

Brief Communication

A Case-Control Study of Asthma and Ovarian Cancer

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ABSTRACT. Epidemiologic studies have found inverse associations between allergy and the development of certain tumors. The authors sought to determine if there was an association between asthma and ovarian cancer. A case-control study was conducted using Florida hospital data (year 2001). Discharge diagnoses were coded using the ICD-9-CM (*International Classification of Diseases, Ninth Revision, Clinical Modification*). Cases were 1,582 women whose principal discharge diagnosis was a malignant neoplasm of the ovary. Two control series were used: 4,744 women whose principal diagnosis was an upper limb bone fracture, and 21,830 women whose principal diagnosis was an acute myocardial infarction. Odds ratios (ORs) adjusted for age, race-ethnicity, Medicaid status, obesity, and smoking were calculated. Cases were 30% less likely than fracture control to be asthmatics (adjusted OR = 0.70, 95% confidence interval [CI]: 0.49–0.99, $p = .04$). Similarly, cases when compared to acute myocardial infarction controls were significantly less likely to have asthma (adjusted OR = 0.62, 95% CI: 0.45–0.87, $p = .005$). The results of this statewide exploratory study suggest that individuals with asthma may have a lower risk of developing ovarian cancer than nonasthmatics.

KEYWORDS: asthma, case-control study, epidemiology, hospital databases, ovarian cancer, Florida

Epidemiologic studies have found inverse associations between allergy and the development of certain tumors.^{1,2} Turner and colleagues reported that a history of both asthma and hay fever protected against colorectal cancer mortality.¹ Brenner et al found an inverse association between a history of any allergies and glioma.² Laboratory data support the hypothesis that allergies reduce the risk of glioma. Interleukin-4, a cytokine that plays a prominent role in the allergic response, has been shown to inhibit the growth of glioma cells in vitro.^{3,4} The likely mechanism of this antitumorigenic activity is inhibition of tumor angiogenesis.⁵

Certain previous investigators have either not focused on gynecologic malignancies when studying allergic conditions and cancer outcomes^{2,4} or simply have not found a significant correlation between allergy and gynecologic

tumors.¹ Turner et al examined the relationship between self-reported physician-diagnosed asthma and/or hay fever and the outcome of mortality due to various cancers.¹ They did not detect any association between allergy and ovarian cancer mortality, or allergy and mortality due to cancer of the corpus and uterus not otherwise specified. Kallen and colleagues studied the risk of 30 different types of cancer in Swedish asthmatics and found that asthmatics were 48% less likely than nonasthmatics to develop ovarian cancer.⁶

To address the paucity of literature in this area, we conducted a case-control study to determine if there was an association between asthma and malignant neoplasms of the ovary. A statewide hospital discharge database was the setting of our epidemiologic study.

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METHODS

Source Population

Retrospective analyses were performed using a hospital discharge data set that was obtained from the Florida Agency for Health Care Administration (Tallahassee, Florida). This public-use database includes discharge summaries from all non-federal Florida hospitals except state tuberculosis and state mental health hospitals. After data are entered into this system, they are subjected to formatting and logic checks. The primary hospital submitting patient information must then certify the data are correct and verify the accuracy of a summary report before it is released by the Agency for Health Care Administration.

The overall data set contained clinical and demographic information for 2,343,330 patients who were hospitalized for at least 1 day and discharged in calendar year 2001. The principal diagnosis and up to 9 secondary diagnoses were coded using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). According to the data dictionary supplied by the Florida Agency for Health Care Administration, the principal diagnosis, "... is the condition established after study, to be chiefly responsible for occasioning the admission of the patient to the hospital."

Identification of Cases and Controls

Ovarian cancer was defined as ICD-9-CM code 183.0 (malignant neoplasm of ovary). Cases were women who had this code in their principal diagnosis field. To ensure a more homogenous group of histologies, only female patients 20 years of age or older were included in our analysis. For example, a primary malignant neoplasm of the ovary identified using ICD-9-CM code 183.0 may be a germ cell tumor rather than an epithelial ovarian cancer. The former morphology (germ cell tumor) is more common in children than in adults among patients who have primary ovarian malignancies.

