

Original Article

Atopy and Development of Cancer: A Population-Based Prospective Study

Tea Skaaby, MD^a, Lise Lotte Nystrup Husemoen, PhD^a, Nina Roswall, PhD^b, Betina Heinsbaek Thuesen, PhD^a, and Allan Linneberg, PhD^{a,c,d} Glostrup and Copenhagen, Denmark

What is already known about this topic? Previous epidemiologic studies that investigated the association of atopy and allergic diseases with cancer have shown inconsistent results.

What does this article add to our knowledge? In a large population-based study with longitudinal and complete registry-based follow-up on cancer incidence, we did not observe any statistically significant associations between atopy (specific IgE to inhalants) and risk of any cancer or specific types of cancer.

How does this study impact current management guidelines? The risk of cancer may not be a particular concern of persons with atopy.

BACKGROUND: Atopy is the familial or personal propensity to develop IgE antibodies against environmental allergens. Atopy, theoretically, could both prevent and promote the development of cancer. However, evidence from epidemiologic studies has been inconclusive.

OBJECTIVE: We investigated the longitudinal association between atopy and the incidence of total and specific types of cancers of 5 Danish population-based studies.

METHODS: Atopy was defined as serum specific IgE positivity against inhalant allergens. A total of 14,849 persons were followed up prospectively by linkage to the Danish Cancer Registry. We used Cox regression analysis, and risk was expressed as hazard ratios (HR) (95% CIs) for persons with atopy versus those without atopy.

RESULTS: There were 1919 incident cancers (median follow-up, 11.8 years). There were no statistically significant associations between atopy and risk of any cancer (HR 1.00 [95% CI, 0.89-1.12]), any cancer excluding nonmelanoma skin cancer (HR 0.93 [95% CI, 0.82-1.07]), head and neck cancer (HR 1.74 [95%

CI, 0.98-3.09]), colorectal cancer (HR 0.92 [95% CI, 0.64-1.32]), cancer of the bronchus and lung (HR 0.78 [95% CI, 0.54-1.13]), breast cancer (HR 1.00 [95% CI, 0.73-1.37]), cancer of the uterus (HR 0.90 [95% CI, 0.43-1.88]), prostate cancer (HR 0.79 [95% CI, 0.53-1.18]), urinary cancer (HR 1.08 [95% CI, 0.60-1.96]), malignant melanoma (HR 0.95 [95% CI, 0.54-1.66]), and nonmelanoma skin cancer (HR 1.20 [95% CI, 0.98-1.47]). **CONCLUSION:** Our data did not support the hypothesis that atopy is associated with an altered risk of total cancer development, although effects of atopy on specific types of cancer cannot be excluded. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■-■)

Key words: Atopy; Cancer; Breast cancer; Lung cancer; Colorectal cancer; Prostate cancer; Nonmelanoma skin cancer; Head and neck cancer; Serum specific IgE; Inhalant allergens

Atopy is the familial or personal propensity to develop IgE antibodies against common environmental allergens.¹ The immunologic basis of atopy is often viewed as a deviation toward the Th2-cell-mediated immune response and a decreased Th1 response,² and Th2-related cytokines have a key role in the initiation, maintenance, and amplification of allergic inflammation.² Accordingly, it has been shown that persons without atopy usually recognize most allergens, but the response is mainly characterized by the Th1-polarizing cytokine, IFN- γ , rather than Th2-type cytokine production, and they have no allergic symptoms or inflammatory response to allergens.² Individuals with atopy are at high risk of developing atopic diseases, such as allergic rhinitis, allergic asthma, atopic dermatitis, and food allergies. Atopic diseases and atopy have increased markedly in Westernized, urbanized, and affluent populations.³ In Denmark, a more than 2-fold increase in prevalence of atopy documented by measurements of serum specific IgE against inhalant allergens has occurred among adults ages 30 to 60 years over a 25-year period,³ and this was accompanied by increases in symptoms and

^aResearch Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark

^bDanish Cancer Society Research Centre, Copenhagen, Denmark

^cDepartment of Clinical Experimental Research, Glostrup University Hospital, Glostrup, Denmark

^dDepartment of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

The present study was financially supported by the Health Insurance Foundation (grant 2010 B 131).

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication April 7, 2014; revised May 21, 2014; accepted for publication June 20, 2014.

Available online ■■

Corresponding author: Tea Skaaby, MD, Research Centre for Prevention and Health, Glostrup Hospital, Nordre Ringvej 57, DK-2600 Glostrup, Denmark. E-mail: tea.skaaby.01@regionh.dk.

2213-2198

© 2014 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2014.06.010>

Abbreviations used

BMI- body mass index

HR- Hazard ratio

ICD- International Classification of Diseases

ICD-7- International Classification of Diseases, Seventh Revision

ICD-10- International Classification of Diseases, Tenth Revision

NMSC- nonmelanoma skin cancer

diagnoses of allergic respiratory disease.⁴ The high and increasing prevalence of atopy warrant studies that investigate any possible health effects of atopy beyond atopic disease.

There has been a long-standing interest in determining whether individuals with atopic diseases have an altered risk of developing cancer. Atopy could theoretically both prevent and induce the development of cancer.⁵ According to the hyperreactive state and/or immune surveillance theory, allergic disease may reduce the risk of cancer by increasing the ability of the immune system to recognize and destroy malignant cells. However, the chronic inflammation—antigenic stimulation theory suggests that allergy causes repeated inflammation, damage, and repair of the tissue, which, in turn, may increase the risk of cancer.

Several studies investigated the association between atopic diseases and specific cancers. Asthma, hay fever, and atopic dermatitis have been associated with the risk of several specific cancers, such as pancreatic cancer, lymphomas, brain tumors, and leukemia, although inconsistently.^{6–9} Vojtechova and Martin⁵ found no association between atopic disease and breast or colorectal cancer in a meta-analysis of 16 observational studies, most of which used self-reported atopic disease as a measure of atopy. In the same meta-analysis, atopy (skin prick test or serum specific IgE positivity against inhalant allergens) was associated with a higher risk of prostate cancer, but there was no association with a history of asthma, hay fever, or any allergy.⁵ Another meta-analysis, by Wang and Diepgen,¹⁰ suggested that atopic disease may be associated with a higher risk of lung cancer and a lower risk for pancreatic cancer, childhood leukemia, and brain tumors.

Because associations appear to be site-specific, the association between atopy and specific types of cancer needs clarification. The inconsistency of results from previous studies may be at least partly due to differences in defining atopy and atopic diseases, and few studies have used an objective marker of atopy. Determination of serum specific IgE against inhalant allergens is considered a valid objective marker of atopy. We, therefore, investigated the association between serum specific IgE positivity and the incidence of a registry-based diagnosis of any cancer and specific types of cancer according to the International Classification of Diseases (ICD) in 5 Danish cohort studies.

METHODS

Ethics statement

All the participants gave their informed written consent, and the studies were approved by the Danish Data Protection Agency and the ethics committee of Copenhagen. The recommendations of the Declaration of Helsinki were followed.

Study populations

We used the 5 population-based studies, Monica1, Inter99, Health2006, the 1936-cohort, and Allergy98, recruited from the Danish Central Personal Register as random samples of the population in the southern part of Copenhagen. An overview of

studies performed in this area has previously been published.¹¹ The studies included questionnaires, physical examinations, and blood tests. In The Monica1 study (1982–1984), 4807 persons with Danish citizenship (ages, 30, 40, 50, and 60 years old) were invited. The participation rate was 79%, which yielded a total of 3785 participants.¹²

In the Inter99 study, from 1999 to 2001, 12,934 persons (ages, 30–60 years) were invited. A total of 6784 persons participated, which gave a participation rate of 52.5%.¹³ The study was a population-based randomized controlled trial (CT00289237, ClinicalTrials.gov) and investigated the effects of lifestyle intervention on cardiovascular disease.¹³ In the Health2006 study, a sample of 7931 persons from 18 to 69 years old, was invited to a general health examination.¹⁴ A total of 3471 persons (43.8%) were examined from 2006 to 2008. The Copenhagen Allergy study began in 1990 and included a group of persons randomly selected from the general population and a selected group of persons with allergic respiratory symptoms (recruited from a random sample of the general population by a screening questionnaire). We used data from the follow-up health examination in 1997 to 1998 (referred to as “Allergy98”), in which a total of 1966 persons ages 15 to 77 years with Danish nationality were invited, and 1216 (61.9%) participated.¹⁵

The 1936-cohort comprised a random sample, drawn from the Danish Civil Registration System, of persons living in 4 municipalities of Copenhagen County. In 1976, a total of 1200 randomly selected persons born in 1936 (age 40 years at the time of the study) were invited by a letter for a health examination that focused on cardiovascular disease risk factors. A questionnaire on medical history and of health and lifestyle was enclosed to be completed in advance. Between August 1976 and July 1977, a total of 1052 persons were examined (participation rate, 87.7%). The 1936-cohort has previously been described.^{16,17}

From these 5 studies, a total of 15,098 individuals had measurements of atopy (Monica1, 3481; Inter99, 5999; Allergy98, 1186; 1936-cohort, 989; Health2006, 3443). Of these, a total of 249 persons participated in more than 1 of the studies, and these persons were included only as participants in the study in which they were first examined and excluded from the subsequent studies (see [Figures E1–E5](#) in this article's Online Repository at www.jaci-inpractice.org). Thus, we included a total of 14,849 persons (Monica1, 3481; Inter99, 5961; Allergy98, 1172; 1936-cohort, 989; Health2006, 3246).

Assessment of atopy

In the 1936-cohort and the Monica1 studies, serum specific IgE positivity measurements were performed by using the ADVIA Centaur Allergy Screen assay (Bayer HealthCare Diagnostics Division, Tarrytown, NY),¹⁸ which is a multi-allergen assay for the qualitative detection of specific serum IgE antibodies to common inhalant allergens. The assay includes 19 common inhalant allergens, and atopy was defined as a positive result according to manufacturer's instructions. In both the Allergy98 and the Health2006 studies, the ADVIA Centaur Specific IgE assay (Bayer Corp, New York, NY) was used for measurements of serum specific IgE to mite (*Dermatophagoides pteronyssinus*), cat, grass, and birch (in the Allergy98 study, in addition, dog and mugwort).¹⁹ In the Inter99 study, serum samples were analyzed for specific IgE to mite (*D pteronyssinus*), cat, grass, and birch by the IMMULITE 2000 Allergy Immunoassay System (Siemens Medical Solutions Diagnostics,

TABLE I. Baseline characteristics of the study populations

Study population	Monica1	Allergy98	Inter99	Health2006	1936-cohort
Year of examination	1982-1984	1997-1998	1999-2001	2006-2008	1976-1977
Age (y), mean $\pm$ SD	45.0 $\pm$ 11.1	40.0 $\pm$ 15.1	46.1 $\pm$ 7.9	49.0 $\pm$ 13.1	40.4 $\pm$ 0.4
Men, % (no.)	50.6 (1761)	45.7 (535)	49.2 (2930)	45.2 (1467)	46.7 (462)
Alcohol (drinks/wk), mean $\pm$ SD	8.9 $\pm$ 11.5	6.8 $\pm$ 8.0	10.4 $\pm$ 13.5	9.7 $\pm$ 10.3	8.6 $\pm$ 11.2
No education beyond basic, % (no.)	29.9 (1041)	28.8 (336)	16.8 (962)	13.8 (440)	28.5 (282)
BMI (kg/m ²), mean $\pm$ SD	24.6 $\pm$ 3.9	25.7 $\pm$ 4.6	26.3 $\pm$ 4.5	25.9 $\pm$ 4.7	23.9 $\pm$ 3.7
Low physical activity, % (no.)*	28.3 (985)	26.0 (303)	21.6 (1257)	18.5 (595)	34.7 (343)
Never smokers, % (no.)	25.7 (895)	41.9 (492)	35.0 (2087)	41.9 (1345)	32.8 (324)
History of cancer, % (no.)	2.0 (68)	2.8 (33)	2.4 (143)	5.3 (173)	0.8 (8)
Atopy, % (no.)†	17.1 (594)	37.3 (437)	34.5 (2058)	23.4 (758)	14.9 (147)

*Sedentary leisure time physical activity.

