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Cancer Incidence in Patients with Hereditary Hemorrhagic Telangiectasia

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Abstract

Purpose—Hereditary hemorrhagic telangiectasia (HHT) is a genetic disorder characterized by deficiency in endoglin, an angiogenic protein. We previously showed that HHT, in which systemic endoglin expression is reduced, was associated with better survival outcomes in cancer patients (Duarte et al., 2014). Here, we evaluated whether HHT was associated with reduced cancer incidence.

Methods—A matched case control analysis using SEER-Medicare was conducted to evaluate the effect of HHT on diagnosis with breast, colorectal, lung, or prostate cancer between 2000 and 2007 (n=633,162). Cancer and non-cancer patients were matched on age, sex, SEER registry region, and length of the ascertainment period for HHT. We assessed crude association using a McNemar's test and then adjusted for demographic variables, cancer type, cancer stage, comorbidities, and ascertainment period with a conditional logistic regression model for cancer incidence.

Results—The McNemar's test showed no significant association between HHT and cancer incidence (p=0.74). Adjusting for covariates with the conditional logistic regression model did not change the result (HHT odds ratio 0.978; 95% CI: (0.795, 1.204)). The lack of association between HHT and cancer incidence is unexpected given the previously discovered significant association between HHT and improved survival outcomes (Duarte et al., 2014).

Conclusions—We conclude that the protective effect of reduced systemic endoglin expression in cancer is specific to cancer progression through its effect on vascularization and other stromal effects but does not extend to cancer initiation.

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Keywords

SEER/Medicare; endoglin; HHT; case control; cancer incidence

1. Introduction

HHT is most commonly due to mutations in endoglin (McAllister et al., 1994) which leads to deficient endoglin production. HHT is a vascular disease with symptoms such as arteriovenous malformations (AVMs), tissue ischemia, and reperfusion defects (Saluja and White, 2004, Sabba et al., 2006, Sabba et al., 2007). A clinical diagnosis of HHT is based on the presence of three or more of the following clinical findings: nosebleeds (epistaxis), telangiectasia, internal lesions including AVMs, and a family history of HHT (Shovlin et al., 2000).

We have previously shown that HHT patients with cancer showed improved survival outcomes compared with non-HHT cancer patients, controlling for covariates (Duarte et al., 2014). This result was informative given the potential for opposing effects on tumor progression for endoglin expressed in the tumor, versus the tumor microenvironment, and may inform on decisions for therapeutic treatment based on anti-endoglin therapies (Rosen et al., 2012). A related question is whether reduced endoglin levels are protective for promoting cancer development. For example, stromal fibroblasts may participate in different aspects of carcinoma development and progression (Bhowmick et al., 2004). In our own work we have demonstrated that tumor-expressed endoglin may negatively influence prostate cancer invasion and metastasis (Lakshman et al., 2011) in a mechanism involving BMP (bone morphogenetic protein) signaling (Breen et al., 2013), whereas stromal fibroblast-expressed endoglin is required for tumor stroma formation (Romero et al., 2011). Cancer initiation is due to many molecular mechanisms, and the role of endoglin in cancer incidence is unclear.

We sought to examine the association between HHT diagnosis and cancer incidence by performing a matched case control study using the SEER-Medicare database. We chose to examine the top four cancers (breast, colorectal, lung, and prostate cancer) and to match according to age, sex, and SEER region as in previous studies of cancer incidence using SEER Medicare (Fisher et al., 2013, Trabert et al., 2015). In addition, we matched on ascertainment period for HHT after first matching on the first 3 variables and then choosing an ascertainment period for the pair as the maximum eligibility period shared by the pair prior to the case diagnosis date, with truncation to one of the following eligibility periods: 2 years, 3 years, 4 years, 5 years, or 8 years.

2. Materials and Methods

2.1. Data Source

Data for this analysis came from the SEER-Medicare linked dataset released every 2 years by NIH. This data includes information on 97% of incident cancer cases that occur within a SEER region linked to each patient's Medicare claims data. SEER collects data on age, sex,

race and ethnicity, disease stage, and month and year of diagnosis. Medicare claims data includes information on each patient's pattern of care via diagnosis and procedure codes. The data only includes complete claims for patients that are eligible for Medicare parts A and B that were not enrolled in an HMO. SEER-Medicare also contains a non-cancer control dataset which consists of a random sample of Medicare beneficiaries living in each SEER region and captures their demographic data and Medicare claims. Data for the cancer patients came from the 2010 linkage while the non-cancer control data came from the 2012 linkage. The different linkages used to derive the cases and controls does not introduce bias because the controls are matched to the cases based on age at the case's cancer diagnosis date, and claims are searched prior to this index date (case diagnosis date) for the pair.