Two control series were used. The first series was composed of women who had a principal diagnosis of a fracture of an upper limb (ICD-9-CM codes 810–819) and did not have a secondary diagnosis of ovarian cancer. Codes 810 through 819 include fractures of the clavicle, humerus, and metacarpal bones. The second group of controls was comprised of women who had a principal diagnosis of acute myocardial infarction (AMI) (ICD-9-CM code 410) and did not have a secondary diagnosis of ovarian cancer. These 2 conditions (fractures and AMI) were chosen in an effort to identify women who had serious morbidity but who were free of ovarian cancer, thereby creating 2 control series that had similar probabilities of having asthma noted in their electronic records as the cases. As with the case series, controls were selected from the group of women who were 20 years of age or older.

Asthma was the exposure variable of interest. Asthma was defined as the presence of ICD-9-CM code 493 in any of the 9 secondary diagnosis positions.

Statistical Analysis

Data were analyzed using The SAS System for Windows 9.1 (SAS Institute, Cary, NC). Unadjusted and adjusted asthma exposure odds ratios (ORs) were calculated using PROC LOGISTIC. An OR was considered statistically significant if the 95% confidence interval for the population OR excluded the null value of 1.

The following variables were treated as confounders and were entered into the full model: Age (in years), race/ethnicity, health insurance status, current or former smoker, and obesity. Harmful correlations between the independent variables (collinearity) were not detected.

In our data set, Hispanic ethnicity and race were not treated as mutually exclusive categories. Race/ethnicity was originally an 8-level variable (7 racial ethnic groups plus a category for missing). This variable was converted to a 4-level categorical variable due to the small numbers of patients in certain racial-ethnic groups: White Hispanic, Black non-Hispanic, Other racial/ethnic group, and White non-Hispanic (referent). Asian and Pacific Islanders, Black Hispanics, American Indians/Eskimo/Aleut, and patients of Other racial/ethnic groups were collapsed into a new Other group. Our binary health insurance variable was created using the principal payer variable (a polytomous variable) found in the database. Patients who were Medicaid beneficiaries, that is, patients whose principal payor was listed as Medicaid or a Medicaid health maintenance organization, were compared to the remaining patients. This referent category included several groups including Medicare beneficiaries, Veteran's Affairs, charity, and patients with commercial health insurance.

Given that obesity may be linked to ovarian cancer and has been shown to increase the incidence of asthma and reduce asthma control, we considered obesity to be a potential confounder in our analysis.^{7,8} Obesity (including morbid obesity) was defined as the occurrence of ICD-9-CM codes 278.00 or 278.01 in any of the secondary discharge diagnosis fields. Cigarette smoking has been identified as a risk factor for mucinous ovarian cancer.⁹ If either of the following codes were found in the patient's record, she was considered to be a current or former smoker: 305.1 (Tobacco use disorder) or V15.82 (History of tobacco use).

Multiparity and oral contraceptive use were both initially identified as potential confounders in our study but could not be included in our adjusted model. Compared to nulliparous women, parous women have a lower risk of developing epithelial ovarian cancer.¹⁰ Multiparity was defined as ICD-9-CM code V61.5. The inverse relationship between oral contraceptive use and ovarian cancer is well known.¹⁰ The ICD-9-CM codes indicating oral contraceptive use are V25.01 and V25.41. We could not evaluate oral contraceptive use or the multiparity variable for confounding since none of the cases and controls had these ICD-9-CM codes in their discharge records.

Table 1.—Demographic and Clinical Characteristics of the Study Population

Characteristic	Ovarian cancer cases (<i>n</i> = 1582)	Fracture controls* (<i>n</i> = 4744)	Acute myocardial infarction controls* (<i>n</i> = 21,830)
Asthmatic, <i>n</i> (%)	42 (2.7)	170 (3.6)	782 (3.6)
Median age in years (min–max) [†]	63 (20–96)	75 (20–105)	76 (20–110)
Race/ethnicity, <i>n</i> (%)			
White Hispanic	131 (8.3)	469 (9.9)	2,362 (10.8)
Black non-Hispanic	105 (6.6)	199 (4.2)	1,799 (8.2)
Other race/ethnicity	57 (3.6)	79 (1.7)	413 (1.9)
White non-Hispanic	1,289 (81.5)	3,997 (84.3)	17,256 (79.1)
Medicaid beneficiary, <i>n</i> (%)	96 (6.1)	152 (3.2)	799 (3.7)
Obese, <i>n</i> (%)	37 (2.3)	154 (3.3)	1,371 (6.3)
Smoker, <i>n</i> (%)	102 (6.5)	301 (6.3)	2,856 (13.1)

*Controls were women who had either a principal discharge diagnosis of an upper limb bone fracture or acute myocardial infarction and did not have a secondary diagnosis of ovarian cancer.