†Serum specific IgE positivity to inhalant allergens.

TABLE II. Baseline characteristics according to atopic status

Characteristics	Nonatopic	Atopic	P value*
Age (y), mean $\pm$ SD	46.3 $\pm$ 10.9	43.7 $\pm$ 10.4	<.001
Sex, % (no.)			
Men	46.1 (5006)	53.8 (2149)	<.001
Women	53.9 (5849)	46.2 (1845)	
Alcohol (drinks/wk), mean $\pm$ SD	9.3 $\pm$ 11.9	10.0 $\pm$ 11.9	<.001
Education, % (no.)			
No	22.3 (2380)	17.4 (681)	<.001
Yes	77.7 (8276)	82.6 (3235)	
BMI (kg/m ²), mean $\pm$ SD	25.5 $\pm$ 4.4	25.8 $\pm$ 4.5	<.001
Physical activity, % (no.)			
Sedentary	24.1 (2585)	22.8 (898)	.003
Light	57.6 (6179)	56.4 (2219)	
Moderate or vigorous	18.3 (1963)	20.8 (817)	
Smoking habits, % (no.)			
Never smokers	32.7 (3545)	40.2 (1598)	<.001
Former smokers	24.2 (2621)	22.6 (901)	
Current smokers, <15 g/d	18.3 (1984)	16.0 (635)	
Current smokers, 15 to <25 g/d	19.0 (2056)	16.1 (640)	
Current smokers, $\geq$ 25 g/d	5.8 (623)	5.1 (204)	

*Kruskal-Wallis test or χ^2 test.

Tarrytown, NY).²⁰ In the Allergy98, the Health2006, and the Inter99 studies, the analyses for specific IgE were positive if the measurement was ≥ 0.35 kU/L. Specific IgE positivity, atopy, was defined as one or more positive tests for specific IgE against the allergens tested.

Registry-based diagnoses

Persons who live in Denmark have a unique and permanent personal civil registration number that permits linkage of individual level data from national registers. Information on cancer diagnoses was obtained from the Danish Cancer Register.^{21,22} It has been mandatory to report to the Cancer Register since 1987. The Register was classified according to the modified International Classification of Diseases, Seventh Revision (ICD-7) from 1943 to 1978 and in accordance with the International Classification of Diseases, Tenth Revision (ICD-10) from 1978 and onward.²¹ Information on emigration status and death from any cause was

obtained from the Danish Civil Registration System.²³ Persons were followed up until July 11, 2011.

The considered groups of diagnoses were the following: all cancers (ICD-7, 140-205, ICD-10, C00-C97); all cancers excluding nonmelanoma skin cancer (NMSC) (ICD-7, 140-205 excluding 191, ICD-10: C00-C97 excluding C44); cancer of the bronchus and lung (ICD-7, 162; ICD-10, C34); head and neck cancer (ICD-7, 140-148 and 160-161; ICD-10, C00-C14 and C30-C32); colorectal cancer (ICD-7, 153-154; ICD-10, C18-C20); breast cancer (ICD-7, 170; ICD-10, C50); prostate cancer (ICD-7, 177; ICD-10, C61); cancer of the uterus (ICD-7, 172-174; ICD-10, C54-C55); cancer of the urinary organs (ICD-7, 180-181; ICD-10, C64-C68); NMSC (ICD-7, 191; ICD-10, C44); and malignant melanoma (ICD-7, 190; ICD-10, C43). Incident cancer was defined as a diagnosis of the cancer during follow-up (only ICD-10 codes) among those without a history of the specific cancer at baseline. A history of cancer was defined as a diagnosis of the cancer before baseline (ICD-7 and ICD-10 codes), that is, the date of health examination and blood drawing.

Covariates

The questionnaires provided information on the covariates education/vocational training (no education [only basic education]; education, including students); physical activity during leisure time (sedentary, light, or moderate and/or vigorous); alcohol consumption (drinks per week); smoking habits (never smokers; former smokers; current smokers <15 g/d; current smokers 15 to <25 g/d; ≥ 25 g/d). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²).

The number of missing values for each of the covariates was: sex ($N_{\text{missing}} = 0$), education ($N_{\text{missing}} = 277$), physical activity during leisure time ($N_{\text{missing}} = 188$), alcohol consumption ($N_{\text{missing}} = 580$), smoking habits ($N_{\text{missing}} = 42$), BMI ($N_{\text{missing}} = 7$), which yielded a total of 880 persons (5.9%) with missing values in at least 1 of the covariates (Figures E1-E5).

Statistical analyses

The analyses were performed with SAS, version 9.4 (SAS Institute Inc, Cary, NC). All *P* values were 2-sided, and *P* values <.05 were considered statistically significant. Data from the 5 cohorts were pooled. Multivariate Cox regression analyses were used to determine the association of atopy with the incidence of cancers. Age was the underlying time axis, and we used delayed

TABLE III. Numbers and types of incident cancer during follow-up according to study population

Cancer type	Monica1, % (no.)	Allergy98, % (no.)	Inter99, % (no.)	Health2006, % (no.)	1936-cohort, % (no.)
Any cancer	25.4 (868)	8.3 (94)	9.0 (526)	3.9 (121)	31.6 (310)
Any cancer excluding NMSC	21.0 (718)	5.9 (68)	6.4 (374)	3.1 (96)	25.4 (249)
Head and neck cancer	0.8 (27)	0.3 (4)	0.4 (22)	0.1 (3)	0.7 (7)
Colorectal cancer	3.1 (109)	0.6 (7)	0.9 (54)	0.4 (12)	2.9 (29)
Cancer of the bronchus and lung	4.1 (143)	1.1 (13)	0.6 (35)	0.2 (5)	5.1 (50)
Breast cancer	3.3 (115)	0.9 (10)	1.3 (78)	0.9 (28)	4.5 (44)
Cancer of the uterus	0.7 (23)	0.3 (3)	0.3 (17)	0 (0)	0.9 (9)
Prostate cancer	2.2 (76)	1.1 (13)	0.8 (49)	0.5 (16)	2.7 (27)
Cancer of the urinary organs	1.3 (45)	0.3 (3)	0.2 (11)	0.2 (6)	1.4 (14)
Malignant melanoma	0.8 (26)	0.3 (4)	0.4 (26)	0.3 (8)	0.9 (9)
NMSC	6.2 (216)	2.7 (31)	3.0 (180)	1.2 (38)	8.2 (81)

TABLE IV. Main cancer types during follow-up according to atopy

Cancer type	Nonatopic, % (no.)	Atopic, % (no.)	P value, χ^2 test
Any cancer	14.4 (1520)	10.3 (399)	<.001
Any cancer excluding NMSC	11.4 (1215)	7.4 (290)	<.001
Head and neck cancer	0.4 (42)	0.5 (21)	.249
Colorectal cancer	1.6 (170)	1.0 (41)	.014
Cancer of the bronchus and lung	2.0 (213)	0.8 (33)	<.001
Breast cancer	2.0 (220)	1.4 (55)	.009
Cancer of the uterus	0.4 (43)	0.2 (9)	.118
Prostate cancer	1.4 (150)	0.8 (31)	.003
Cancer of the urinary organs	0.6 (65)	0.4 (14)	.065
Malignant melanoma	0.5 (56)	0.4 (17)	.484
NMSC	3.8 (410)	3.4 (136)	.281

entry. The date of entry (baseline) was the date of the health examination and blood drawing. The few participants lost to follow-up ($n = 128$) contributed risk time until the date of their last registered activity. Estimates are presented as hazard ratios (HR) (95% CIs). Only participants with complete information on all considered variables were included. In model 1, we adjusted for sex and study population. In model 2, we further adjusted for education, physical activity, smoking habits, alcohol intake, and BMI. In the analysis of cancer of the breast and uterus, only women were included, and only men were included in the analysis of prostate cancer. There was no statistically significant interaction between atopy and study population (all $P > .1$). In additional analyses, we excluded diagnoses of cancer in the first 2 years after baseline (participants contributed risk time from 2 years after baseline) (see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org).

We used Stata, version 12.1 (StataCorp LP, College Station, Texas) to perform meta-analyses of the study-specific estimates that were obtained from Cox regression models for each cohort separately. We combined the HR estimates by using the inverse variance method in both fixed and random-effects models (see [Figures E6-E16](#) in this article's Online Repository at www.jaci-inpractice.org). The heterogeneity across studies was assessed by the I^2 test. There were no signs of heterogeneity except for a slight heterogeneity across studies in the analysis of atopy and of head and neck cancer ($I^2 = 14.6\%$).

RESULTS

Baseline characteristics according to study population are shown in [Table I](#). The prevalence of atopy ranged from approximately 15% to 37%, which reflects both differences in age composition and time trends of atopy. Baseline characteristics according to atopic status are shown in [Table II](#). Individuals with atopy were younger, drank more alcohol, were more frequently men, were more educated, had a higher BMI, and smoked less than individuals without atopy. The distribution of cancer during follow-up is presented in [Table III](#). There were a total of 425 prevalent cancers (individuals with a history of cancer at baseline) and 1919 incident cancers. Among the 14,424 individuals with no history of cancer before baseline, there were 3893 with atopy and 10,531 without atopy. Any cancer, any cancer excluding NMSC, colorectal cancer, cancer of the bronchus and lung, breast cancer, and prostate cancer were unequally distributed among individuals without atopy and individuals with atopy, when the effects of age were not taken into account ([Table IV](#)).

