Published OnlineFirst November 5, 2013; DOI: 10.1158/1055-9965.EPI-13-0665

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Improved Survival Outcomes in Cancer Patients with Hereditary Hemorrhagic Telangiectasia

Christine W. Duarte[1], Kimberly Murray[1], F. Lee Lucas[1], Kathleen Fairfield[1], Heather Miller[1], Peter Brooks[2], and Calvin P.H. Vary[2]

Abstract

Background: Hereditary hemorrhagic telangiectasia (HHT) is a genetic disorder characterized by deficiency in endoglin, an angiogenic protein. The net effect of endoglin expression on cancer outcomes from animal studies has proven controversial. We evaluated whether reduced systemic endoglin levels, expected in patients diagnosed with HHT, impacted clinical outcomes for cancer.

Methods: A retrospective cohort analysis using Surveillance, Epidemiology, and End Results–Medicare was conducted to evaluate the effect of HHT on survival among patients diagnosed with breast, colorectal, lung, or prostate cancer between 2000 and 2007 ($n = 540{,}520$). We generated Kaplan–Meier survival curves and Cox models to compare the effect of HHT on all-cause survival for a composite of the four cancers, and separate models by cancer, adjusting for demographic variables, cancer type, cancer stage, and comorbidities.

Results: All-cause survival analysis for a composite of the four cancers showed an adjusted HR of 0.69 [95% confidence interval (CI) of 0.51–0.91; $P = 0.009$] for HHT, indicating significantly improved survival outcome. When stratified by cancer type, HHT diagnosis showed a significant protective effect among breast cancer patients with an adjusted HR of 0.31 (95% CI, 0.13–0.75; $P = 0.009$).

Conclusions: There was a significant association between HHT and improved survival outcome for a composite of patients with breast, prostate, colorectal, and lung cancer, and in analysis stratified by cancer, the association was significant for HHT patients with breast cancer.

Impact: This study supports the hypothesis that systemically educed endoglin expression is associated with improved survival outcome in multiple cancers, and suggests that anti-endoglin antibody therapy may have broad-based application. *Cancer Epidemiol Biomarkers Prev; 23(1); 117–25. ©2013 AACR.*

Introduction

Although tremendous advances in cancer treatment have occurred in recent years, new therapies are needed for tumors that do not respond to standard treatment or that acquire resistance. Endoglin is required for angiogenesis (1–3), and shows promise as a therapeutic target in cancer treatment. Early phase clinical trials of anti-endoglin therapy (4) suggest efficacy, but the basic mechanisms of endoglin targeting affecting cancer progression remain poorly understood. Most of our knowledge of endoglin and cancer progression has been gained from cell and animal studies, but another potential source of information is from the study of patients with a rare genetic disorder that results in a natural deficiency of endoglin, occurring with hereditary hemorrhagic telangiectasia (HHT).

Current studies of endoglin and cancer progression

Endoglin is a transmembrane glycoprotein that interacts with the TGF-β receptors (5), including ALK1 (*ACVRL1*; ref. 6), and modulates TGF-β and bone morphogenetic protein signaling (7). It is normally expressed in endothelial cells of the developing vasculature where it is required for angiogenesis (1, 3, 8). Endoglin is a prognostic marker for a variety of malignancies (9–11), likely reflecting the degree of tumor angiogenesis. These include prostate (12, 13), breast (14), lung (15), and colon (16) cancers (reviewed in refs. 17 and 18).

Studies using human prostate cancer cell line xenograft models demonstrate that overexpression of endoglin in prostate cancer cells inhibits tumor cell invasion (19) and metastasis (20–22). This suggests that sustained expression of tumor-associated endoglin might provide a plausible strategy to inhibit metastasis. However, data obtained using an autochthonous mouse model of prostate cancer indicates that endoglin is required for the support of prostate tumors by cancer-associated myofibroblasts, promoting tumor vascularization and subsequent progression to metastatic disease (23). The apparently opposing

Authors' Affiliations: [1]The Center for Outcomes Research and Evaluation; and [2]The Center for Molecular Medicine, Maine Medical Center Research Institute, Maine Medical Center, Scarborough, Maine

C.W. Duarte and K. Murray contributed equally to this work.

Corresponding Author: Christine W. Duarte, Center for Outcomes Research and Evaluation (CORE), Maine Medical Center Research Institute (MMCRI), 509 Forest Ave., Suite 200, Portland, ME 04101. Phone: 207-661-7657; Fax: 207-662-3110; E-mail: duartc@mmc.org

doi: 10.1158/1055-9965.EPI-13-0665

Published OnlineFirst November 5, 2013; DOI: 10.1158/1055-9965.EPI-13-0665

consequences of endoglin expression in the tumor (antimetastatic) versus stromal microenvironment (prometastatic) raise pivotal questions about the relative impact of endoglin expression in the tumor, stromal, and vascular compartments, on cancer progression. Thus, it remains unclear whether, and how, endoglin expression affects treatment outcome and survival for the most prevalent malignancies.