[†]Women under 20 years of age were excluded.

A total of 1,582 ovarian cancer cases, 4,744 fracture controls, and 21,830 AMI controls were identified. Analyses of this data set were deemed exempt from formal review by the Institutional Review Board of the Texas Tech University Health Sciences Center School of Medicine at El Paso.

RESULTS

Demographic and clinical features of the study subjects are shown in Table 1. The ovarian cancer cases were younger than either of the 2 control series. The cases were approximately twice as likely as the fracture controls to be Medicaid beneficiaries (6.1% compared to 3.2%). The prevalence estimates of obesity and smoking were highest in the AMI controls.

Unadjusted and adjusted exposure ORs are presented in Table 2. Neither of the unadjusted ORs is statistically significant. After controlling for the 5 demographic and clinical factors listed in Table 1, ovarian cancer cases were 30% less likely than upper limb bone fracture controls to be asthmatic (adjusted OR = 0.70). This result is statistically significant at the .05 level, since the 95% confidence interval excludes 1. Similarly, the asthma OR when AMI controls were used indicated a protective association for the outcome of ovarian cancer (adjusted OR = 0.62, *p* = .005).

COMMENT

The body of evidence linking allergy or allergy-related conditions to cancer contains conflicting results. Certain previous investigators have found inverse associations between allergy and cancer, whereas others have found positive relationships between allergy and malignant neoplasms. Our study found that asthma was associated with ovarian cancer in an inverse manner. We chose to focus on asthma because

the sensitivity and specificity of the ICD-9-CM coding of asthma in an inpatient database is most likely higher than that of less serious conditions such as allergic rhinitis. However, the proportion of asthma that is attributable to allergy is usually less than 50% and hence the use of asthma as a marker for allergy is a limitation of our study.¹¹ If a protective effect of asthma on ovarian cancer risk does exist, then it may be due to other mechanisms.

This study has several strengths. First, we utilized a large, statewide database obtained from the Florida Agency for Health Care Administration. The majority of civilian hospitals in Florida are required to report their discharge data to the Agency for Health Care Administration. Second, we used 2 control series to minimize the chance of reporting a false association. Finally, our results are similar to those of a large study conducted by Kallen and colleagues. Kallen et al.⁶ found a statistically significant reduction in the risk of cancer of the ovary in 64,346 asthmatics (standardized morbidity ratio = 0.52). Unlike Kallen et al.,⁶ however, we did not test the association between asthma and a large number of tumors. Kallen and colleagues calculated standardized morbidity ratios for 30 types of cancer. Instead we focused on a single outcome, ovarian cancer. Multiple significance testing tends to increase the type I error or false-positive rate.

Other investigators have reported elevated but statistically nonsignificant measures of association. Among Swedish residents who were skin prick tested at an allergy clinic, the standardized incidence ratio for ovarian cancer was 1.37 (95% confidence interval: 0.17–4.96) in asthmatics, and 1.95 (0.53–5.00) in rhinitis sufferers.¹² McWhorter¹³ found an OR of 1.62 for the combined outcome of uterine, cervical, and ovarian cancers associated with the presence of any allergy, which was defined as asthma, hay fever, hives, food allergy, or other allergy. This OR was adjusted for age, race,

Table 2.—Unadjusted and Adjusted* Odds Ratios for the Association Between Asthma (Present versus Absent) and the Outcome of Ovarian Cancer

Control Series	Unadjusted odds ratio	95% CI†	p value	Adjusted odds ratio	95% CI†	p value
Upper limb bone fracture	0.73	0.52–1.03	.08	0.70	0.49–0.99	.04
Acute myocardial infarction	0.73	0.54–1.01	.055	0.62	0.45–0.87	.005

Note. Women with ovarian cancer were compared to women free of ovarian cancer who had suffered an upper limb bone fracture or myocardial infarction.

*Each adjusted odds ratio is adjusted for age, race-ethnicity, Medicaid status, obesity, and smoking.

†CI = confidence interval.

smoking status, gravidity, and body mass index, and was not statistically significant at the .05 level: 95% confidence interval: 0.75–3.51.