The multivariable Cox regression analyses of incident cancer according to atopic status are shown in [Table V](#). The median follow-up time was 11.8 years (minimum, <0.1 years; maximum 36.7 years) in the analyses of any cancer. The median follow-up times were 4.0, 11.5, 13.1, 29.1, and 35.5 years for the Health2006, the Inter99, the Allergy98, the Monica1, and the 1936-cohort studies, respectively. In short, most of the statistically significant crude associations between atopy and cancer, shown in [Table IV](#), were not seen in Cox regressions analysis when using age as the underlying time axis and delayed entry in which persons enter the analysis at their baseline age, thereby taking confounding by age into account. There was no association between atopy and incidence of any cancer. In the partly adjusted analyses, there were a significantly higher risk of NMSC and a borderline significantly lower risk of cancer of the bronchus and lung among individuals with atopy ([Table V](#), model 1), but these associations were attenuated and not statistically significant in the fully adjusted models ([Table V](#), model 2).

There was a borderline significantly higher risk of head and neck cancer among individuals with atopy in the fully adjusted model (HR 1.74 [95% CI, 0.98-3.09]). The results from meta-analyses of the study-specific estimates obtained by analysis of each study separately were summarized in [Figure 1](#). These results are similar to the estimates from the pooled analyses ([Table V](#)).

TABLE V. Risk of incident cancer associated with atopy

Cancer type*	Events/persons included (person years)	Model 1, HR (95% CI)†	P	Model 2, HR (95% CI)‡	P
Any cancer			.912		.975
Nonatopic	1,476/9,908 (146,587)	1 (reference)		1 (reference)	
Atopic	379/3,662 (47,293)	0.99 (0.89-1.12)		1.00 (0.89-1.12)	
Any cancer excluding NMSC			.197		.306
Nonatopic	1,182/10,008 (149,996)	1 (reference)		1 (reference)	
Atopic	274/3,694 (48,255)	0.92 (0.80-1.05)		0.93 (0.82-1.07)	
Head and neck cancer			.151		.059
Nonatopic	40/10,203 (157,164)	1 (reference)		1 (reference)	
Atopic	18/3,755 (50,011)	1.52 (0.86-2.70)		1.74 (0.98-3.09)	
Colorectal cancer			.635		.639
Nonatopic	168/10,200 (156,521)	1 (reference)		1 (reference)	
Atopic	38/3,756 (49,886)	0.92 (0.64-1.31)		0.92 (0.64-1.32)	
Cancer of the bronchus and lung			.055		.193
Nonatopic	209/10,210 (157,066)	1 (reference)		1 (reference)	
Atopic	33/3,757 (50,042)	0.69 (0.48-1.01)		0.78 (0.54-1.13)	
Breast cancer§			.920		.995
Nonatopic	211/5,402 (82,636)	1 (reference)		1 (reference)	
Atopic	51/1,701 (22,624)	1.02 (0.74-1.39)		1.00 (0.73-1.37)	
Cancer of the uterus§			.781		.777
Nonatopic	41/5,443 (84,187)	1 (reference)		1 (reference)	
Atopic	9/1,718 (23,070)	0.90 (0.43-1.88)		0.90 (0.43-1.88)	
Prostate cancer			.293		.256
Nonatopic	144/4,758 (72,254)	1 (reference)		1 (reference)	
Atopic	31/2,036 (26,805)	0.81 (0.54-1.20)		0.79 (0.53-1.18)	
Cancer of the urinary organs			.964		.788
Nonatopic	64/10,199 (156,983)	1 (reference)		1 (reference)	
Atopic	14/3,755 (50,018)	1.01 (0.56-1.83)		1.08 (0.60-1.96)	
Malignant melanoma			.990		.861
Nonatopic	55/10,181 (156,794)	1 (reference)		1 (reference)	
Atopic	17/3,749 (49,941)	1.00 (0.57-1.76)		0.95 (0.54-1.66)	
NMSC			.049		.079
Nonatopic	396/10,107 (153,585)	1 (reference)		1 (reference)	
Atopic	132/3,723 (49,011)	1.23 (1.00-1.50)		1.20 (0.98-1.47)	

*Complete case analysis; persons who had the cancer of interest at baseline were excluded.

†Adjusted for study and sex (age is underlying time axis).

‡Further adjusted for education, physical activity, smoking habits, alcohol intake, and BMI.

§Only women were included in the analyses.

||Only men were included in the analyses.

All estimates remained statistically nonsignificant and in the same direction in sensitivity analyses when cases of cancer during the period 2 years after baseline were excluded (Table E1).

DISCUSSION

To our knowledge, this is the largest prospective study with the highest number of incident cases of cancer that examined the association between an objective marker of atopy and the incidence of total and specific cancer. We found no statistically significant associations between atopy and incidence of total cancer or specific types of cancer in multivariable analyses. However, atopy tended to associate with higher risk of head and neck cancer, but this was not statistically significant. To our knowledge, no previous study has examined the association between atopy and the incidence of head and neck cancer, and this finding needs further investigation in future studies. If confirmed, it may be speculated that treatment with

immunosuppressive drugs, that is, local or systemic steroids, could provide a potential underlying mechanism for an association between atopy and head and neck cancer.

We confirmed the lack of association between atopy and development of any cancer reported by Eriksson et al,²⁴ who examined a cohort of 13,811 persons (335 cases of incident cancer) and found no association between atopy as assessed by skin prick test reactivity to inhalant allergens and total cancer incidence. Of potential interest to this article is that we recently found that loss-of-function mutations in the filaggrin gene known to be strongly associated with allergic diseases were not associated with the incidence of cancer.²⁵ This finding adds indirect evidence against the hypothesis that atopic disease is associated with cancer risk.

Results from previous studies on the association between atopy and breast cancer have been inconsistent. The observed lack of association between atopy and breast cancer in the present study is in line with results of a large case-control study that reported no

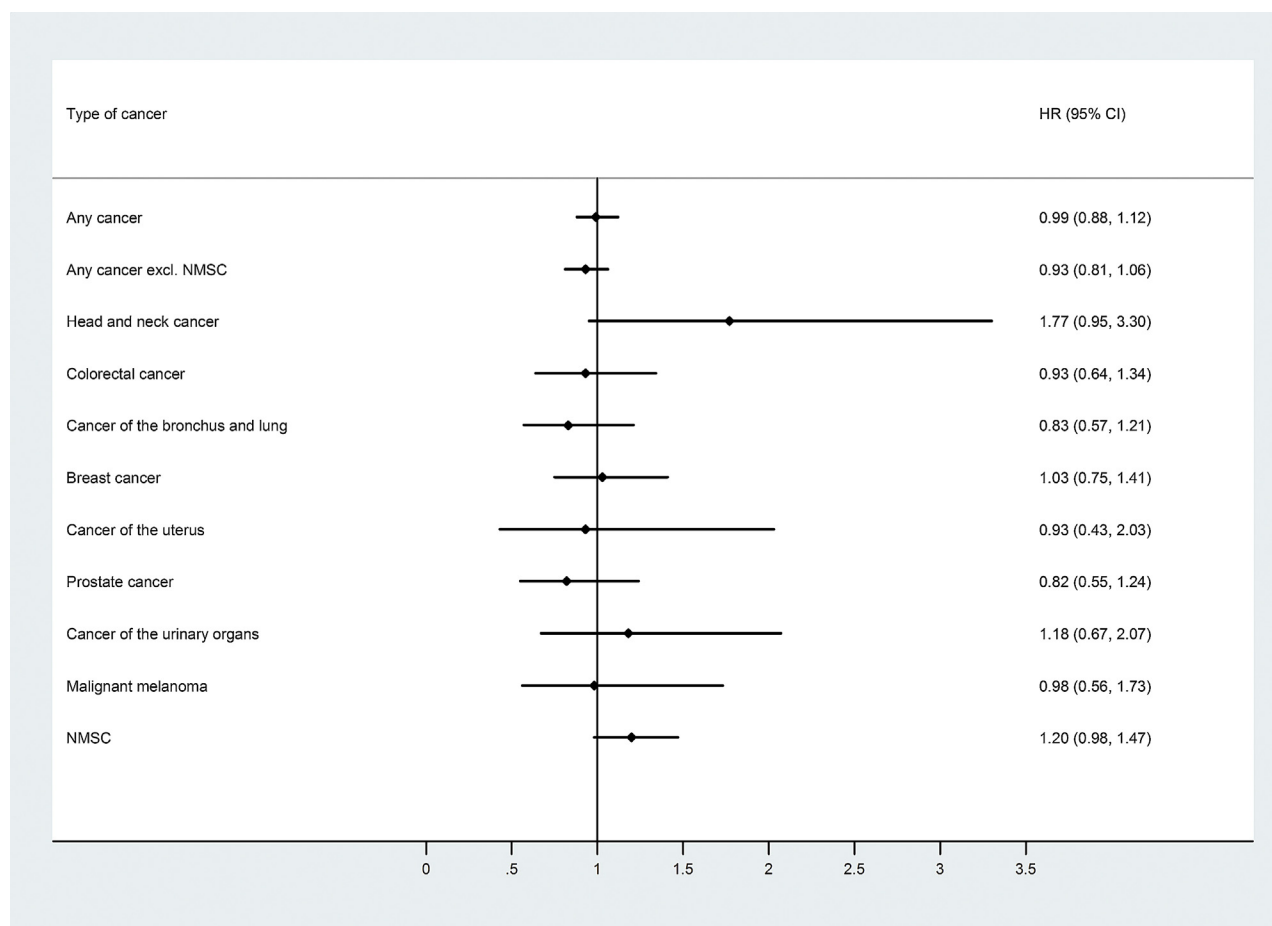


FIGURE 1. Meta-estimates of the study-specific estimates from fixed effect models of the association between being individuals with atopy compared with individuals without atopy and the risk of cancer.

statistically significant association between breast cancer and specific IgE positivity.⁶ Our results, however, are inconsistent with the results by Eriksson et al,⁸ who found a positive association between a positive skin prick test and the incidence of breast cancer, although in a later study found no association.²⁴ Likewise, in a small case-control study, Petridou et al⁷ found a borderline significant positive association between a specific IgE score based on specific IgE to 12 allergens and breast cancer.

With regard to prostate cancer, the observed lack of association in our study is inconsistent with the results of Talbot-Smith et al⁹ who performed a study on a subset of 1005 participants from the 1981 Busselton Health Survey and found that having a positive skin prick test to inhalant allergens more than doubled the risk of prostate cancer. Likewise, Wang found a higher risk of prostate cancer among subjects with specific IgE positivity.⁶ The observed lack of association with lung cancer and colorectal cancer in the present study also was in line with the results of previous studies.^{6,8,24}

The inconsistent results of previous studies may be due to insufficient study sample size, publication bias, selection bias, lack of adjustment for confounding factors, and the use of different definitions of atopy. In the present study, individuals with atopy were younger than individuals without atopy, and age showed to be a strong confounder; in crude analyses, most cancers were unequally distributed among individuals without atopy and those with atopy, but when age was used as the

underlying time axis, thereby fully taking into account the effect of age, associations attenuated and hardly any association remained statistically significant. This observation emphasizes the importance of proper adjustment for age in studies of the association of atopy with cancer. Also, because atopy has been shown to be inversely related to smoking habits,²⁶ smoking habits may be a confounder of the associations between atopy and smoking-related cancers. Although we adjusted the analyses for smoking habits, there may be some residual confounding.

