

Allergy and the risk of selected digestive and laryngeal neoplasms

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The relation between allergy and cancer has been investigated within an integrated series of case-control studies of digestive tract and laryngeal neoplasms conducted in Italy since the early 1990s. These included 598 patients with incident, histologically confirmed cancer of the oral cavity and pharynx, 304 of the oesophagus, 1225 of the colon, 728 of the rectum, 460 of the larynx and 4999 controls, selected among patients admitted to the same network of hospitals as cases for acute, non-neoplastic diseases. Inverse associations with history of allergy were found for all cancer sites examined (odds ratio=0.44 for oral cavity and pharynx, 0.80 for oesophagus, 0.76 for colon, 0.54 for rectum and 0.33 for larynx). The associations were consistent in strata of age and sex, and when subjects with a first diagnosis of allergy 5 or more years before cancer diagnosis or hospital admission were considered. The present study therefore provides further

evidence for a possible protective effect of prior history of allergy on cancer risk. *European Journal of Cancer Prevention* 13:173–176 © 2004 Lippincott Williams & Wilkins.

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Introduction

Several studies have considered the relation between allergy and cancer (Vena *et al.*, 1985; Källén *et al.*, 1993; Eriksson *et al.*, 1995; Talbot-Smith *et al.*, 2003). There are suggestions that allergic conditions may reduce the risk of lymphatic and haematopoietic neoplasms (Doody *et al.*, 1992; Holly *et al.*, 1999; Schüz *et al.*, 2003), gliomas (Schwartzbaum *et al.*, 2003) and pancreatic cancer (Bueno de Mesquita *et al.*, 1992; Dai *et al.*, 1995; Anderson *et al.*, 1996; Silverman *et al.*, 1999; Holly *et al.*, 2003), although the evidence remains inconsistent (McWorter, 1988; Farrow and Davis, 1990; La Vecchia *et al.*, 1990, 1992; Cooper *et al.*, 1996; Schwartzbaum *et al.*, 2003). Data are scanty and the evidence is even more conflicting for other forms of cancers (Kinlen, 1996), including digestive tract ones.

With specific reference to digestive tract neoplasms, a case-control study from the USA on more than 13 000 cancer cases and 4000 non-neoplastic controls reported a reduced risk of cancer of the oral cavity, pharynx, as well as larynx, in relation to various allergy-related conditions (Vena *et al.*, 1985). Another case-control study from Shanghai reported a reduced risk of oesophageal cancer in relation to history of allergy (Dai *et al.*, 1997). Two cohorts of asthmatic patients from Sweden and Finland reported a reduced risk of cancer of the lip, pharynx, oesophagus (Källén *et al.*, 1993) and of the larynx (Vesterinen *et al.*,

1993), compared with the national population. A moderate excess risk was reported, however, for adenocarcinoma of the oesophagus and gastric cancer in another cohort of asthmatic patients, which tended to be restricted to patients who also had a history of gastro-oesophageal reflux (Ye *et al.*, 2001). No association was found for squamous cell oesophageal cancer in the same study.

With reference to colorectal cancer, inverse relations with allergic conditions were found in case-control studies conducted in the USA (Vena *et al.*, 1985), Canada (Vobecky *et al.*, 1983) and Italy (La Vecchia *et al.*, 1991; Negri *et al.*, 1999), and in a Swedish cohort of asthmatics (Källén *et al.*, 1993). However, no clear picture emerged from a case-control study from Australia (Kune *et al.*, 1988), from cohort studies conducted in the USA (McWorter, 1988; Mills *et al.*, 1992) and Australia (Talbot-Smith *et al.*, 2003), as well as from a Finnish cohort of asthmatic patients (Vesterinen *et al.*, 1993).

We have collected information on history of allergic diseases in a uniform and structured way within an integrated series of case-control studies of digestive tract and laryngeal neoplasms conducted in Italy since the early 1990s. We have previously published results on colorectal cancer (Negri *et al.*, 1999), and provide here a comprehensive analysis based on more than 3300 digestive and laryngeal cancer cases and 5000 controls.

Materials and methods

Between 1991 and 2000 we conducted a series of case-control studies on digestive and laryngeal neoplasms in various regions of Italy. Detailed descriptions of the studies have been previously given (La Vecchia *et al.*, 1997; Franceschi *et al.*, 1999; Bosetti *et al.*, 2000, 2002). Briefly, the present analysis included 598 patients (512 men, 86 women) with cancer of the oral cavity and pharynx, 304 (275 men, 29 women) with squamous cell oesophageal cancer, 1225 (688 men, 537 women) with cancer of the colon, 728 (437 men, 291 women) with cancer of the rectum, and 460 (415 men, 45 women) with laryngeal cancer. In all studies, cases were incident and histologically confirmed cancers, diagnosed within 1 year from interview and with no previous history of cancer.