HHT patients and the role of endoglin

Human population-based multicancer studies that address the effect of systemic endoglin expression on cancer survival outcomes is lacking. Mutations in endoglin (24) lead to deficient endoglin production and HHT, a vascular disease whose symptoms include arteriovenous malformations (AVM), tissue ischemia, and reperfusion defects (25–27). A clinical diagnosis of HHT is based on the presence of 3 or more of the following clinical findings: nosebleeds (epistaxis), telangiectasia, internal lesions including AVMs, and a family history of HHT (28). The potential for opposing effects on tumor progression for endoglin expressed in the tumor, versus the tumor microenvironment, may have profound implications for therapeutic treatment based on anti-endoglin therapies (4), and it is important to elucidate which of these effects is dominant in human cancer before anti-endoglin therapies can be directed appropriately. To define the effect of reduced endoglin expression on cancer patients, we used linked Surveillance Epidemiology and End Results (SEER)/Medicare data to determine whether HHT patients, who are presumed to be endoglin deficient, have different outcomes in cancer survival compared with those without an HHT diagnosis.

Materials and Methods

Data sources

Data for this analysis came from the linkage of the SEER registries with health care claims reported to Medicare. The population-based registries participating in the SEER program represent defined geographic areas and have changed over time. An estimated 97% of incident cancer cases are captured by cancer registrars within the SEER regions (29), which are representative of the U.S. population (30). For each reported malignancy, SEER registries collect data on: age at diagnosis, sex, race and ethnicity, disease stage, histologic type, month and year of diagnosis, and date and cause of death, among other variables. SEER registrars follow detailed manuals for tumor reporting to ensure standardized methods and reporting across sites.

Sociodemographic data from the 2000 census was linked with the cases at the census tract level. Linked Medicare data included claims for inpatient and outpatient care, and physician services. Our combined dataset contained SEER data from 2000 to 2007 (and thus, cancer diagnosis dates in this interval) and linked Medicare claims data from 1998 to 2009. Thus, the censoring date for this study is December 31, 2009, with all individuals still alive at this date considered censored and lost to follow up. An overview of the SEER Medicare database, including the validity of the survival outcomes, is described elsewhere (31).

Informed consent

The Institutional Review Board of Maine Medical Center approved this study. All patient data within the SEER-Medicare dataset are based on registry data and are de-identified. Thus, it was not possible to seek informed consent from each participant, and we received a Waiver of Consent.

Cohort definition

We identified patients who were diagnosed with breast, colorectal, lung, or prostate cancer between 2000 and 2007. Patients were included if they were continuously enrolled as disabled or aged (65 years or older) in the fee-for-service Medicare Parts A and B for 2 years before their cancer diagnosis, with no health maintenance organization (HMO) enrollment during this time period. Continuous enrollment allowed us to capture all medical claims for these patients during this time period. We did not have access to HMO claims, thus patients seen by an HMO were excluded. Two years of eligibility rather than one was required to extend the ascertainment period for HHT. Less prevalent cancers were not evaluated because of insufficient numbers of such patients with an HHT diagnosis. We did not exclude patients based on age, although less than 1% of our cohort was younger than 52 years because of the prevalence of aged rather than disabled patients in the Medicare population and the increasing incidence of cancer with age. The youngest subject was 21 years old.

Covariates

We categorized subjects into 4 age groups based on age at diagnosis ($\leq$65, 66–69, 70–79, and 80+). Race was defined as black (yes/no) and marital status as married (yes/no). Disease stage according to the American Joint Committee on Cancer (AJCC) classification was obtained from SEER records. Comorbidities were ascertained from inpatient and physician visit claims (including Part B and Outpatient claims; ref. 32) for 12 months before the cancer diagnosis using the Deyo implementation (33) of the Charlson comorbidity score (34). We categorized subjects as HHT if they had an HHT diagnosis during the 2-year ascertainment period [International Classification of Diseases 9th Revision, Clinical Modification (ICD-9) code 448.0]. The diagnosis criteria for HHT is based on the Curaçao criteria, which has recently been studied in (35), and found to have good predictive performance, with "positive predictive value of a definite clinical diagnosis of 100% (95% CI, 97.8–100)" and "negative predictive value of an unlikely diagnosis of 97.7% (95% CI, 87.9–99.6)." We also recorded rates of AVMs in both HHT and non-HHT patient groups. AVMs represent a heterogeneous group of lesions comprising multiple codes. Three ICD codings

Published OnlineFirst November 5, 2013; DOI: 10.1158/1055-9965.EPI-13-0665

were considered representative for the purposes of this study (ICD-9 codes 747.6, 417.0, and 747.81).

Rurality (reported in SEER) is based on the 2003 Rural/Urban Continuum Codes (RUCC) defined by the Economic Research Services, Department of Agriculture.[1] We collapsed the RUCCS into 2 categories because of the sparseness of the data among patients with HHT: population of greater than 1 million, and population less than 1 million. U.S. 2000 Census data for median household income and educational attainment were used as proxies for economic status.

Statistical analyses

Demographic and clinical characteristics were compared between HHT and non-HHT groups using a χ^2 goodness of fit test, with *P*-values of 0.05 or less considered significant. Cells sizes with counts less than 11 were suppressed in accordance with SEER-Medicare guidelines. All cause survival analyses were performed by constructing Kaplan–Meier curves stratified by HHT status. The log-rank statistic was used to test for difference in survival curves across strata (36). We constructed Cox proportional hazards models and adjusted for confounding effects on survival because of differences in the demographic and clinical characteristics between HHT and non-HHT groups. Specifically, we built 5 models, 1 composite model for all 4 cancers, and then a separate model for each cancer type. The first primary cancer was assigned to each patient so that each patient fell into a single cancer group. If a patient had 2 primary cancers diagnosed on the same day, they were excluded from the study.