The strengths of our study include the longitudinal design and the large population-based samples, the availability of data on important confounders, and an objective marker of atopy. Serum specific IgE positivity to inhalant allergens is considered a valid measure of atopy and/or allergy in epidemiologic studies. We used commercially available immunoassays for determination of serum specific IgE, and we have previously found that results obtained with these assays are in agreement with skin prick test reactivity and a diagnosis of allergic respiratory disease.^{18,19} Most of the previous studies use self-reported atopic disease as a measure of atopy based on self-reported diagnoses or symptoms, which may be subject to some misclassification.^{5,6} However, although a positive *in vitro* allergy test is a well-accepted biomarker of allergy and immune deviation toward a Th2 response, it should be borne in mind that a positive allergy test reflects allergic sensitization and not allergic respiratory disease

per se. Thus, we have only investigated the association of a marker of allergic respiratory disease, and not allergic respiratory disease *per se*, with the incidence of cancer. Furthermore, we used 3 different methods for measurement of serum specific IgE positivity, and this could potentially bias our results. However, we did not find any evidence of heterogeneity among results obtained in the cohorts included.

The validity of the cancer diagnoses in the Danish Cancer Registry is high. The proportion of morphologically verified tumors is 89%.²¹ The validity and quality are secured through daily quality control routines and, for example, by manual coding of complex cases.²¹ Linkage of our study population to the Danish Cancer Registry provided longitudinal follow-up, with almost no loss to follow-up. Furthermore, we were able to exclude persons with a history of cancer before the time of assessment of atopy, thereby minimizing the risk of reverse causation, that is, cancer having an influence on atopic status. Thus, in sensitivity analyses, we excluded persons who developed cancer during the period 2 years after baseline and assessment of atopy to exclude possible effects of cancer on atopic status.

There also are limitations of the present study. Although the precision of the risk estimate for total cancer was reasonably high, our study may have lacked power to detect effects of atopy on some of the specific types of cancer. Thus, larger studies are needed to exclude that atopy could have an effect on the risk of specific types of cancer. The relatively low participation rate in some of the cohorts may limit the generalizability of the results and induce selection bias. However, another similar Danish study that used registry-based outcomes with almost complete follow-up of participants but with lower baseline participation than in the present study has been shown not to be biased by baseline nonparticipation.²⁷ It also is a potential limitation that we used data from 5 somewhat different studies, which could induce biases. In addition to the data analyses of the pooled data at the individual level, we also performed a meta-analysis of results obtained within the data set of each study separately. The meta-analysis results were very similar to the results of pooled analyses.

In conclusion, we found no statistically significant associations between atopy and the incidence of cancer. The observed borderline-significant higher risk of head and neck cancer among individuals with atopy needs to be explored in future studies. Our results are reassuring in a time when atopic disease is becoming more frequent.

REFERENCES

- Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;113:832-6.
- Romagnani S. The increased prevalence of allergy and the hygiene hypothesis: missing immune deviation, reduced immune suppression, or both? *Immunology* 2004;112:352-63.
- Linneberg A, Gislum M, Johansen N, Husemoen LL, Jorgensen T. Temporal trends of aeroallergen sensitization over twenty-five years. *Clin Exp Allergy* 2007;37:1137-42.
- Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Increasing prevalence of specific IgE to aeroallergens in an adult population: two cross-sectional surveys 8 years apart: the Copenhagen Allergy Study. *J Allergy Clin Immunol* 2000;106:247-52.
- Vojtechova P, Martin RM. The association of atopic diseases with breast, prostate, and colorectal cancers: a meta-analysis. *Cancer Causes Control* 2009;20:1091-105.
- Wang H, Rothenbacher D, Low M, Stegmaier C, Brenner H, Diepgen TL. Atopic diseases, immunoglobulin E and risk of cancer of the prostate, breast, lung and colorectum. *Int J Cancer* 2006;119:695-701.
- Petridou ET, Chavelas C, Dikaloti SK, Dessypris N, Terzidis A, Nikoulis DI, et al. Breast cancer risk in relation to most prevalent IgE specific antibodies: a case control study in Greece. *Anticancer Res* 2007;27:1709-13.
- Eriksson NE, Holmen A, Hogstedt B, Mikoczy Z, Hagmar L. A prospective study of cancer incidence in a cohort examined for allergy. *Allergy* 1995;50:718-22.
- Talbot-Smith A, Fritschi L, Divitini ML, Mallon DF, Knuiman MW. Allergy, atopy, and cancer: a prospective study of the 1981 Busselton cohort. *Am J Epidemiol* 2003;157:606-12.
- Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. *Allergy* 2005;60:1098-111.
- Osler M, Linneberg A, Glumer C, Jorgensen T. The cohorts at the Research Centre for Prevention and Health, formerly 'The Glostrup Population Studies'. *Int J Epidemiol* 2011;40:602-10.
- Linneberg A, Hertzum I, Husemoen LL, Johansen N, Jorgensen T. Association between alcohol consumption and aeroallergen sensitization in Danish adults. *Clin Exp Allergy* 2006;36:714-21.
- Jorgensen T, Borch-Johnsen K, Thomsen TF, Ibsen H, Glumer C, Pisinger C. A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: baseline results Inter99. *Eur J Cardiovasc Prev Rehabil* 2003;10:377-86.
- Berg ND, Husemoen LL, Thuesen BH, Hersoug LG, Elberling J, Thyssen JP, et al. Interaction between filaggrin null mutations and tobacco smoking in relation to asthma. *J Allergy Clin Immunol* 2012;129:374-80. 380.e1-2.
- Husemoen LL, Fenger M, Friedrich N, Tolstrup JS, Beenfeldt FS, Linneberg A. The association of ADH and ALDH gene variants with alcohol drinking habits and cardiovascular disease risk factors. *Alcohol Clin Exp Res* 2008;32:1984-91.
- Drivsholm T, Eplov LF, Davidsen M, Jorgensen T, Ibsen H, Hollnagel H, et al. Representativeness in population-based studies: a detailed description of non-response in a Danish cohort study. *Scand J Public Health* 2006;34:623-31.
- Linneberg A, Friedrich N, Husemoen LL, Thuesen B, Gonzalez-Quintela A, Vidal C, et al. Incidence and remission of specific IgE aeroallergen sensitization from age of 40 to 60 years, and association with alcohol consumption. *Int Arch Allergy Immunol* 2010;151:142-8.
- Linneberg A, Husemoen LL, Nielsen NH, Madsen F, Frolund L, Johansen N. Screening for allergic respiratory disease in the general population with the ADVIA Centaur Allergy Screen Assay. *Allergy* 2006;61:344-8.
- Petersen AB, Gudmann P, Milvang-Gronager P, Morkeberg R, Bogestrand S, Linneberg A, et al. Performance evaluation of a specific IgE assay developed for the ADVIA centaur immunoassay system. *Clin Biochem* 2004;37:882-92.
- Thuesen BH, Husemoen LL, Ovesen L, Jorgensen T, Fenger M, Gilderson G, et al. Atopy, asthma, and lung function in relation to folate and vitamin B (12) in adults. *Allergy* 2010;65:1446-54.
- Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health* 2011;39(Suppl):42-5.
- Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry: history, content, quality and use. *Dan Med Bull* 1997;44:535-9.
- Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39(Suppl):22-5.
- Eriksson NE, Mikoczy Z, Hagmar L. Cancer incidence in 13811 patients skin tested for allergy. *J Investig Allergol Clin Immunol* 2005;15:161-6.
- Skaaby T, Husemoen LL, Thyssen JP, Meldgaard M, Thuesen BH, Pisinger C, et al. Filaggrin loss-of-function mutations and incident cancer: a population-based study. *Br J Dermatol* 2014 Mar 14 [Epub ahead of print].
- Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Smoking and the development of allergic sensitization to aeroallergens in adults: a prospective population-based study. The Copenhagen Allergy Study. *Allergy* 2001;56:328-32.
- Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology* 2006;17:413-8.

APPENDIX

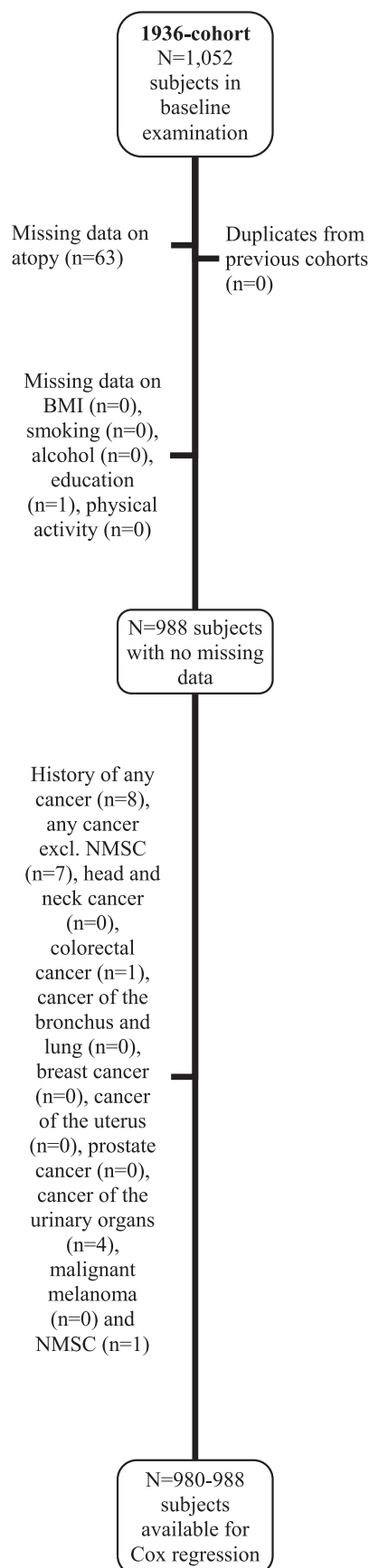


FIGURE E1. Flowchart of the 1936-cohort.

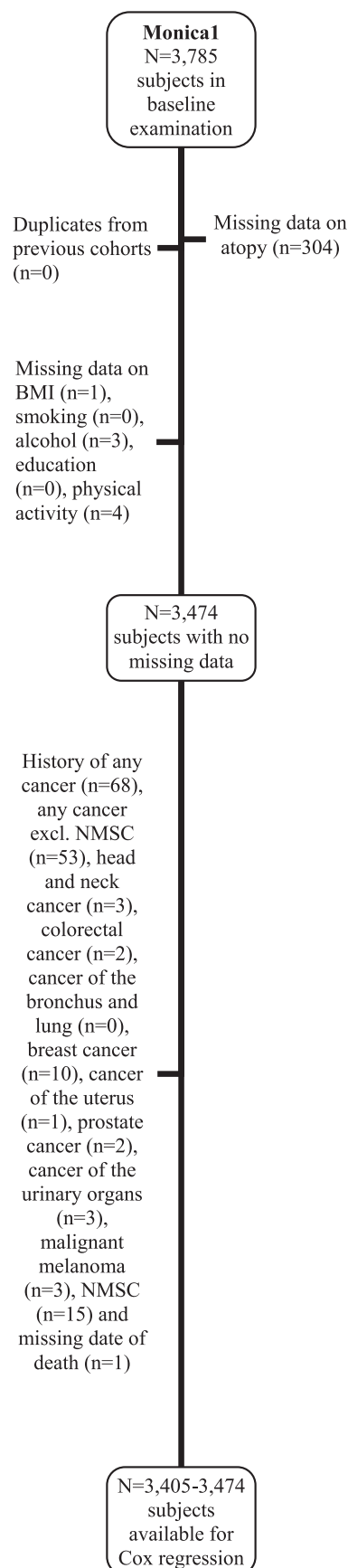


FIGURE E2. Flowchart of the Monica1 study.