2.2. Cohort Definition

Cases were identified as patients diagnosed with breast, colorectal, lung, or prostate cancer between 2000 and 2007. Patients were included in the study if they were eligible for Medicare parts A and B and not enrolled in an HMO for 27 months prior to the month of their cancer diagnosis. Patients were excluded if their cancer diagnosis was not microscopically confirmed or if their diagnosis date was outside the study period. For each cancer patient, the first diagnosis in the study period that matched one of the four cancers in our study was used as their diagnosis date, considering the first five cancers listed for each patient. For patients who were diagnosed with more than one cancer during the study period, only the first diagnosis matching one of the four cancers in our study was considered. The relatively small number of patients who were diagnosed with multiple cancers on the same day were excluded. Matched controls were selected from the 5% non-cancer sample and were required to have at least 27 months of continuous eligibility. Figure 1 shows the consort diagram for the cohort in this study.

2.3. Matching

Cases and controls were matched on age, sex, and SEER region using an iterative greedy algorithm. Specifically, we required matches to be born within one year of each other, be of the same sex, live in the same registry region during the year of the case's cancer diagnosis, and have continuous eligibility (Medicare A&B with no HMO) for at least 27 months prior to the case's diagnosis date. For each case, the first matching control (without replacement) was selected from the list of potential controls. We selected one control per case as selecting 2 or more controls per case significantly decreased the number of cases that could be included. We found 316,581 matched pairs (representing 65% of eligible cases). Once a match was established, we determined the pair's exposure window by taking the longest period of eligibility for both case and control prior to the case's diagnosis date, with truncation to allow assignment of the pair to one of the following eligibility period groups: 2 years, 3 years, 4 years, 5 years, or 8 years. For instance, if the case had 27 months of eligibility prior to the diagnosis date and the control had 48 months of eligibility prior to that date, the 27 month period would be used for both and the pair would be assigned to the 2 year group.

2.4. Exposure Assessment

HHT diagnosis is our primary exposure of interest and was determined if one or more claims with an ICD9 code associated with HHT (448.0) was found during the assigned eligibility period. Comorbidities were assessed using the Deyo implementation (Deyo, 2002) of the Charlson comorbidity score (Charlson et al., 1987). Comorbidities were assessed in the year prior to the case's cancer diagnosis date for the case and matched control.

2.5. Analysis

Matched pairs were cross classified based on their HHT exposure, and a McNemar's test was performed as a test of univariate association between the exposure and the outcome before adjusting for covariates. Adjustment for demographics and covariates was performed by fitting a conditional logistic regression model, which models the probability that a cancer case had the exposure (HHT) and their matched control did not given that exactly one of the pair did have the exposure. The multivariate conditional regression model was constructed by adding covariates (see Table 1) to the model which were all found to be significant ($p < 0.05$), and was implemented using Proc PHReg (SAS Version 9.2). These covariates were chosen based on clinical relevance and based on inclusion in our previous models for cancer survival outcomes (Duarte et al., 2014).

3. Results

The characteristics of the study cohort are found in Table 1. Perfect balance in the matching variables sex and SEER region was achieved and good balance in age was found. Most of the other variables showed good balance with the exception of the Charlson Comorbidity Index which tended to be higher in the cancer cases as is expected.

Table 2 shows the contingency table for cases and controls with and without HHT exposure and the McNemar's test results. Slightly more cancer cases than controls showed HHT exposure (219 vs. 212) in each matched pair, although these results were not significant ($p = 0.7$). The final logistic regression model is shown in Table 3. The odds ratio for the HHT effect was 0.978 (95% CI: 0.795, 1.204) and was not significant. Thus we do not have evidence to conclude that there is a difference in the probability of cancer incidence for HHT versus non-HHT patients in the crude or adjusted analyses.

4. Discussion

In a study of the four most prevalent cancers (breast, colorectal, lung, or prostate cancer) from the SEER-Medicare database we have found no difference in cancer incidence for patients with HHT diagnoses versus those with no HHT diagnosis during the ascertainment period. Our study included matching on sex, age, SEER region, and length of ascertainment period and adjustment for other covariates to account for the effect of these potential confounding variables on cancer incidence and HHT diagnosis. Because HHT ascertainment is more likely given a longer ascertainment period, we used the length of ascertainment as a matching variable to prevent any bias this may introduce.

While the null result of this study is unexpected given the previously-obtained result that HHT patients with cancer had improved cancer survival outcomes (Duarte et al., 2014), this null results renders more specific the protective effect of reduced systemic endoglin expression in cancer. The combination of these two studies suggests that cancer initiation is not affected by a reduction in endoglin expression, but that once cancer is initiated, its progression is influenced by endoglin expression. These two results combined give further insight into the mechanistic role of endoglin in cancer etiology.