The comparison group included 4999 patients (2724 men, 2275 women) admitted to the same network of hospitals as cases for acute, non-neoplastic diseases, unrelated to known or likely risk factors for the neoplasms studied, including alcohol and tobacco consumption, and long-term modification of diet. Twenty-five per cent of controls were admitted for traumas, 30% for other non-traumatic orthopaedic conditions, 18% for acute surgical disorders, and 27% for other miscellaneous illnesses, including ear, nose, throat, skin and dental conditions. In all studies, response rate was over 95% for both cases and controls.

All subjects were interviewed using a standard questionnaire, including information on sociodemographic factors, anthropometric measures, general lifestyle habits, including tobacco smoking and alcohol consumption, physical activity, a validated food frequency section, and family history of cancer. The subjects were also asked if they have had a prior diagnosis of selected medical conditions, and the age at first diagnosis. A specific

question on allergy was included, covering a broad spectrum of conditions, such as allergic rhinitis, asthma, atopic dermatitis, etc. No data were collected on treatments.

Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were estimated using unconditional multiple logistic regression models (Breslow and Day, 1980), including terms for age, sex, study centre, years of education, body mass index, alcohol and tobacco consumption, plus a measure of physical activity for colon and rectum. The heterogeneity of estimates in strata of various covariates was tested by computing the difference in the $-2 \log$ likelihood between models with and without interaction terms, and referring it to the chi-square distribution with degrees of freedom equal to the number of interaction terms.

Results

Table 1 gives the distribution of selected digestive and laryngeal cancer cases and controls, and the corresponding ORs, according to history of allergy, and age at first diagnosis. Inverse associations with history of allergy were found for all cancer sites examined: the ORs were 0.44 (95% CI 0.26–0.75) for oral and pharyngeal cancer, 0.80 (95% CI 0.46–1.39) for oesophageal cancer, 0.76 (95% CI 0.59–0.97) for colon cancer, 0.54 (95% CI 0.37–0.77) for rectal cancer, and 0.33 (95% CI 0.18–0.61) for laryngeal cancer. The mean time between diagnosis of allergy and diagnosis of cancer was 19 years. The relations were apparently stronger in subjects with a diagnosis of allergy before 30 years of age for cancer of the oral cavity and pharynx (OR = 0.29) and the oesophagus (OR = 0.44), and in subjects with a diagnosis of allergy at 30 years or more for colon (OR = 0.71), rectal (OR = 0.42) and laryngeal cancer (OR = 0.25). The estimates, however, were not heterogeneous, and all the ORs were below

Table 1 Distribution of 598 cases with cancer of the oral cavity and pharynx, 304 of the oesophagus, 1225 of the colon, 728 of the rectum, and 460 of the larynx, and 4999 controls, according to history of allergy, with corresponding odds ratios (OR) and 95% confidence intervals (CI). Italy, 1991–2000

	History of allergy, OR ^a (95% CI)			
	Never ^b	Ever	Age at diagnosis	
			<30 years	≥ 30 years
Cancer cases				
Oral cavity and pharynx	579	19 0.44 (0.26–0.75)	6 0.29 (0.11–0.77)	13 0.54 (0.29–1.00)
Oesophagus	282	22 0.80 (0.46–1.39)	3 0.44 (0.12–1.65)	19 0.93 (0.51–1.70)
Colon	1145	80 0.76 (0.59–0.97)	28 0.86 (0.57–1.32)	52 0.71 (0.52–0.96)
Rectum	694	34 0.54 (0.37–0.77)	15 0.82 (0.47–1.42)	19 0.42 (0.26–0.68)
Larynx	446	14 0.33 (0.18–0.61)	6 0.54 (0.21–1.42)	8 0.25 (0.12–0.56)
Controls	4566	433	141	292

^aEstimates from unconditional multiple logistic regression models, including terms for age, sex, study centre, education, body mass index, alcohol and tobacco consumption, plus physical activity for colon and rectum.

^bReference category.

Table 2 Odds ratio (OR) and corresponding 95% confidence intervals (CI) for selected digestive and laryngeal cancers according to history of allergy, in strata of sex and age. Italy, 1991–2000

Cancer	History of allergy, OR ^{a,b} (95% CI)			
	Sex		Age	
	Male	Female	< 60 years	≥ 60 years
Oral cavity and pharynx	0.29 (0.15–0.57)	1.64 (0.67–4.05)	0.40 (0.19–0.82)	0.47 (0.21–1.06)
Oesophagus	0.76 (0.42–1.37)	1.23 (0.28–5.50)	0.74 (0.34–1.61)	0.86 (0.39–1.92)
Colon	0.57 (0.39–0.85)	1.00 (0.71–1.41)	0.98 (0.70–1.37)	0.56 (0.38–0.82)
Rectum	0.59 (0.37–0.95)	0.49 (0.27–0.87)	0.49 (0.28–0.85)	0.58 (0.36–0.94)
Larynx	0.34 (0.18–0.65)	0.34 (0.04–2.69)	0.54 (0.24–1.23)	0.20 (0.08–0.51)

^aEstimates from unconditional multiple logistic regression models, including terms for age, sex, study centre, education, body mass index, alcohol and tobacco consumption, plus physical activity for colon and rectum.