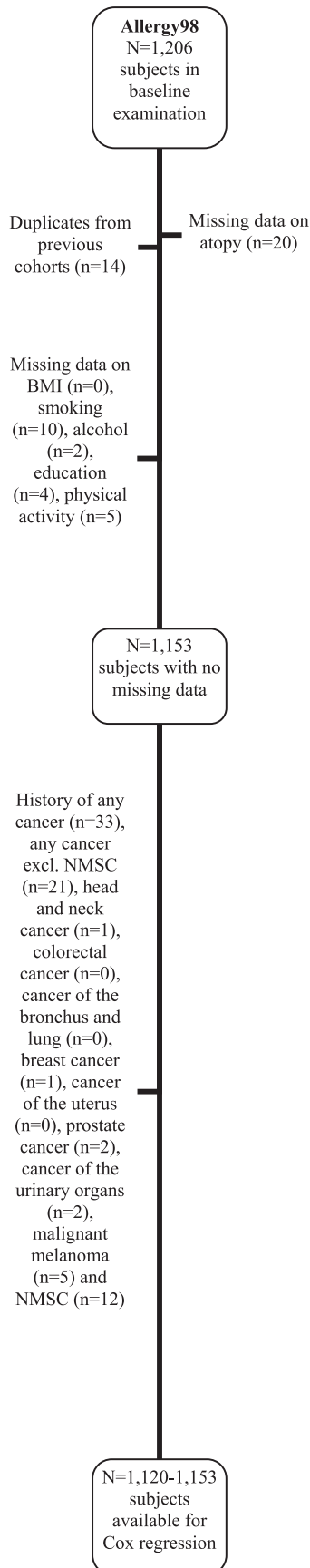


FIGURE E3. Flowchart of the Allergy98 study.

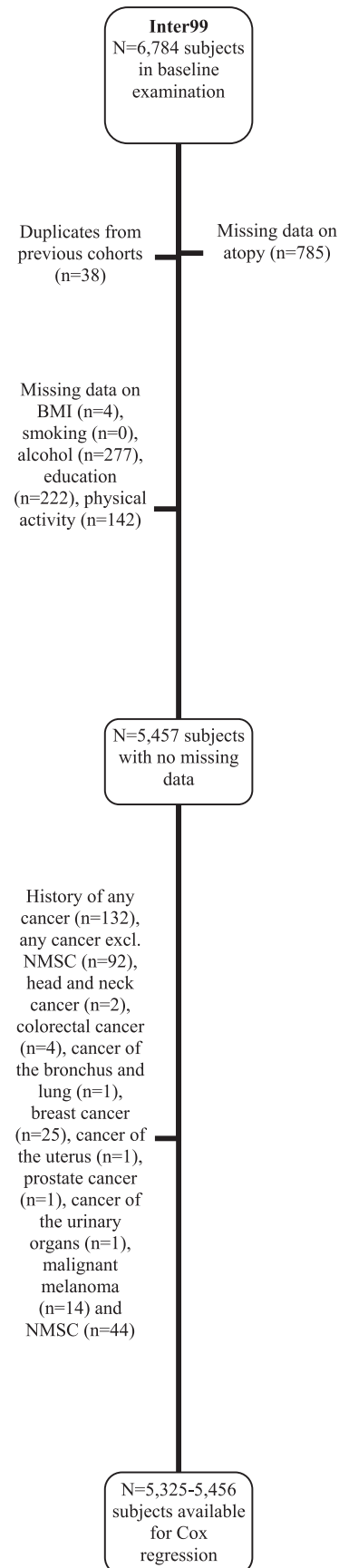
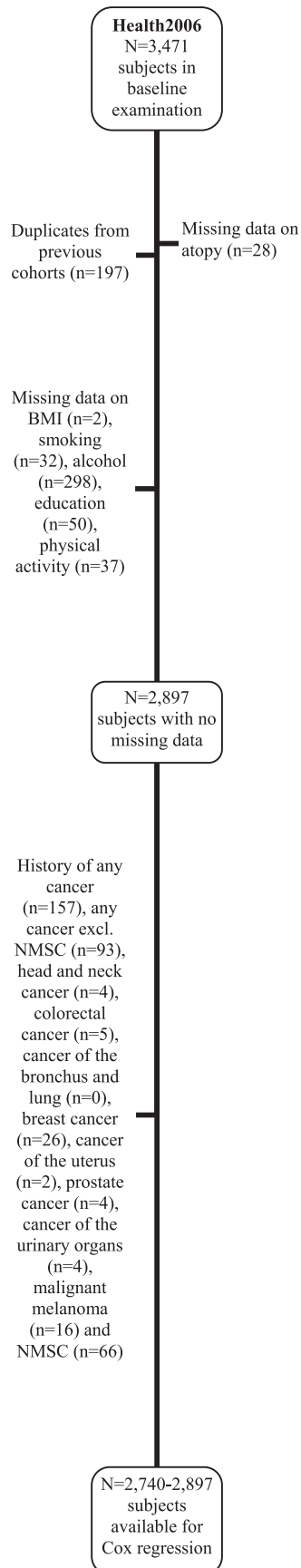


FIGURE E4. Flowchart of the Inter99 study.

**FIGURE E5.** Flowchart of the Health2006 study.

Atopy and NMSC

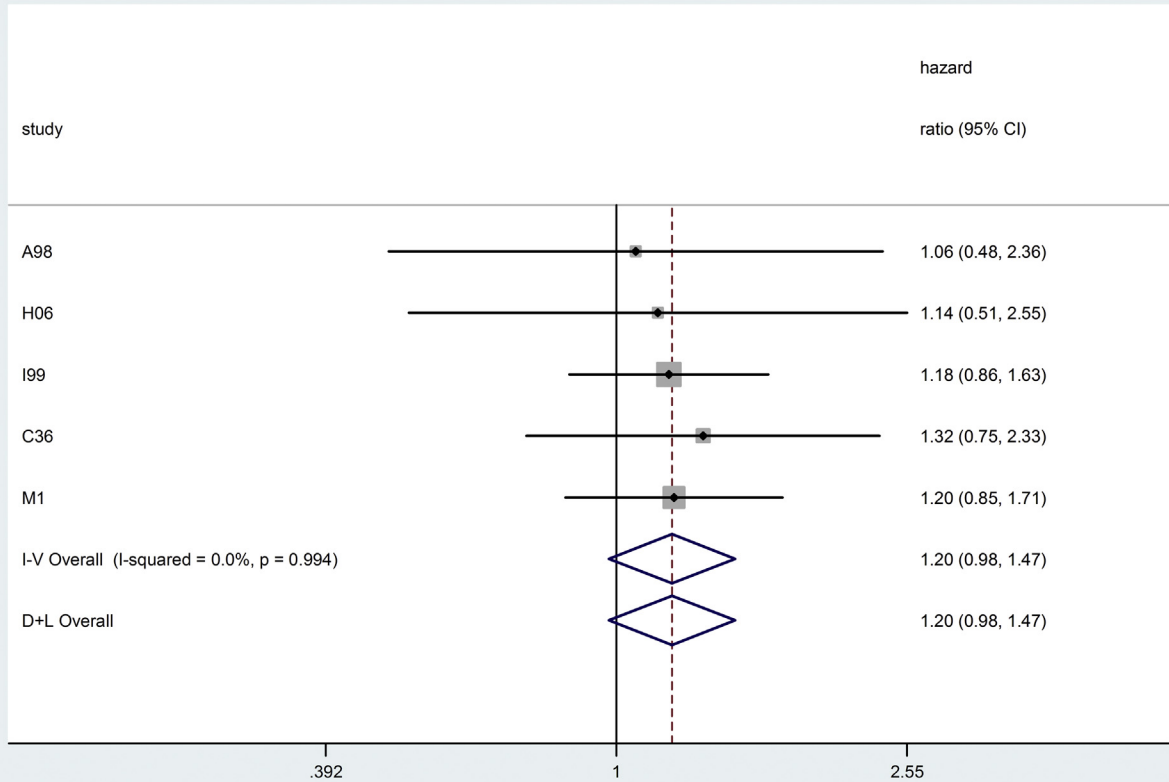


FIGURE E6. Meta-analysis of the study-specific estimates of the association between atopy and non-melanoma skin cancer (NMSC). Abbreviations: A98, Allergy98; C36, 1936-cohort; H06, Health2006; I99, Inter99; M1, Monica1; CI, confidence interval; NMSC, non-melanoma skin cancer.

Atopy and cancer of the urinary organs

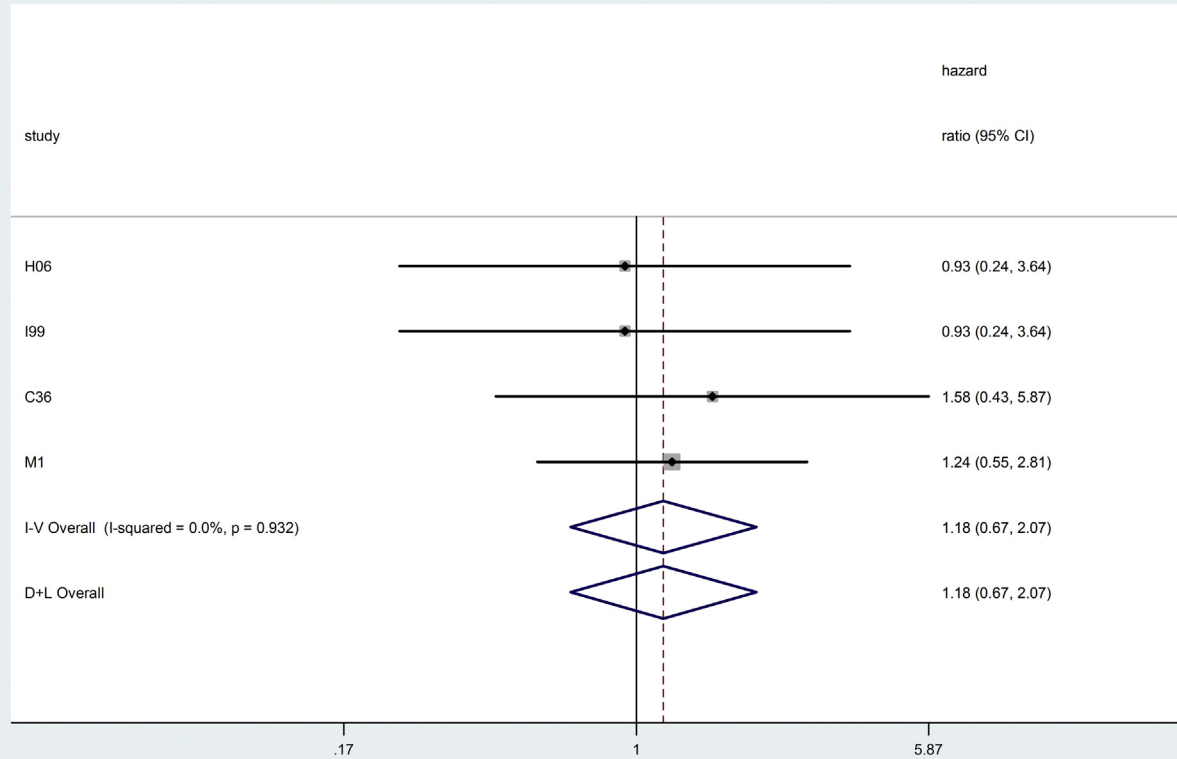


FIGURE E7. Meta-analysis of the study-specific estimates of the association between atopy and cancer of the urinary organs. Abbreviations: A98, Allergy98; C36, 1936-cohort; H06, Health2006; I99, Inter99; M1, Monica1; CI, confidence interval.