Each survival model contained a term for HHT (yes or no), type of cancer (breast, prostate, colorectal, or lung), sex (for all cancer and colorectal and lung cancer models), age, education (by census tract), black race, cancer stage (early as stage 0–2; advanced stage 3–4; and unknown stage), and the presence of one or more comorbidities. For comparison, we also fit the same set of models but using the raw Charlson Comorbitiy Index (CCI) rather than the dichotomized variable of one or more comorbidities. Some individual comorbidities were reported in Table 1 for descriptive purposes, but were not included individually in the survival models. Also for comparison, we fit crude Cox models with a term for HHT, to present HRs with confidence intervals for both the crude models and the full (adjusted) models. Analyses were conducted using SAS (SAS version 9.3 for Windows; SAS Institute). We tested the proportional hazards assumption for each Cox model using a previously proposed method (37, 38) in which an interaction term with a time-varying covariate was added and tested for significance. We also performed a meta-analysis of the crude and adjusted survival models across the 4 cancers using an inverse variance approach as implemented in the function metagen in the R package meta (39, 40). All statistical tests were performed at a level of 0.05 unless otherwise stated. Power analyses were performed to estimate the expected power for our given sample size for a composite of the 4 cancers and for each cancer separately using Proc Power in SAS 9.2. We used the 2 sample survival option in SAS, inputting the observed median survival time for the non-HHT group and the expected survival time in the HHT group given different values of the HR.

Results

Description of cohort

A summary of the demographic and clinical characteristics of the cohort for HHT and non-HHT patients is given in Table 1. Our observed HHT rate was found to be 2.3 HHT subjects per 10,000, which is consistent with current estimates of prevalence in the United States (1–2 subjects per 10,000 people; ref. 41). The number of HHT patients found in the Medicare claims may be higher than in the general population because of the enrichment for elderly subjects, in which HHT is better ascertained, and because of enrichment for subjects receiving medical treatment through the Medicare system. HHT may be under-ascertained in the general population for a variety of reasons, including rarer, uncharacterized mutations leading to HHT (42).

The age distribution for HHT and non-HHT groups were roughly the same, with slightly more HHT subjects in the 70–79 range (53.5% vs. 48.4%) and slightly less in the above 80 category (24.4% vs. 31.1%; overall *P* value for age was 0.44). The gender distribution was roughly the same between groups. Race rates between HHT and non-HHT groups could not be reported in Table 1 because of the suppression of small cell sizes in the HHT group; however, it was found that there were significantly more black patients in the non-HHT group as compared with the HHT group. HHT patients were more represented in the higher income categories (45.7% vs. 26.6% in the $58K plus median income category, $P < 0.001$), and were more highly educated ($P = 0.009$). The distribution of cancer type in the HHT and non-HHT groups was not significant ($P = 0.06$). HHT patients were less likely to be late stage compared with non-HHT patients (19.7% vs. 30.9%, $P = 0.008$). As expected, incidence of AVMs was higher among the HHT population (10.2% vs. 1.9%, $P < 0.001$). Finally, HHT patients show slightly higher rates of comorbid conditions, although these differences were not statistically significant.

Survival analysis

Kaplan–Meier survival curves stratified by HHT diagnosis for a composite of the 4 cancers and separately by cancer are shown in Figs. 1 and 2, respectively. In the composite cancer model, patients with a diagnosis of HHT had a significantly increased survival (Fig. 1, $P < 0.0001$). For individual cancers, breast cancer showed the strongest association between HHT diagnosis and survival (Fig. 2A, $P = 0.0056$). Prostate cancer also achieved statistical significance (Fig. 2B, $P = 0.025$). In contrast, although lung and colorectal cancers showed similar trends, the improvement of survival with HHT diagnosis

Published OnlineFirst November 5, 2013; DOI: 10.1158/1055-9965.EPI-13-0665

Table 1. Patient demographic and clinical characteristics ($N = 540,520$)

