Research Article

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The Association between Age-Related Macular Degeneration and Renal Cell Carcinoma: A Nested Case–Control Study

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Abstract

Background: Overexpression of VEGF is implicated in the pathogenesis of both renal cell carcinoma (RCC) and age-related macular degeneration (AMD). We evaluated the association between AMD and RCC risk.

Methods: We conducted a matched case–control study within a population-representative database from the United Kingdom. Study cases were defined as individuals with any diagnostic code of RCC. For every case, four eligible controls were matched on age, sex, practice site, calendar time, and duration of follow-up. Exposure of interest was diagnosis of AMD prior to cancer diagnosis. Adjusted ORs and 95% confidence intervals (CI) for RCC were estimated using conditional logistic regression. In a secondary analysis, we evaluated the association between other retinopathies and RCC and AMD and the hypovascular pancreatic cancer.

Results: The study population included 1,547 patients with RCC and 6,066 matched controls. Median follow-up time was 6 years (IQR, 3–9). AMD diagnosis was associated with a significantly increased RCC risk (OR, 1.89; 95% CI, 1.09–3.29). In contrast, there was no association between other retinopathies and RCC risk (OR, 0.8; 95% CI, 0.56–1.15). AMD was associated with a lower risk for pancreatic cancer (OR, 0.47; 95% CI, 0.35–0.64).

Conclusions: Patients with AMD may be at higher risk for RCC. Providers should be aware of this potential link and consider screening for RCC within this population.

Impact: Providers should be aware of the potential link between AMD and RCC. *Cancer Epidemiol Biomarkers Prev; 26(5); 743–7. ©2017 AACR.*

Introduction

Overexpression of VEGF has been implicated in the pathogenesis of both renal cell carcinoma (RCC), the most common cancer of the kidney (1, 2), and age-related macular degeneration (AMD; refs. 3, 4), the leading cause of blindness in the western population (5). Anti-VEGF agents are also commonly used and have significantly improved the management of both RCC (6) and AMD (7). In addition, AMD and RCC share other similar risk factors, including cigarette smoking, hypertension, obesity, and activation of genes involved in inflammation and oxidative stress (8, 9).

To date, there are no data on a potential association between AMD and RCC risk. The only prior study to assess the association between AMD and cancer had small sample size and was able to demonstrate higher cancer-associated mortality only among lung cancer patients with AMD (8).

In this nested case–control study, we sought to analyze the association between AMD and RCC risk in a large population-representative cohort. If present, this association may have clinical significance in defining a novel group of individuals at higher risk for RCC that may benefit screening. Currently, individuals at higher risk for RCC due to genetically inherited syndromes, such as von Hippel–Lindau disease, are often recommended regular abdominal imaging.

Materials and Methods

Study design

We conducted a nested case–control study with incidence density sampling to examine the association between AMD and RCC risk. The study was approved by the Institutional Review Board at the University of Pennsylvania (Philadelphia, PA) and by the Scientific Review Committee of The Health Improvement Network (THIN).

Data source

THIN, is a large population-based electronic medical records database from the United Kingdom, containing comprehensive information on approximately 11 million patients (more than 5% of the United Kingdom population) treated by general practitioners. The demographic and geographic distributions of the THIN population are broadly representative of those in the general United Kingdom population (10). All practices contributing data to THIN follow a standardized protocol of

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Table 1. Characteristics of RCC cases and matched controls

Variable	Cases ($n = 1,547$)	Controls ($n = 6,066$)	*P*
Age (median, IQR)	68.5 (59.1–76.6)	68.2 (59.1–76.2)	NA
Male sex (*n*, %)	959 (62.0)	3,752 (61.9)	NA
Duration of follow-up (median, IQR)	6.0 (3.0–9.0)	6.0 (3.0–9.0)	NA
Obesity (*n*, %)	402 (26.0)	1,187 (19.6)	<0.0001
Ever smoking (*n*, %)	803 (51.9)	2,521 (41.6)	<0.0001
Hypertension (*n*, %)	602 (38.9)	1,743 (28.7)	<0.0001
Diabetes mellitus (*n*, %)	204 (13.2)	535 (8.8)	<0.0001
Hyperlipidemia (*n*, %)	526 (34.0)	1,674 (27.6)	<0.0001

entering information and transmitting information to the central database. Each medical diagnosis is defined using read diagnostic codes, which is the standard coding system used by general practitioners in the United Kingdom (11, 12). The data quality is monitored through routine analysis of the entered data to determine whether the protocol has been followed and to perform quality assessment checks. Data from practices that fail to meet criteria are not entered as valid data onto the database (13).