^bReference category: no history of allergy.

unity. A similar inverse relation with history of allergy was observed excluding subjects who reported to be first diagnosed within 5 years before cancer diagnosis, or admission to hospital (OR = 0.34 for oral cavity and pharynx, 0.60 for oesophagus, 0.83 for colon, 0.61 for rectum and 0.37 for larynx).

The ORs for selected digestive and laryngeal cancers in relation to history of allergy were also analysed in strata of sex and age at cancer diagnosis (Table 2). Inverse associations for oral and pharyngeal, oesophageal and colon cancers were observed in men. The estimates for cancers of the oral cavity, pharynx and oesophagus among women were however based on a very small numbers of subjects, given the rarity of these neoplasms in women. No differences between men and women were observed for cancers of the rectum and larynx. Likewise clear pattern emerged across strata of age (< 60 years and ≥ 60 years).

Discussion

The present study, based on more than 3000 cases of digestive tract and laryngeal cancers, provides further evidence for a protective effect of prior history of allergy on cancer risk. Significant inverse associations have been found for all cancer sites considered, in agreement with previous results on colorectal cancer (Vobecky *et al.*, 1983; Vena *et al.*, 1985; La Vecchia *et al.*, 1991; Källén *et al.*, 1993; Negri *et al.*, 1999) and other digestive and laryngeal cancers (Vena *et al.*, 1985; Källén *et al.*, 1993; Vesterinen *et al.*, 1993; Dai *et al.*, 1997). Similar protective effects for asthma and allergic diseases in general have also been reported for other digestive tract cancers, including those of the pancreas (Bueno de Mesquita *et al.*, 1992; Dai *et al.*, 1995; Anderson *et al.*, 1996; Silverman *et al.*, 1999; Holly *et al.*, 2003), liver (La Vecchia *et al.*, 1990) and stomach (Källén *et al.*, 1993; Vesterinen *et al.*, 1993). Our results, however, are not in agreement with other studies, which did not support an inverse relation of allergic conditions and digestive cancers (Kune *et al.*, 1988; McWorter, 1988; Ye *et al.*, 2001; Mills *et al.*, 1992; Vesterinen *et al.*, 1993; Talbot-Smith *et al.*, 2003). These inconsistent results may be due to the small numbers of cases in several studies,

variable definition of allergic conditions, and inadequate adjustment for confounding factors. More important, publication bias is a relevant issue, since significant results may have been selectively published.

The results were consistent across strata of sex, age and other covariates, and were essentially unchanged after subjects with a recent diagnosis of allergy were excluded from the analysis, thus confirming a possible causal role of allergy in the development of cancer.

Potential sources of bias should be considered in the interpretation of the results. In particular, recall bias could be of concern, since in our study information on history of allergy was self-reported, and no clinical confirmation of the disease was available. Allergy-related diseases are however likely to be adequately recalled, since they usually involve long-term treatments. Further, information of history of allergy collected in our studies was satisfactorily reproducible (Bosetti *et al.*, 2001). Hospital controls may differ from the general population in several aspects of medical history, but careful attention was paid to exclude from the control group subjects with diagnosis likely related to chronic diseases such as the allergic conditions studied, and the comparable results obtained across different disease categories are reassuring against any possible selection or information bias. Moreover, the hospital setting may have improved the comparability of information on medical history. Among other strengths of the study are the comparable catchment area of cases and controls, the almost complete participation and the adjustment for a large number of potential confounding factors for the cancers studied, including body mass index, tobacco and alcohol consumption, plus physical activity for cancers of the colon and rectum.

A possible interpretation of the inverse relation between history of allergy and cancer risk can be related to a stimulation of the immune system induced by allergic conditions. It is indeed possible that individuals with a prior history of allergic conditions have a modified and enhanced immune response to carcinogens or malignant

cells, and are consequently at lower risk of developing cancer (Vena *et al.*, 1985; Kripke, 1988; Roitt *et al.*, 1989). However, the general nature of the information on allergy collected in our studies, and the lack of any measure of the degree of atopy in these patients does not provide insight into the underlying immunologic mechanisms. The association between allergy and cancer appears in any case complex and far from being adequately understood, given the inconsistencies of the findings for various cancer sites and different types of allergic diseases.

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