	No. (%) of patients		
	Non-HHT ($N = 540,393$)	**HHT ($N = 127$)**	***P*-value[a]**
No. of events (death)	307,798 (57.0)	47 (37.0)	<0.001
Age group			
≤65	28,285 (5.2)	[b]	0.44
66–69	82,364 (15.2)	[b]	
70–79	261,506 (48.4)	68 (53.5)	
80+	168,238 (31.1)	31 (24.4)	
Gender (%)			
Female	253,933 (47.0)	68 (53.5)	0.14
Male	286,460 (53.0)	59 (46.5)	
Race (%)			
Black	49,646 (9.2)	[b]	[b]
Non-Black	490,747 (90.8)	[b]	
Percent of persons (in census tract) age 25 years or older with <12 years of education[c]			
Greater than 20%	199,187 (36.9)	29 (22.8)	0.009
10 to 20%	176,265 (32.6)	51 (40.2)	
Less than 10%	144,080 (26.7)	43 (33.9)	
Median income for census tract[c]			
$0 to $40K	201,733 (37.3)	28 (22.0)	
$40K to $58K	167,240 (30.9)	35 (27.6)	<0.001
$58K+	143,819 (26.6)	58 (45.7)	
Urban[c]			
1 million + population	299,035 (55.3)	95 (74.8)	<0.001
Less than 1 million	241,358 (44.7)	32 (25.2)	
Cancer			
Breast	119,415 (22.1)	36 (28.3)	0.06
Colorectal	116,814 (21.6)	16 (12.6)	
Lung	154,661 (28.6)	36 (28.3)	
Prostate	149,503 (27.7)	39 (30.7)	
Stage			
Early (0,1,2)	290,451 (53.7)	85 (66.9)	
Late (3,4)	167,167 (30.9)	25 (19.7)	0.01
Unknown (5)	82,775 (15.3)	17 (13.4)	
HHT symptoms			
AVM occurrence	10,432 (1.9)	13 (10.2)	<0.001
Comorbidities			
1 or more comorbidities	237,711 (44.0)	61 (48.0)	0.36
Diabetes	100,982 (18.7)	32 (25.2)	0.06
COPD	99,390 (18.4)	31 (24.4)	0.08
CHF	51,875 (9.6)	12 (9.5)	0.95
Cerebrovascular disease	32,184 (6.0)	[b]	[b]
Peripheral vascular disease	27,686 (5.1)	[b]	[b]
Cause of death[d]			
Cancer	176,627 (57.4)	29 (61.7)	0.55
Other cause	131,171 (42.6)	18 (38.3)	
Survival			
Days (median)	1,268.2	1,583.6	<0.001[e]
Months (median)	41.2	51.5	

[a] χ^2 test for association.
[b] Values suppresssed in accordance with SEER-Medicare guidelines for cell size <11.
[c] Category of missing omitted.
[d] Denominator = decedents (no. of events).
[e] Log-rank test for equality of strata for Kaplan–Meier curves.

Published OnlineFirst November 5, 2013; DOI: 10.1158/1055-9965.EPI-13-0665

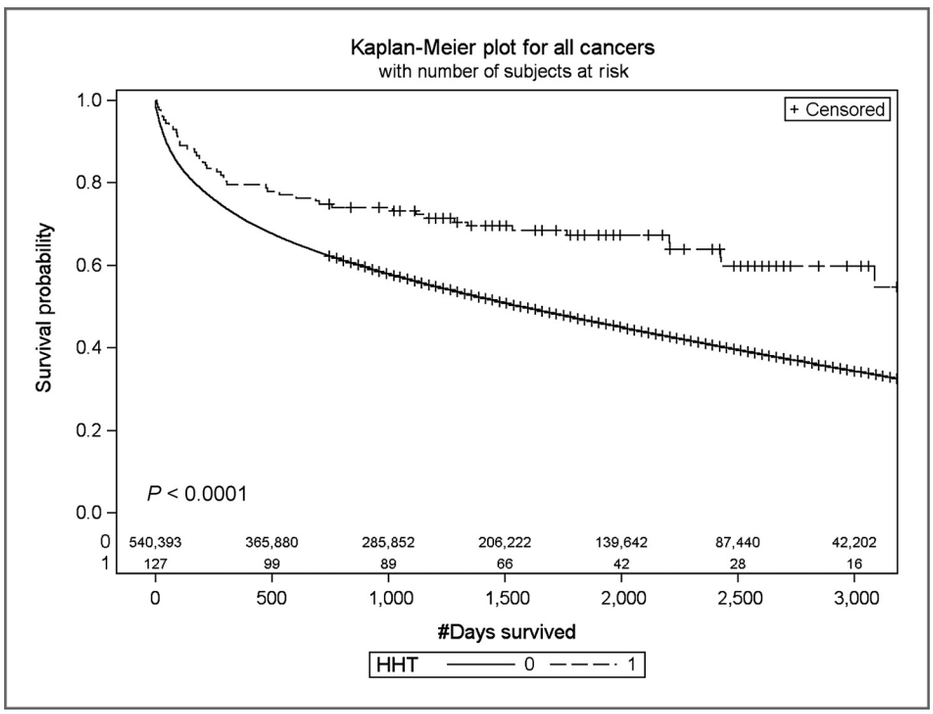

Figure 1. Kaplan–Meier survival curves for a composite of the 4 cancers (breast, prostate, lung, and colorectal) and a diagnosis of HHT. Diagnosis of normal non-HHT or HHT is indicated by 0 and 1, respectively. Log-rank *P* value is indicated in the figure.

for these cancers did not achieve statistical significance (Fig. 2C, $P = 0.080$; Fig. 2D, $P = 0.301$, respectively).

Crude and adjusted Cox proportional hazards models were built for a composite of the 4 cancers and by cancer type. The results of the adjusted survival composite cancer model are shown in Table 2. The HR for HHT vs. non-HHT patients was found to be strongly protective, with HR = 0.69 (95% CI, 0.51–0.91; $P = 0.009$). The unadjusted (crude) HR was slightly smaller (HR = 0.56; 95% CI, 0.42–0.74; $P<0.001$), showing that correcting for confounding factors accounted for some, but not all of the HHT protective effect.