Numerous pharmacoepidemiologic studies have been performed using THIN and have shown excellent quality of information on medical diagnosis and cancer specifically (10, 13–15).

Study cohort

All people receiving medical care from 1995 to 2013 from a THIN practitioner were potentially eligible for inclusion. Follow-up started at the later of either the date of the THIN practice started using the electronic medical record software, or the date at which the patient registered with their general practitioner, and ended on the earliest of RCC diagnosis date, date of death, transferring out of the database, or the end date of the database.

Case selection

Cases were defined as all individuals in the cohort with at least one medical code for RCC during follow-up period medcode (B4A.11, B4A0000, B4A1.00, B4A1000, B4A1z00, BB5a000, BB5a011, BB5a012, BBL7.00, BBL7z00). Index date was defined as the date of RCC diagnosis. The coding for RCC included all stages of disease.

Selection of controls

Selection of the control group was based on incidence density sampling (16, 17). The potentially eligible control pool for each case comprised of all individuals from the THIN database who remained at risk for RCC on the calendar date when the case patient was first diagnosed with the disease. For each case, up to 4 eligible control patients were randomly selected matched on age, sex, practice site, and both calendar time and duration of follow-up. Controls were assigned the same index date as their matched cases.

Exposures and covariates

The primary exposure of interest was any diagnosis of AMD (according to medical codes) before RCC diagnosis in cases and corresponding index date in controls. As possible confounders, we evaluated obesity (defined as BMI >30 kg/m^2), smoking status (defined as ever vs. never smoking), and a comprehensive list of medical comorbidities associated with the metabolic syndrome, including diabetes mellitus, hypertension, and hyperlipidemia, all known risk factors for RCC that are also associated with several diseases of the retina (18–20).

Statistical analysis

The baseline characteristics of cases and controls were compared using χ^2 tests for categorical variables and *t* tests for continuous variables. The primary analysis was a multivariable conditional logistic regression to estimate ORs and 95% confidence interval (CI) for the association between AMD and RCC risk. As tumorigenesis is a multistep process occurring over a period of several years, we further analyzed only AMD cases that were diagnosed more than one year prior to RCC diagnosis. The analyses were stratified according to age, a known risk factor for both RCC (more prevalent among males) and AMD (more prevalent among females). In secondary analyses, we also evaluated the association between other retinopathies (mainly diabetic and hypertensive retinopathies) and RCC risk and between AMD and cancers other than RCC, such as bladder cancer, to evaluate possible shared risk factors (e.g., smoking) other than angiogenesis. In addition, we evaluated the association between AMD and pancreatic cancer, a malignancy characterized by fibrous stroma and hypovascularity in contrast to the hypervascularity of RCC. Adjustment was performed according to two models: adjustment for classical confounders associated with both AMD and RCC, such as smoking, obesity, and hypertension, and adjustment for classical confounders as well as factors associated with the metabolic syndrome, such as diabetes and hyperlipidemia. All statistical analyses were performed using STATA 13 (STATA Corp). All statistical tests were two-sided.

Results

The study population included 1,547 individuals with RCC and 6,066 matched controls. The median age of the study

Table 2. The association between AMD and RCC risk stratified according to sex

Model	Cases with AMD (*n*, %)	Controls with AMD (*n*, %)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Overall	21 (1.4)	43 (0.7)	1.99 (1.15–3.44)	1.91 (1.10–3.32)	1.89 (1.09–3.29)
Males	11 (1.2)	23 (0.6)	1.97 (0.92–4.18)	1.79 (0.84–3.82)	1.78 (0.83–3.80)
Females	10 (1.7)	20 (0.9)	2.02 (0.91–4.45)	2.07 (0.93–4.61)	1.97 (0.87–4.45)

Abbreviation: CI, confidence interval.

