectal neoplasm/

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