Atopy and cancer excl. NMSC

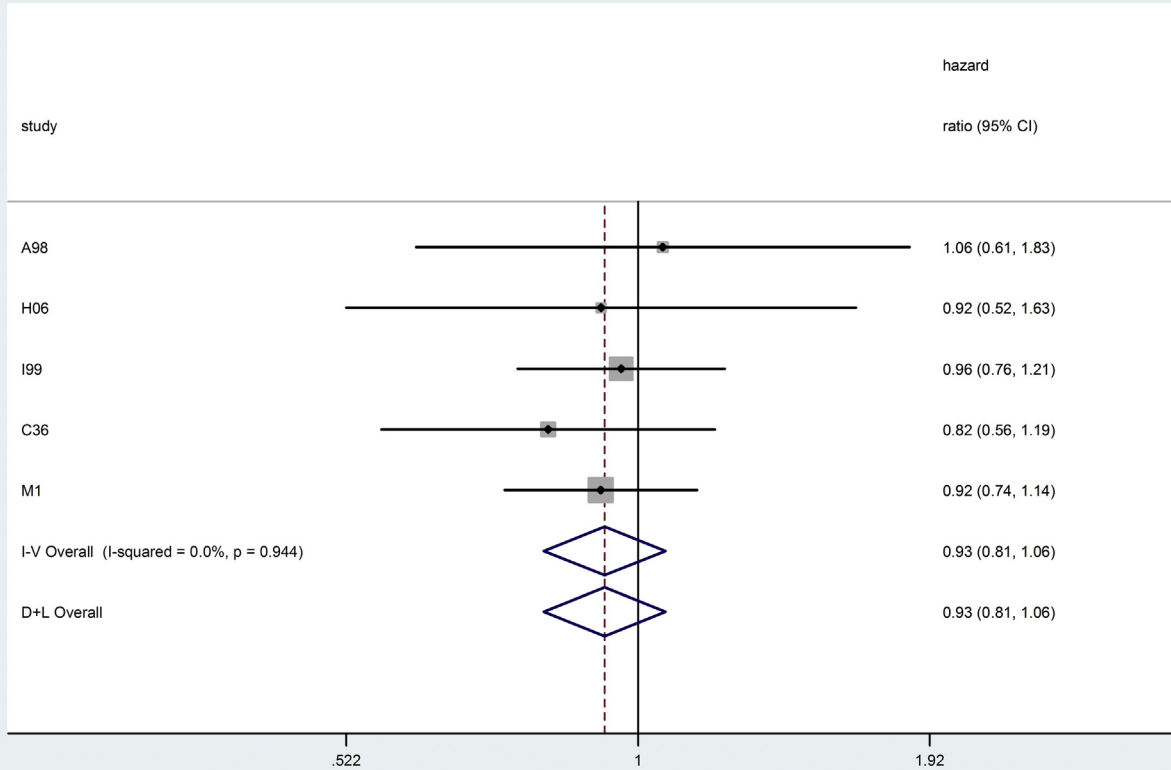


FIGURE E8. Meta-analysis of the study-specific estimates of the association between atopy and total cancer excluding non-melanoma skin cancer (NMSC). Abbreviations: A98, Allergy98; C36, 1936-cohort; H06, Health2006; I99, Inter99; M1, Monica1; CI, confidence interval; NMSC, non-melanoma skin cancer.

Atopy and prostate cancer

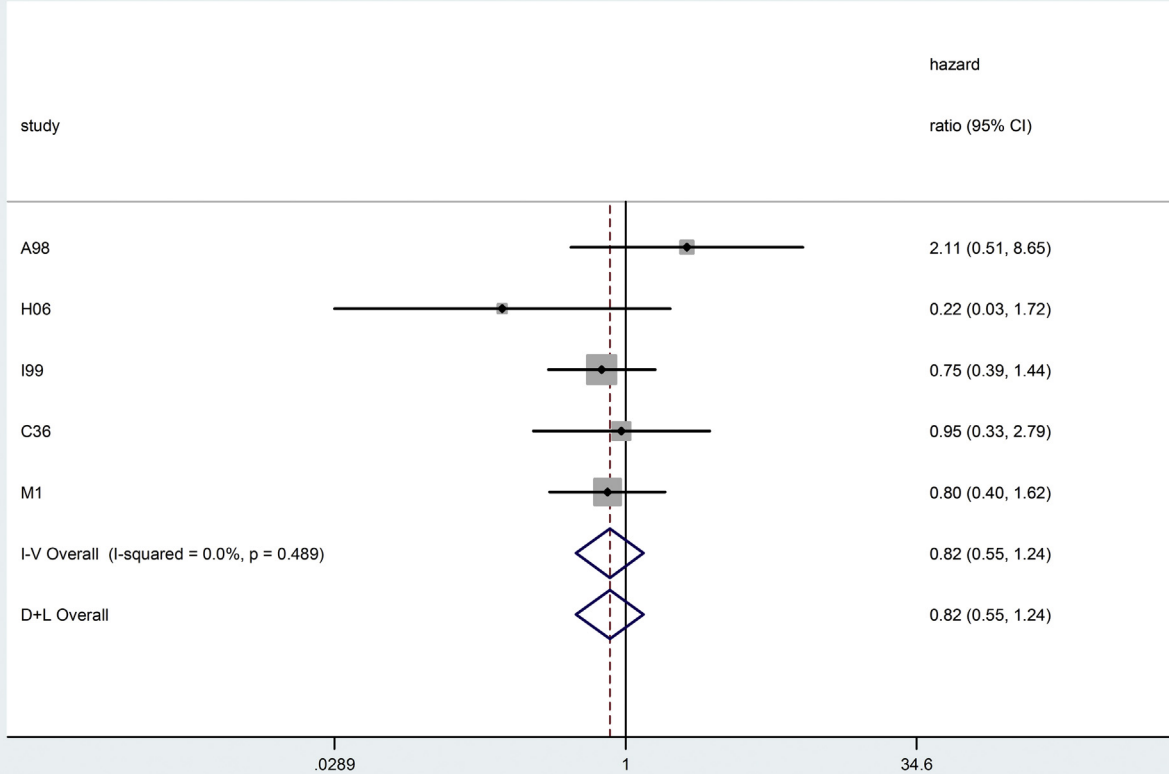


FIGURE E9. Meta-analysis of the study-specific estimates of the association between atopy and prostate cancer. Abbreviations: A98, Allergy98; C36, 1936-cohort; H06, Health2006; I99, Inter99; M1, Monica1; CI, confidence interval.

Atopy and cancer of the bronchus and lung

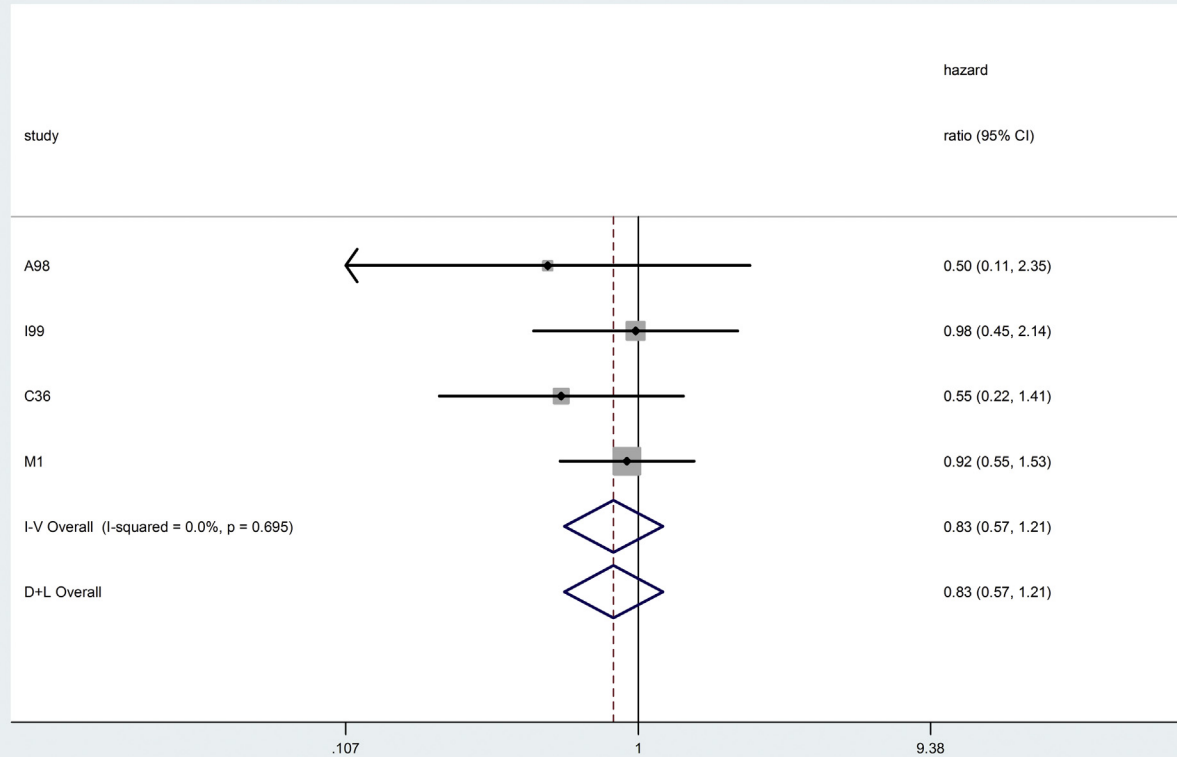


FIGURE E10. Meta-analysis of the study-specific estimates of the association between atopy and cancer of the bronchus and lung. Abbreviations: A98, Allergy98; C36, 1936-cohort; H06, Health2006; I99, Inter99; M1, Monica1; CI, confidence interval.