[a]Model 1: Adjusted for obesity (BMI > 30), ever smoking, and hypertension.

[b]Model 2: In addition to model 1, adjusted for medical history of diabetes mellitus and hyperlipidemia.

Table 3. The association between AMD and RCC risk stratified according to sex only among patients diagnosed with AMD more than 1 year before cancer diagnosis

Model	Cases with AMD (*n*, %)	Controls with AMD (*n*, %)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Overall	17 (1.1)	31 (0.5)	2.21 (1.21–4.03)	2.30 (1.25–4.23)	2.27 (1.23–4.19)
Males	7 (0.7)	15 (0.4)	1.90 (0.76–4.73)	1.94 (0.77–4.89)	1.93 (0.76–4.87)
Females	10 (1.7)	16 (0.7)	2.49 (1.11–5.57)	2.64 (1.17–5.97)	2.53 (1.10–5.80)

Abbreviation: CI, confidence interval.
[a]Model 1: Adjusted for obesity (BMI > 30), ever smoking, and hypertension.
[b]Model 2: In addition to model 1, adjusted for medical history of diabetes mellitus and hyperlipidemia.

population was 68.2 [interquartile range (IQR), 59.1–76.3]; 61.9% were males and the median duration of follow-up before index date was 6 years (IQR, 3–9). Characteristics of cases and controls are presented in Table 1. As expected, cases were more likely to be obese, ever smokers, or have a medical history of diabetes, hypertension, and hyperlipidemia, as part of the metabolic syndrome.

The prevalence of AMD diagnosis was higher in cases compared with controls (1.4% vs. 0.7%, respectively). AMD diagnosis before index date was associated with a significantly elevated risk of RCC in the entire study population (adjusted OR, 1.89; 95% CI, 1.09–3.29). There was no change in risk after stratification according to gender with an OR of 1.78 (95% CI, 0.83–3.80) and 1.97 (95% CI, 0.87–4.45) for males and females, respectively (Table 2).

The association between AMD and RCC was also present when AMD was defined as patients who were diagnosed more than one year prior to RCC diagnosis to assess possible reverse causality (in which contrary to the presumption, the outcome preceded the exposure). This association was seen both in the entire study population (OR, 2.27; 95% CI, 1.23–4.19) as well as after stratification according to gender (OR, 1.93; 95% CI, 0.76–4.87 for males and OR, 2.53; 95% CI, 1.10–5.80 for females; Table 3).

Furthermore, there was no association between other retinopathies and RCC risk or between AMD and bladder cancer risk with ORs of 0.80 (95% CI, 0.56–1.15) and 0.99 (0.81–1.20) respectively (Tables 4 and 5). Of interest, AMD was associated with a significantly lower risk for pancreatic cancer (OR, 0.47; 95% CI, 0.35–0.64) a known hypovascular malignancy (Table 5).

Discussion

The current large nested case–control study demonstrated a significantly higher RCC risk among individuals with prior diagnosis of AMD (OR, 1.89). The association persisted after adjustment to known risk factors for RCC and AMD, including metabolic risk factors and after a 1-year time lag to minimize reverse causality. The risk did not change after stratification according to gender.

As hypertension and diabetes are common risk factors for RCC, patients are more likely to be evaluated by an ophthalmologist due to their higher risk for retinopathies. To rule out this possible bias, we assessed the association between other retinopathies and RCC risk and observed no change in risk. We also evaluated the association between AMD and bladder cancer that share similar risk factors to RCC and observed no increase in cancer risk. Of note, angiogenic pathways are important in RCC tumorigenesis and less so in bladder cancer development.