The cancer-specific survival models are shown in Table 3, with the HRs shown for HHT both for the full (adjusted) model and in the unadjusted (crude) model. The adjusted HR for HHT patients with breast cancer was found to be highly significant, with a HR of 0.31 (95% CI, 0.13–0.75; $P = 0.0009$). The adjusted HR for prostate cancer was not significant, with HR = 0.56 (95% CI, 0.27–1.18; $P = 0.13$). Colorectal cancer results also were not significant (HR = 0.60; 95% CI, 0.30–1.30; $P = 0.21$) in the adjusted model, and lung cancer showed a neutral effect for HHT after accounting for adjustments in the model (HR = 1.02; 95% CI, 0.70–1.49; $P = 0.90$). The unadjusted (crude) HRs were significant for both breast cancer (HR = 0.31; 95% CI, 0.13–0.75; $P = 0.009$) and prostate cancer (HR = 0.44; 95% CI, 0.21–0.92; $P = 0.03$). In testing the proportional hazards assumption for each of the crude (unadjusted) models, there were no violations with the exception of breast cancer, which did show a significant violation for the HHT effect. However, when testing the proportional hazards assumption in the adjusted model, there was no longer a significant violation. Thus, the violation was handled as recommended by the addition of stratification variables (43). The adjusted model for the composite of 4 cancers also did not show a violation of this assumption. Fitting survival models using the raw Charlson Comorbidity Index (CCI) rather than the dichotomized indicator variable of one or more comorbidities resulted in nearly identical models. For instance, for the model with the composite of 4 cancers, the HR for HHT versus non-HHT patients was HR = 0.65 (95% CI, 0.49–0.87; $P = 0.0036$), as compared with HR = 0.69 (95% CI, 0.51–0.91; $P = 0.009$) using the dichotomized indicator variable. The HR for the CCI was HR = 1.186 (95% CI, 1.18–1.19; $P < 0.0001$), which indicates the HR per increase in one comorbidity. For the breast cancer model, the other adjusted model that showed significance, the HR for HHT was HR = 0.31 (95% CI, 0.13–0.74; $P = 0.0084$), as compared with a HR of 0.31 (95% CI, 0.13–0.75; $P = 0.0009$) using the dichotomized indicator variable.

A power analysis showed that our study had good power (88%) to detect the observed HR of 0.7 for the HHT group for the composite adjusted model, and very high power (>99%) to detect a HR of 0.56 in the unadjusted model. For breast cancer, we had 91% power to detect a HR of 0.3 in the HHT group, which was the effect in the adjusted and unadjusted models. For prostate cancer, we had 77% power to detect the unadjusted effect size of 0.44 and only 55% power to detect the adjusted effect size of 0.56. For colorectal cancer, we had less than 38% power to detect the observed effects sizes in the adjusted and unadjusted model; and for lung cancer, we had 57% power to detect the observed effect size of 0.7 in the