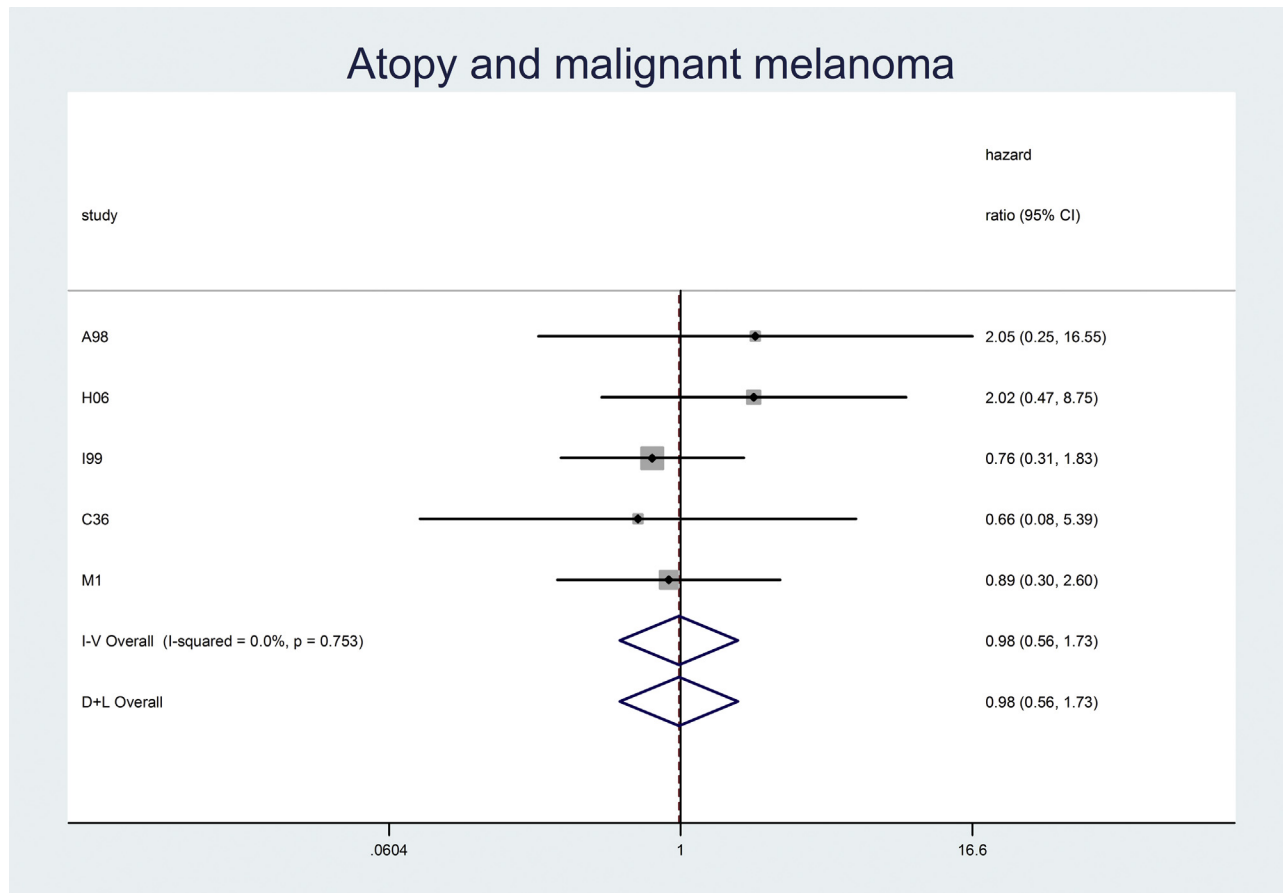


FIGURE E11. Meta-analysis of the study-specific estimates of the association between atopy and malignant melanoma. Abbreviations: A98, Allergy98; C36, 1936-cohort; H06, Health2006; I99, Inter99; M1, Monica1; CI, confidence interval.

Atopy and head and neck cancer

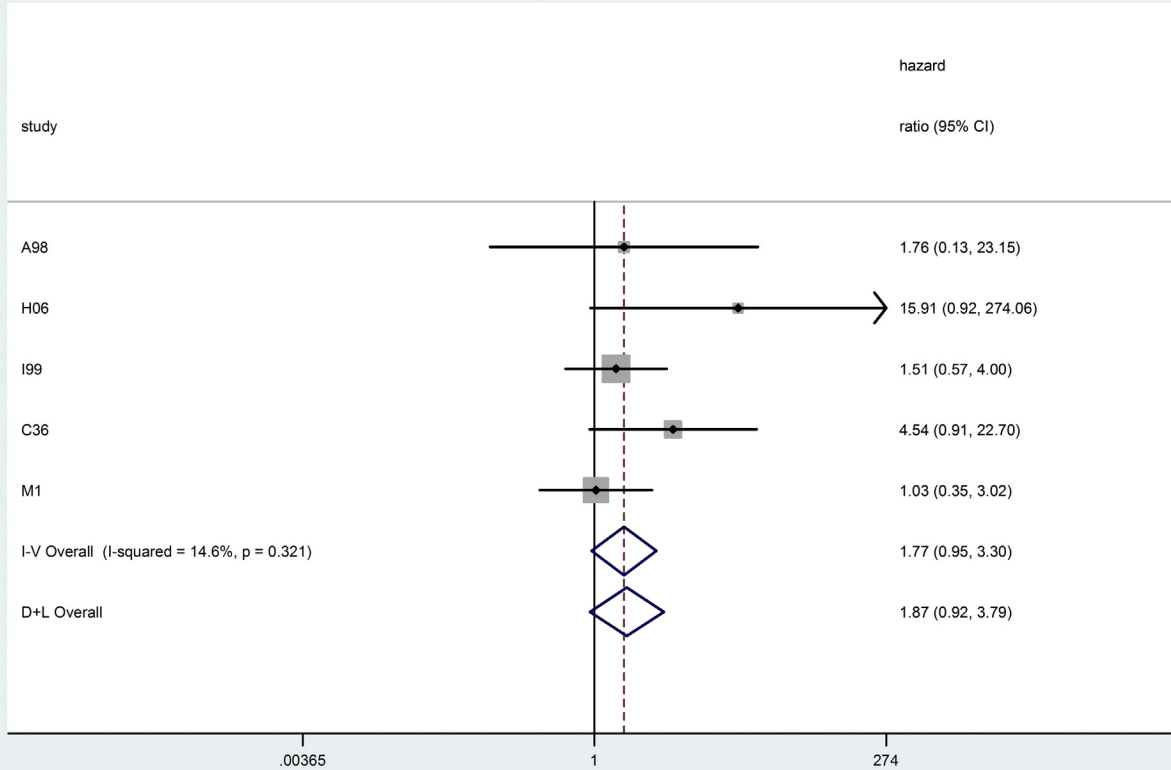


FIGURE E12. Meta-analysis of the study-specific estimates of the association between atopy and head and neck cancer. Abbreviations: A98, Allergy98; C36, 1936-cohort; H06, Health2006; I99, Inter99; M1, Monica1; CI, confidence interval.

Atopy and colorectal cancer

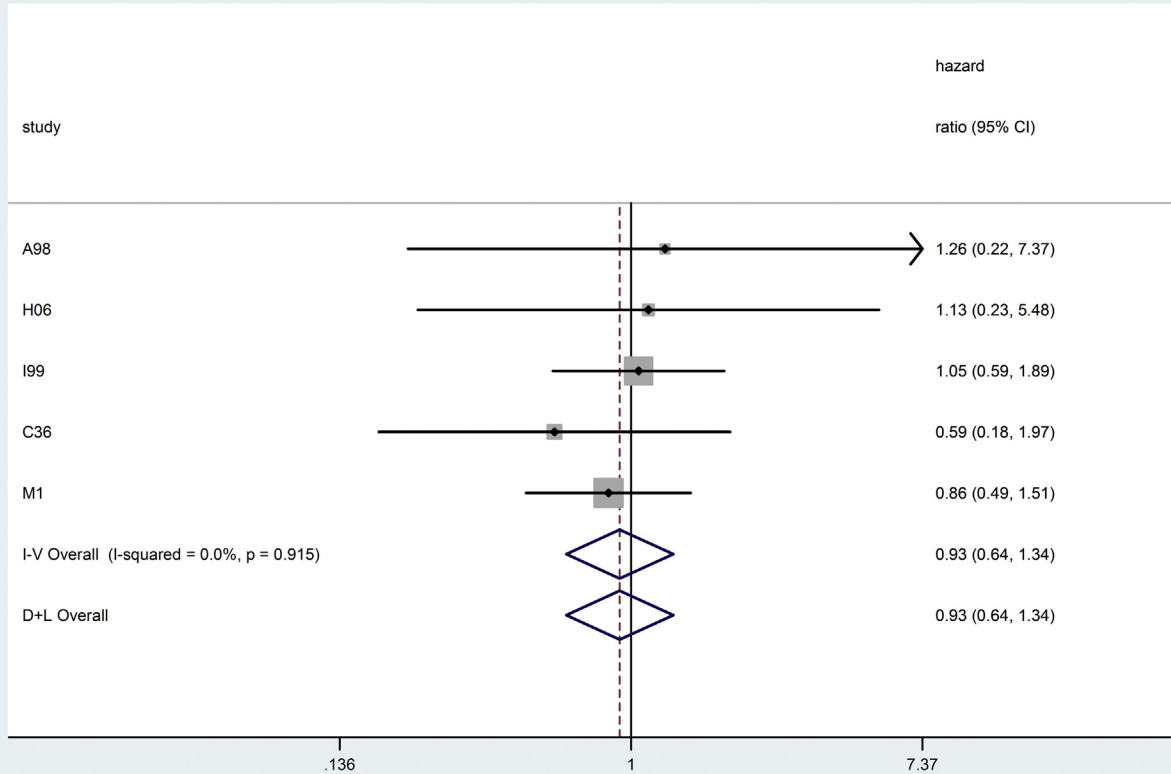


FIGURE E13. Meta-analysis of the study-specific estimates of the association between atopy and colorectal cancer. Abbreviations: A98, Allergy98; C36, 1936-cohort; H06, Health2006; I99, Inter99; M1, Monica1; CI, confidence interval.