Our results are in accordance with a previous study that described higher cancer mortality among patients with AMD (8). However, the current study is the first to describe the association between AMD and RCC risk. Although the association between AMD and cancer risk is incompletely characterized, it is possible that overexpression of the VEGF and the resulting persistent stimulation of its receptor may explain the association between AMD and RCC. Abnormal angiogenesis has been implicated in the pathogenesis of both RCC (1, 2) and AMD (3, 4), and anti-VEGF agents are commonly used for the treatment of both conditions (6, 7). To evaluate the role of this biological pathway in the above association, we further examined the association between AMD and pancreatic cancer, which is a known hypovascular malignancy (21) and found a significantly lower cancer risk (OR, 0.47).

The current study has several strengths. Under the UK National Health Services, 98% of the United Kingdom population receives health care through general practitioners; therefore, the data in THIN reflect the general health care delivery pattern for the entire UK population (22). The diagnostic codes used in THIN have been previously validated, specifically for cancer, ensuring the high quality of case identification (22). The use of incidence density sampling ensured that the ORs generated are interpretable as incidence rate ratios (16-7).

Several potential limitations warrant consideration in this study. The THIN database lacks information regarding tumor staging. Thus, we were unable to evaluate the association between cancer stage and AMD. It is possible that more advanced cancers have higher levels of VEGF and are more commonly associated with AMD. The median duration of follow-up before index date (6 years) in our cohort may be relatively short and limit our ability to evaluate the full influence of AMD on tumor initiation and progression; however, as we observed a significant effect in our analyses, this is probably not an issue (22). Furthermore, we did not have full information regarding dry and wet types of AMD;

Table 4. The association between other retinopathies and RCC risk

Model	Cases with retinopathies (*n*, %)	Controls with retinopathies (*n*, %)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Other retinopathies	52 (3.4)	174 (2.9)	1.18 (0.85–1.62)	0.96 (0.69–1.33)	0.80 (0.56–1.15)
Retinopathies diagnosed >1 year prior to cancer diagnosis	37 (2.4)	82 (1.4)	1.80 (1.20–2.70)	1.47 (0.98–2.22)	1.29 (0.84–2.00)

Abbreviation: CI, confidence interval.
[a]Model 1: Adjusted for obesity (BMI > 30), ever smoking, and hypertension.
[b]Model 2: In addition to model 1, adjusted for medical history of diabetes mellitus and hyperlipidemia.

Table 5. The association between AMD and other malignancies

Model	Cases with AMD (*n*, %)	Controls with AMD (*n*, %)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Bladder cancer (13,440 cases and 52,421 controls)					
All AMD	139 (1.0)	514 (1.0)	1.03 (0.85–1.25)	0.99 (0.81–1.20)	0.99 (0.81–1.20)
AMD diagnosed >1 year prior to cancer diagnosis	114 (0.8)	424 (0.8)	1.03 (0.83–1.27)	0.99 (0.80–1.23)	0.99 (0.80–1.23)
Pancreatic cancer (4,113 cases and 16,072 controls)					
All AMD	49 (1.2)	350 (2.2)	0.53 (0.39–0.72)	0.47 (0.35–0.64)	0.47 (0.35–0.64)
AMD diagnosed >1 year prior to cancer diagnosis	37 (0.9)	153 (1.0)	0.94 (90.65–1.36)	0.87 (0.60–1.26)	0.86 (0.59–1.26)

Abbreviation: CI, confidence interval.

[a]Model 1: Adjusted for obesity (BMI > 30), ever smoking, diabetes mellitus, and number of previous UTIs for bladder cancer. Adjusted for obesity (BMI > 30), ever smoking, and diabetes mellitus for pancreatic cancer.

[b]Model 2: In addition to model 1, adjusted for medical history of hypertension and hyperlipidemia.

this might lead to misclassification of the true exposure of interest and thus bias toward the null. It is possible that the wet type may be associated with an even higher risk of RCC, as it is the type associated with neovascularization and response to anti-VEGF therapies (23). Finally, although our analysis was adjusted to all major risk factors that are associated with both the RCC and AMD, we cannot rule out residual confounding. Moreover, chance finding due to the small number of individuals with AMD (64, 0.8%) in this study is also possible. However, the difference in association among individuals with RCC versus individuals with pancreatic cancer may suggest a biological mechanism and lower this possibility.