Published OnlineFirst November 5, 2013; DOI: 10.1158/1055-9965.EPI-13-0665

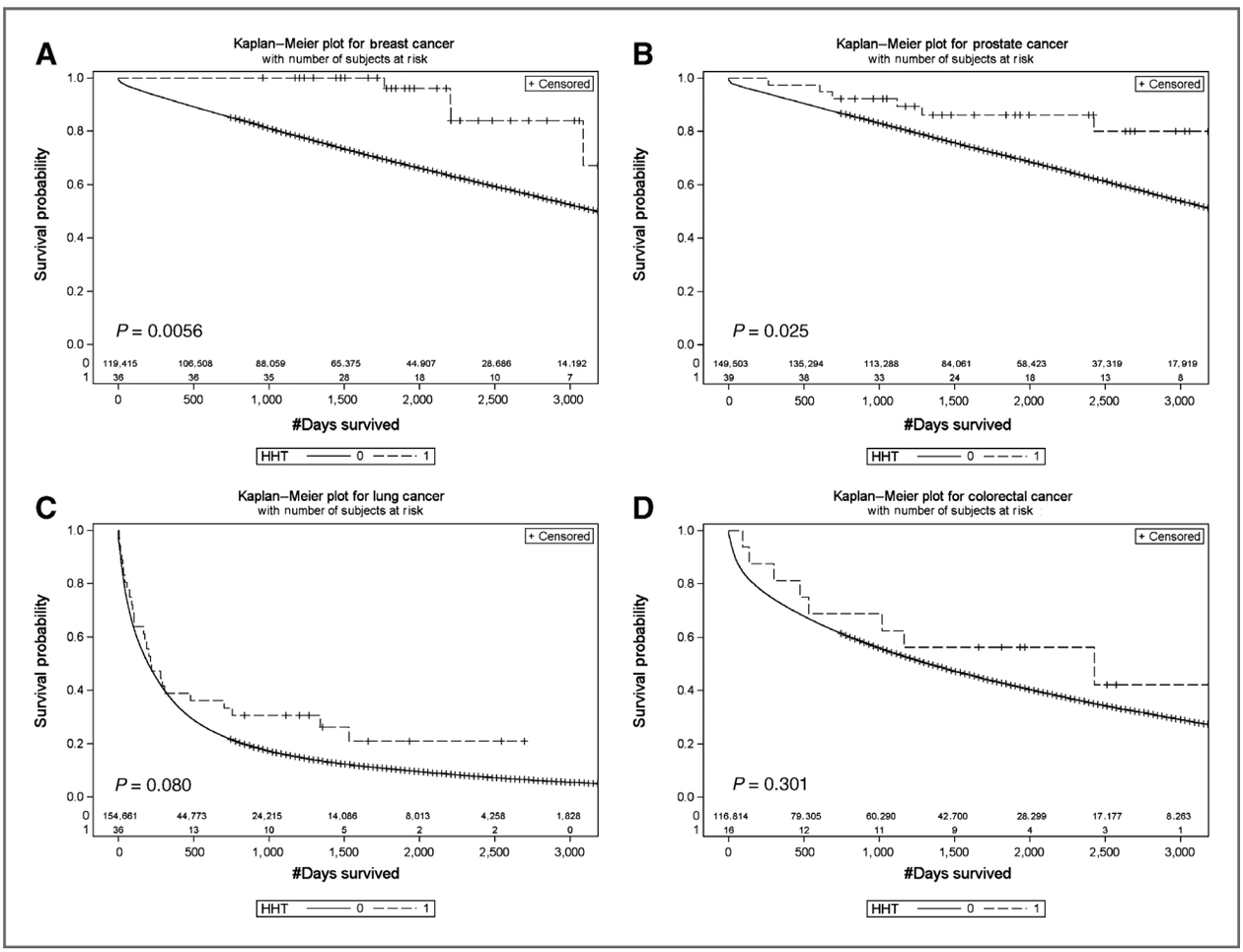

Figure 2. Kaplan–Meier survival curves by specific cancers: A, breast cancer; B, prostate cancer; C, lung cancer; and D, colorectal cancer. Diagnosis of normal non-HHT or HHT is indicated by 0 and 1, respectively. Log-rank *P* values are indicated in the panels.

unadjusted model. Thus, our observed results are consistent with expectations given the power analyses.

In addition to the composite cancer model in which the 4 cancers were combined, we also performed a meta-analysis of the results of both the crude and adjusted survival models. For the crude model analysis, we obtained a significant protective meta HR (HR = 0.61; 95% CI, 0.46–0.81; $P = 0.0006$). For the adjusted model analysis, we obtained a suggestive meta HR (HR = 0.75; 95% CI, 0.57–1.00; $P = 0.053$).

Discussion

Numerous studies support the role of endoglin in tumor progression and metastatic processes for several cancers (18). However, current data are conflicting about the net effect of endoglin expression on cancer progression and raise critical questions about the function of endoglin in different biologic environments. Thus, a dilemma is posed by these studies: is the dominant effect of endoglin expression in cancer operant at the level of inhibiting tumor invasiveness, for example, acting as a tumor suppressor, or does endoglin promote stromal investment of the tumor, leading to better vascularization and enhanced metastatic spread? The translational significance of these studies cannot be fully understood until this question is answered. When considering the findings of the present population-based human study, it suggests that the tumor microenvironment-associated functions of endoglin are dominant, and therefore, highlight the need for further basic research to elucidate critical biological processes, and clinical research to carefully develop and test cell-specific endoglin-targeting therapies. Such data would also clarify the biological significance of endoglin function in different human cancer contexts.

Our results show a highly significant protective effect for a composite of cancer patients with a diagnosis of HHT for the 4 most prevalent cancers in the United States (breast, prostate, colorectal, and lung cancer) in a survival analysis adjusting for confounding demographic and clinical factors. In addition, we show a particularly strong protective effect of HHT in breast cancer. Although we can

Published OnlineFirst November 5, 2013; DOI: 10.1158/1055-9965.EPI-13-0665

Table 2. Results from proportional hazard Cox regression models: adjusted HRs

Full model	HR (95% CI)	*P*-value
Cancer		
Breast	1.00 (referent)	NA
Colorectal	1.50 (1.48–1.52)	<0.0001
Lung	3.77 (3.73–3.82)	<0.0001
Prostate	0.68 (0.67–0.69)	<0.0001
HHT	0.69 (0.51–0.91)	0.009
Sex (male)	1.16 (1.15–1.17)	<0.0001
Age		
65 and younger	1.10 (1.08–1.12)	<0.0001
66–69 years	1.00 (referent)	NA
70–79 years	1.32 (1.30–1.34)	<0.0001
80 and older	2.45 (2.42–2.48)	<0.0001
Race (Black)	1.12 (1.11–1.13)	<0.0001
Education (census tract)		
>20% fewer than 12 years	1.22 (1.21–1.23)	<0.0001
10–20% fewer than 12 years	1.11 (1.10–1.13)	<0.0001
0–10% fewer than 12 years.	1.00 (referent)	NA
Missing	1.12 (1.10–1.15)	<0.0001
Urban		
Large metropolitan 1 million + population	0.97 (0.96–0.98)	<0.0001
Less than 1 million population	1.00 (referent)	NA
Cancer stage		
Early	1.00 (referent)	NA
Advanced	3.05 (3.02–3.07)	<0.0001
Unknown	2.29 (2.26–2.31)	<0.0001
1 or more comorbidities	1.43 (1.42–1.44)	<0.0001