The strength of this study is that it represents a large comprehensive national survey of incident cancer cases and matched controls in the United States. Thus, even given the rarity of HHT, this study was well-powered to test the association between HHT and cancer incidence. The limitations of this study include that it is an observational study, and as such, confounding of HHT diagnosis with other clinical and demographic variables is possible. However, we have attempted to address confounding by matching on the most important covariates (age, sex, length of ascertainment period, and SEER region) and adjusting for other potential confounders (see Table 3). Another limitation is that the use of event-based reporting of HHT status from Medicare (billing) claims data two or more years prior to cancer diagnosis may result in undercounting HHT cases. However, we do not expect HHT reporting through claims data to be affected by differential health care coverage, as our cohort contains patients with Medicare coverage only (no supplementary coverage), thus the undercounting should apply equally across the cohort and not introduce bias.

In conclusion, this is a matched case control study that includes a large representative sample of the United States cancer cases and matched non-cancer controls and thus has sufficient power to address the relation between HHT diagnosis and cancer incidence. The results, based on 316,581 matched pairs and 431 instances of HHT diagnosis, shows that an endoglin-deficient state is independent of cancer initiation, though it was previously shown to be related to cancer progression (Duarte et al., 2014), suggesting a more specific role for endoglin in cancer etiology.

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Abbreviations

HHT	hereditary hemorrhagic telangiectasia
SEER	Surveillance, Epidemiology, and End Results
CI	confidence interval
BMP	bone morphogenetic protein
AVM	arteriovenous malformation

Figure 1.
Consort diagram showing creation of study cohort from SEER Medicare database.

Table 1

Characteristics of the study cohort.

	Cancer case		Non-cancer control	
	N	%	N	%
Total	316,581	100	316,581	100
Age Group				
<=65	27,836	9	28,233	9
66-69	54,349	17	64,969	21
70-79	141,641	45	129,723	41
80+	92,755	29	93,656	30
Race				
White	267,481	84	259,715	82
Black	29,622	9	26,731	8
Other	19,035	6	29,578	9
Unknown	443	0	557	0
Gender				
Male	130,096	41	130,096	41
Female	186,485	59	186,485	59
Median income for census tract				
Missing	16,565	5	11,409	4
\$0-\$40K	117,978	37	122,700	39
\$40K-\$58K	97,741	31	107,238	34
\$58K+	84,297	27	75,234	24
Education: % <12 yrs in census tract				
Missing	14,629	5	11,409	4
<10%	72,101	23	70,037	22
10 to 20%	113,169	36	114,415	36
>20%	116,682	37	120,720	38
Urban				
Missing	30	0	717	0
Less than 1 million	141,903	45	144,213	46
1 million+ population	174,648	55	171,651	54
Stage				
Missing or not applicable	44,538	14	316,581	100
Early (0,1,2)	180,746	57	.	.
Late (3,4)	91,297	29	.	.
Charlson Comorbidity Score				
0	163,306	52	191,000	60
1-5	150,092	47	121,921	39
6-10	3,163	1	3,636	1
11-15	20	0	24	0
Type of cancer				

	Cancer case		Non-cancer control	
	N	%	N	%
No Cancer	.	.	316,581	100
Breast	91,935	29	.	.
Colorectal	72,464	23	.	.
Lung	82,911	26	.	.
Prostate	69,271	22	.	.
SEER Registry				
San Francisco	12,080	4	12,080	4
Connecticut	21,129	7	21,129	7
Detroit	23,906	8	23,906	8
Hawaii	4,778	2	4,778	2
Iowa	19,610	6	19,610	6
New Mexico	8,654	3	8,654	3
Seattle	17,287	5	17,287	5
Utah	8,407	3	8,407	3
Atlanta	10,493	3	10,493	3
San Jose	7,015	2	7,015	2
Los Angeles	24,635	8	24,635	8
Rural Georgia	800	0	800	0
Greater California	61,041	19	61,041	19
Kentucky	27,384	9	27,384	9
Louisiana	22,577	7	22,577	7
New Jersey	46,785	15	46,785	15

Table 2

Contingency table and McNemar test for matched case control pairs and HHT exposure (p=0.7).

Cancer Cases	Non Cancer Controls		
	No HHT	HHT	Total
No HHT	316,150	212	316,362
HHT	219	0	219
Total	316,369	212	316,581

Table 3

Conditional logistic regression model effects.

Full Model	Odds Ratio (95% CI)
HHT	0.978 (0.795, 1.204)
1 or more comorbidities	1.458 (1.442, 1.474)
Urban	
Large metropolitan 1 million + population	1.026 (1.011, 1.041)
Less than 1 million population	1.00 (referent)
Education (census tract)	
0-10% fewer than 12 years	1.00 (referent)
10-20% fewer than 12 years	1.058 (1.042, 1.075)
>20% fewer than 12 years	1.102 (1.081, 1.123)
Median Income (census tract)	
\$0-\$40K	1.00 (referent)
\$40K-\$58K	1.025 (1.01, 1.04)
>\$58K	1.338 (1.312, 1.364)
Race	
White	1.00 (referent)
Black	1.116 (1.093, 1.139)
Other	0.579 (0.566, 0.592)

Abbreviation: NA, not applicable.