In summary, we demonstrated an increased RCC risk among patients with AMD. This association may have clinical significance in defining individuals that may benefit from RCC screening with periodic abdominal imaging. Further studies are required to validate our results in additional databases and evaluate underlying biological mechanism.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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References

1. Li L, Kaelin WG Jr. New insights into the biology of renal cell carcinoma. Hematol Oncol Clin North Am 2011;25:667–86.
2. Na X, Wu G, Ryan CK, Schoen SR, di'Santagnese PA, Messing EM, et al. Overproduction of vascular endothelial growth factor related to von Hippel-Lindau tumor suppressor gene mutations and hypoxia-inducible factor-1 alpha expression in renal cell carcinomas. J Urol 2003;170: 588–92.
3. Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of age-related macular degeneration. Am J Ophthalmol 2004;137:486–95.
4. Chen G, Li W, Tzekov R, Jiang F, Mao S, Tong Y. Bevacizumab versus ranibizumab for neovascular age-related macular degeneration: a meta-analysis of randomized controlled trials. Retina 2015;35:187–93.
5. Fine SL, Berger JW, Maguire MG, Ho AC. Age-related macular degeneration. N Engl J Med 2000;342:483–92.
6. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.
7. CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–908.
8. Cheung N, Shankar A, Klein R, Folsom AR, Couper DJ, Wong TY. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Age-related macular degeneration and cancer mortality in the atherosclerosis risk in communities study. Arch Ophthalmol 2007;125:1241–7.
9. Chakravarthy U, Wong TY, Fletcher A, Piault E, Evans C, Zlateva G, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC Ophthalmol 2010;10:31.
10. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. Inform Prim Care 2011;19: 251–5.
11. Chisholm J. The Read clinical classification. BMJ 1990;300:1092.
12. Benson T. The history of the Read Codes: the inaugural James Read Memorial Lecture 2011. Inform Prim Care 2011;19:173–82.
13. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. Pharmacoepidemiol Drug Saf 2007;16: 393–401.
14. Haynes K, Forde KA, Schinnar R, Wong P, Strom BL, Lewis JD. Cancer incidence in The Health Improvement Network. PDS 2009;18:730–6.
15. Mamtani R, Haynes K, Boursi B, Scott FI, Goldberg DS, Keefe SM, et al. Validation of a coding algorithm to identify bladder cancer and distinguish stage in an electronic medical records database. Cancer Epidemiol Biomarkers Prev 2015;24:303–7.
16. Pearce N. What does the odds ratio estimate in a case-control study? Int J Epidemiol 1993;22:1189–92.
17. Greenland S, Thomas DC. On the need for the rare disease assumption in case-control studies. Am J Epidemiol 1982;116:547–53.

18. Hunt JD, van der Hel OL, McMillan GP, Boffetta P, Brennan P. Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. Int J Cancer 2005;114:101–8.
19. Chow WH, Gridley G, Fraumeni JF Jr, Järvholm B. Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med 2000; 343:1305–11.
20. Lindblad P, Chow WH, Chan J, Bergström A, Wolk A, Gridley G, et al. The role of diabetes mellitus in the aetiology of renal cell cancer. Diabetologia 1999;42:107–12.
21. Craven KE, Gore J, Wilson JL, Korc M. Angiogenic gene signature in human pancreatic cancer correlates with TGF-beta and inflammatory transcriptomes. Oncotarget 2016;7:323–41.
22. Boursi B, Haynes K, Mamtani R, Yang YX. Thyroid dysfunction, thyroid hormone replacement and colorectal cancer risk. J Natl Cancer Inst 2015;107:djv084.
23. Bowes Rickman C, Farsiu S, Toth CA, Klingeborn M. Dry age-related macular degeneration: mechanisms, therapeutic targets, and imaging. Invest Ophthalmol Vis Sci 2013;54:ORSF68–80.