Abbreviation: NA, not applicable.

only hypothesize the underlying cause for the improved survival outcomes among HHT patients, we propose that impaired expression of endoglin in HHT patients contributes a benefit because of reduced stromal support and angiogenesis, which impairs tumor progression. These findings are consistent with an enhancement of TGF-β–mediated stimulation of cancer-associated fibroblasts that promote tumor invasion (44). Thus, our study provides important insight into the existing animal model systems data that has yielded opposing results on the net effect of reduced endoglin expression, depending on the context of endoglin expression: the tumor itself versus the tumor microenvironment. For the first time, population data reflecting endoglin deficiency provide support for the hypothesis that there is a net benefit to reduced endoglin expression, thus underscoring the importance of the stromal microenvironment in specific tumor types, including breast and prostate cancers.

The strength of this study is that it represents a large comprehensive national survey of incident cancer cases in the United States. Thus, even though HHT is a rare disorder, the study sample gave sufficient power to compare survival outcomes of patients with cancer and without a recorded diagnosis of HHT. The limitations of

Table 3. Effect of HHT on survival by cancer

	Crude HR		Adjusted HR	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All	0.56 (0.42–0.74)	<0.0001	0.69 (0.51–0.91)	0.009
Breast	0.31 (0.13–0.75)	0.009	0.31 (0.13–0.75)	0.009
Colorectal	0.70 (0.35–1.39)	0.305	0.60 (0.30–1.21)	0.152
Lung	0.72 (0.49–1.04)	0.083	1.02 (0.70–1.49)	0.902
Prostate	0.44 (0.21–0.92)	0.030	0.56 (0.27–1.18)	0.128

Published OnlineFirst November 5, 2013; DOI: 10.1158/1055-9965.EPI-13-0665

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 adjusting our survival models by variables that are associated with HHT. Another limitation is that we have not recorded and adjusted for potential treatment differences in this cohort, which may influence survival. Although we do not expect variation in treatment to occur across these 2 groups (HHT and non-HHT), we have not specifically addressed this point, which would be challenging to assess because of the differences in standard treatment for the 4 different cancers being considered, so this is a limitation of this study. Another limitation is that the use of event-based reporting of HHT status from Medicare (billing) claims data 2 years before cancer diagnosis may result in undercounting HHT cases. However, we do not expect HHT reporting through claims data to be effected by differential health care coverage, as by design our cohort contains patients with Medicare coverage only (no supplementary coverage).

In conclusion, this is a retrospective study that includes a large representative sample of the United States cancer population and thus has sufficient power to address the relation between HHT diagnosis and survival outcome. The results, based on over 540,520 cancer patients and 127 instances of HHT diagnosis, relates an endoglin-deficient state to cancer outcomes, providing support for the hypothesis that endoglin expression in the stroma, versus the tumor, is a determinant of cancer survival, and suggests which high prevalence cancers might most benefit from endoglin-suppressive anti-endoglin antibody therapies (4).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C.W. Duarte, K. Murray, F.L. Lucas, K. Fairfield, H. Miller, C.P.H. Vary
Development of methodology: C.W. Duarte, K. Murray, F.L. Lucas, K. Fairfield
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Murray, H. Miller
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.W. Duarte, K. Murray, F.L. Lucas, K. Fairfield, P.C. Brooks
Writing, review, and/or revision of the manuscript: C.W. Duarte, K. Murray, F.L. Lucas, K. Fairfield, P.C. Brooks, C.P.H. Vary
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.W. Duarte, K. Murray
Study supervision: C.W. Duarte

Acknowledgments

The authors thank Drs. M. Hansen and M. Jones for helpful discussions.

Grant Support

This work was supported by The National Center for Research Resources (NCRR) grant P30RR030927/P30GM103392 (R. Friesel, PI); P. Brooks was supported by National Cancer Institute (NCI) grant R01 CA91645; C.P.H. Vary was support by National Heart, Lung, and Blood Institute (NHLBI) grant R01 HL083151 [of the National Institutes of Health (NIH)]. All investigators gratefully acknowledge institutional support from the Maine Medical Center.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received June 27, 2013; revised October 11, 2013; accepted October 17, 2013; published OnlineFirst November 5, 2013.