Studies of hospitalized patients in which both the potential risk factor and the outcome are diseases are prone to Berkson's bias.¹⁴ Berkson was a physician at the Mayo Clinic who reported the following phenomenon in 1946^{14,15}: 2 diseases may appear to be correlated with one another in a hospital-based case-control study when in fact they are not simply because individuals with 2 or more conditions are more likely to be hospitalized than patients with 1 disease. The OR from a hospital-based case-control study could be higher or lower than the OR from a similar community-based study.¹⁶ To minimize the probability of committing Berkson's bias, we used controls whose principal discharge diagnoses were not asthma or allergic conditions.¹⁶

Our public-use hospital data set did not contain a unique patient identification number. It is possible that our sample included multiple records of the same individual. Had we been able to identify readmissions, then we could have either deleted subsequent records or included them and accounted for the correlated nature of the data using generalized estimating equations. A failure to account for this violation of statistical independence results in *p* values that are spuriously smaller and confidence intervals that are narrower.

The Florida hospital data set contained the records of 1,577 women who had the ICD-9-CM code for ovarian cancer in their principal discharge diagnosis field and were 20 year of age or older and were Florida residents (data not shown). In comparison, the State of Florida's tumor registry documented 1,530 incident/new cases of ovarian cancer in Florida residents who were 20 years of age or older in year 2001 (personal communication: Jill A. MacKinnon, PhD, CTR, Project Director, Florida Cancer Data System, Miami, Florida). The similarity of these 2 figures (the former figure is only 3.1% higher than the latter) suggests that our study did not contain a higher number of multiple records per patient. For our study we did exclude a small number of patients who had a missing value for race and did not exclude non-Florida residents and therefore it impossible to determine exactly the number of

“duplicate” records using the Florida cancer registry as the gold standard.

A confounder is a variable that is associated with the risk factor (the exposure) and independent of the risk factor is correlated with the outcome. Obesity has been linked to both asthma (our risk factor) and ovarian cancer (the outcome). Obesity leads to inflammation, which may act on the lungs to exacerbate asthma and this action may be mediated by the hormones leptin and adiponectin.⁸ In regards to confounding, we attempted to adjust for obesity; however, this variable may not be recorded faithfully in an electronic hospital discharge record. Similarly, the prevalence rates of smoking in the 3 groups (cases, fracture controls, and AMI controls) reported in Table 1 most likely underestimate the true burden of tobacco use in hospitalized adults. Nonetheless, we do not believe that our cancer cases were more or less likely to have their obesity or tobacco use status misclassified compared to the controls.

We performed sensitivity analyses for unmeasured confounding using standard formulae¹⁷ and recent data on the relationship between obesity, smoking, and ovarian cancer.^{18,19} These calculations also utilized female obesity and tobacco prevalence data from the Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System (Florida estimates)²⁰ and resulted in externally adjusted asthma ORs for ovarian cancer that were similar to our crude OR found in Table 2 for fracture controls (data not shown). These results are available from the corresponding author.

The prevalence of obesity in our cases (2.3%) was lower than the prevalence rates found in the 2 control series (Table 1). This counterintuitive finding merits further discussion. We were unable to distinguish between prevalent (existing) and incident (new) cases of ovarian cancer in our study. Therefore a lower rather than higher prevalence of obesity in our ovarian cancer cases compared to controls may simply be a reflection of the effect of cancer and/or cancer treatment on a patient's body weight. A recent Australian case-control study that found that obesity (defined as a body mass index of 30 or more) was not associated with invasive serous tumors of the ovary and fallopian tube: adjusted OR = 0.80, 95% confidence interval: 0.6–1.0.¹⁸

Our sample contained no data on oral contraceptive use; however, this is not a major limitation. For oral contraceptive use to be a confounder in our epidemiologic study, it must be both associated with the risk factor under study (asthma) and the outcome. Oral contraceptive use is related to our outcome (the development of ovarian cancer), but one would not expect the presence of asthma to be associated with the use of oral contraceptives. To clarify, we have no reason to believe that asthmatics have a higher or lower prevalence of oral contraceptive use than women who are not asthmatics. Finally, our study sample is a very select population. The subjects were not composed of nonhospitalized individuals; nonetheless, this was an exploratory study.

In conclusion, our retrospective case-control study found that women with ovarian cancer were 30% to 38% less likely than women free of ovarian cancer to be asthmatics. Further laboratory and epidemiologic studies are required in this area. In particular, prospective cohort studies of the impact of asthma on cancer risk are warranted. A prospective study design would allow for the optimal control of confounders and elucidation of what proportion of asthmatics had atopic disease.

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