Atopy and cancer

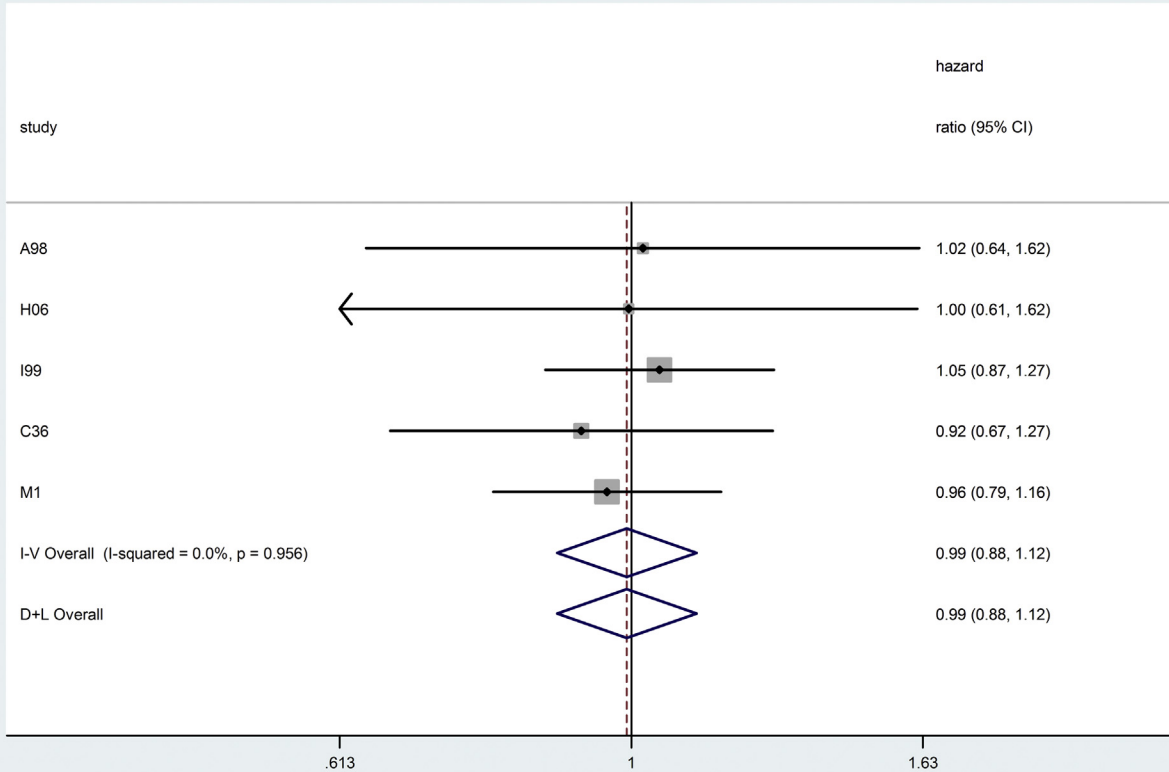


FIGURE E14. Meta-analysis of the study-specific estimates of the association between atopy and cancer. Abbreviations: A98, Allergy98; C36, 1936-cohort; H06, Health2006; I99, Inter99; M1, Monica1; CI, confidence interval.

Atopy and breast cancer

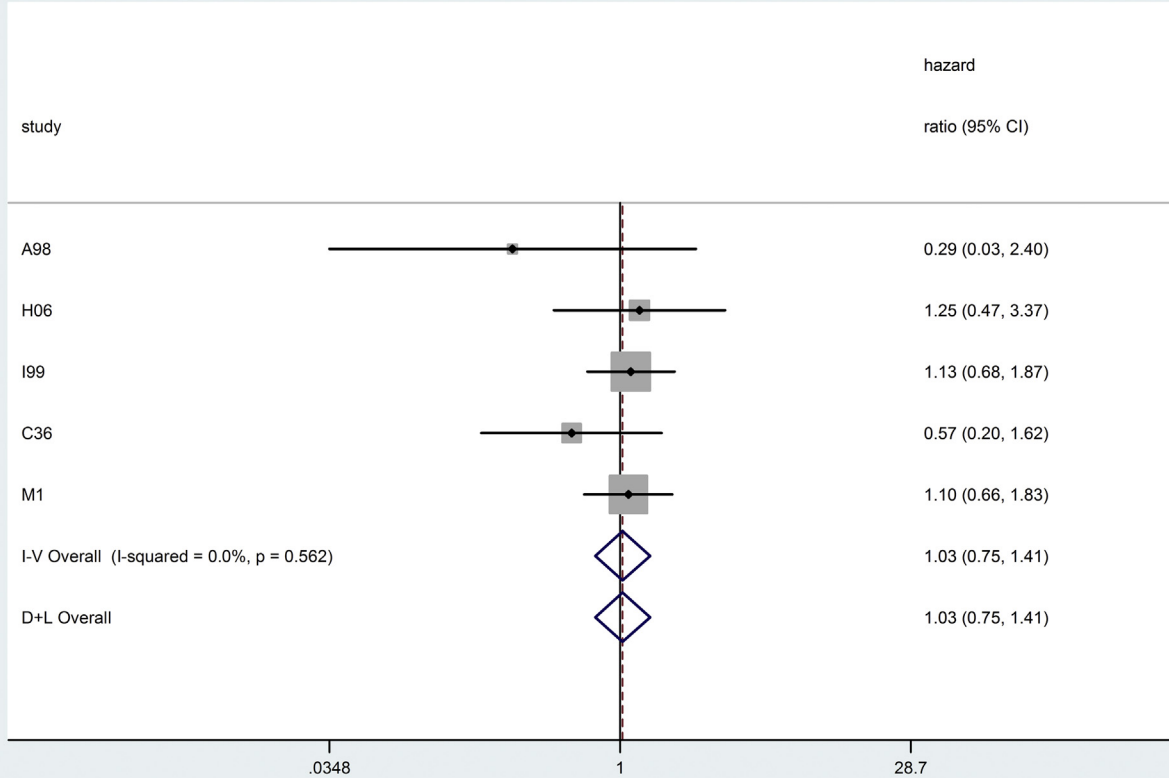


FIGURE E15. Meta-analysis of the study-specific estimates of the association between atopy and breast cancer. Abbreviations: A98, Allergy98; C36, 1936-cohort; H06, Health2006; I99, Inter99; M1, Monica1; CI, confidence interval.

Atopy and cancer of the uterus

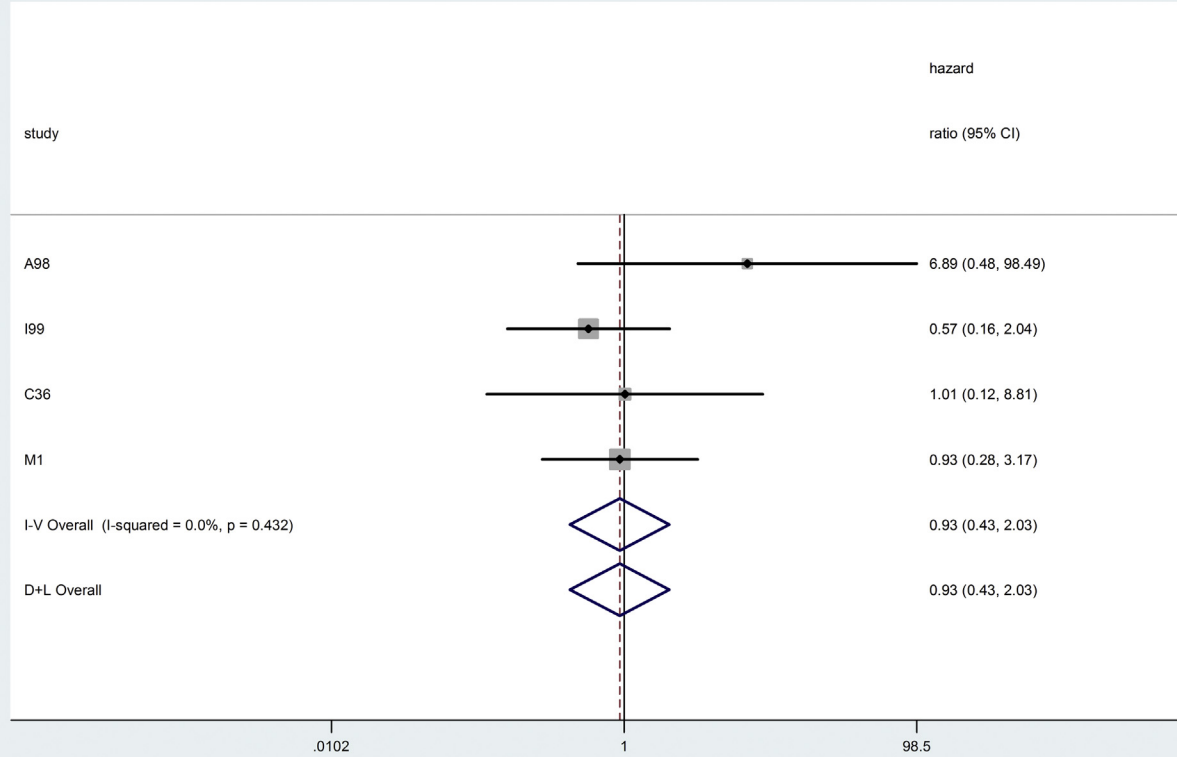


FIGURE E16. Meta-analysis of the study-specific estimates of the association between atopy and cancer of the uterus. Abbreviations: A98, Allergy98; C36, 1936-cohort; H06, Health2006; I99, Inter99; M1, Monica1; CI, confidence interval.

TABLE E1. Hazard ratios and 95% confidence intervals for the associations between atopic status and incident cancer from two years after baseline

	Events (persons included)	Adjusted ^{&} HR (95% CI)
Any cancer	1,706 (13,366)	
Atopic vs. non-atopic		0.97 (0.86, 1.10)
		<i>P</i> = 0.636
Any cancer excluding NMSC	1,345 (13,536)	
Atopic vs. non-atopic		0.91 (0.79, 1.05)
		<i>P</i> = 0.213
Head and neck cancer	52 (13,865)	
Atopic vs. non-atopic		1.38 (0.73, 2.60)
		<i>P</i> = 0.317
Colorectal cancer	196 (13,862)	
Atopic vs. non-atopic		0.92 (0.63, 1.33)
		<i>P</i> = 0.646
Cancer of the bronchus and lung	228 (13,875)	
Atopic vs. non-atopic		0.78 (0.53, 1.14)
		<i>P</i> = 0.199
Breast cancer [*]	238 (7,039)	
Atopic vs. non-atopic		1.04 (0.75, 1.44)
		<i>P</i> = 0.807
Cancer of the uterus [*]	43 (7,112)	
Atopic vs. non-atopic		0.96 (0.44, 2.10)
		<i>P</i> = 0.915
Prostate cancer ^{**}	166 (6,743)	
Atopic vs. non-atopic		0.81 (0.54, 1.22)
		<i>P</i> = 0.309
Cancer of the urinary organs	70 (13,863)	
Atopic vs. non-atopic		1.15 (0.62, 2.13)
		<i>P</i> = 0.649
Malignant melanoma	64 (13,836)	
Atopic vs. non-atopic		0.72 (0.38, 1.36)
		<i>P</i> = 0.309
NMSC	484 (13,699)	
Atopic vs. non-atopic		1.16 (0.94, 1.44)
		<i>P</i> = 0.175

CI, confidence interval; *HR*, hazard ratio; *NMSC*, non-melanoma skin cancer.

Complete case analysis. Persons suffering from the cancer of interest at before and 2 years after baseline were excluded.

[&]Adjusted for study, gender, education, physical activity, smoking habits, alcohol intake, and body mass index (age is underlying time axis).

^{*}Only women included in the analyses.

^{**}Only men included in the analyses.