References

1. Arthur HM, Ure J, Smith AJ, Renforth G, Wilson DI, Torsney E, et al. Endoglin, an ancillary TGF-β receptor, is required for extraembryonic angiogenesis and plays a key role in heart development. Dev Biol 2000;217:42–53.
2. Bourdeau A, Faughnan ME, Letarte M. Endoglin-deficient mice, a unique model to study hereditary hemorrhagic telangiectasia. Trends Cardiovasc Med 2000;10:279–85.
3. Li DY, Sorensen LK, Brooke BS, Urness LD, Davis EC, Taylor DG, et al. Defective angiogenesis in mice lacking endoglin. Science 1999;284:1534–7.
4. Rosen LS, Hurwitz HI, Wong MK, Goldman J, Mendelson DS, Figg WD, et al. A phase I first-in-human study of TRC105 (Anti-endoglin antibody) in patients with advanced cancer. Clin Cancer Res 2012;18:4820–9.
5. Barbara NP, Wrana JL, Letarte M. Endoglin is an accessory protein that interacts with the signaling receptor complex of multiple members of the transforming growth factor-β superfamily. J Biol Chem 1999;274:584–94.
6. Blanco FJ, Santibanez JF, Guerrero-Esteo M, Langa C, Vary CP, Bernabeu C. Interaction and functional interplay between endoglin and ALK-1, two components of the endothelial transforming growth factor-beta receptor complex. J Cell Physiol 2005;204:574–84.
7. Scherner O, Meurer SK, Tihaa L, Gressner AM, Weiskirchen R. Endoglin differentially modulates antagonistic transforming growth factor-β1 and BMP-7 signaling. J Biol Chem 2007;282:13934–43.
8. Bourdeau A, Dumont DJ, Letarte M. A murine model of hereditary hemorrhagic telangiectasia. J Clin Invest 1999;104:1343–51.
9. El-Gohary YM, Silverman JF, Olson PR, Liu YL, Cohen JK, Miller R, et al. Endoglin (CD105) and vascular endothelial growth factor as prognostic markers in prostatic adenocarcinoma. Am J Clin Pathol 2007;127:572–9.
10. Saad RS, Liu YL, Nathan G, Celebrezze J, Medich D, Silverman JF. Endoglin (CD105) and vascular endothelial growth factor as prognostic markers in colorectal cancer. Mod Pathol 2004;17:197–203.
11. Smith SJ, Tilly H, Ward JH, Macarthur DC, Lowe J, Coyle B, et al. CD105 (Endoglin) exerts prognostic effects via its role in the microvascular niche of paediatric high grade glioma. Acta Neuropathol 2012;124:99–110.
12. Kassouf W, Ismail HR, Aprikian AG, Chevalier S. Whole-mount prostate sections reveal differential endoglin expression in stromal, epithelial, and endothelial cells with the development of prostate cancer. Prostate Cancer Prostatic Dis 2004;7:105–10.
13. Wikstrom P, Lissbrant IF, Stattin P, Egevad L, Bergh A. Endoglin (CD105) is expressed on immature blood vessels and is a marker for survival in prostate cancer. Prostate 2002;51:268–75.
14. Gomez-Esquer F, Agudo D, Martinez-Arribas F, Nunez-Villar MJ, Schneider J. mRNA expression of the angiogenesis markers VEGF and CD105 (endoglin) in human breast cancer. Anticancer Res 2004;24:1581–5.
15. Takase Y, Kai K, Masuda M, Akashi M, Tokunaga O. Endoglin (CD105) expression and angiogenesis status in small cell lung cancer. Pathol Res Pract 2010;206:725–30.

Published OnlineFirst November 5, 2013; DOI: 10.1158/1055-9965.EPI-13-0665

16. Minhajat R, Mori D, Yamasaki F, Sugita Y, Satoh T, Tokunaga O. Endoglin (CD105) expression in angiogenesis of colon cancer: analysis using tissue microarrays and comparison with other endothelial markers. Virchows Arch 2006;448:127–34.
17. Bernabeu C, Lopez-Novoa JM, Quintanilla M. The emerging role of TGF-β superfamily coreceptors in cancer. Biochim Biophys Acta 2009;1792:954–73.
18. Perez-Gomez E, Del Castillo G, Juan Francisco S, Lopez-Novoa JM, Bernabeu C, Quintanilla M. The role of the TGF-beta coreceptor endoglin in cancer. Sci World J 2010;10:2367–84.
19. Liu Y, Jovanovic B, Pins M, Lee C, Bergan RC. Over expression of endoglin in human prostate cancer suppresses cell detachment, migration and invasion. Oncogene 2002;21:8272–81.
20. Lakshman M, Huang X, Ananthanarayanan V, Jovanovic B, Liu Y, Craft CS, et al. Endoglin suppresses human prostate cancer metastasis. Clin Exp Metastasis 2011;28:39–53.
21. Craft CS, Romero D, Vary CP, Bergan RC. Endoglin inhibits prostate cancer motility via activation of the ALK2-Smad1 pathway. Oncogene 2007;26:7240–50.
22. Romero D, Terzic A, Conley BA, Craft CS, Jovanovic B, Bergan RC, et al. Endoglin phosphorylation by ALK2 contributes to the regulation of prostate cancer cell migration. Carcinogenesis 2010;31:359–66.
23. Romero D, O'Neill C, Terzic A, Contois L, Young K, Conley BA, et al. Endoglin regulates cancer-stromal cell interactions in prostate tumors. Cancer Res 2011;71:3482–93.
24. McAllister KA, Grogg KM, Johnson DW, Gallione CJ, Baldwin MA, Jackson CE, et al. Endoglin, a TGF-β binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Nat Genet. 1994;8:345–51.
25. Saluja S, White RI. Hereditary hemorrhagic telangiectasia of the liver: hyperperfusion with relative ischemia—poverty amidst plenty. Radiology 2004;230:25–7.
26. Sabba C, Gallitelli M, Pasculli G, Suppressa P, Resta F, Tafaro GE. HHT: a rare disease with a broad spectrum of clinical aspects. Curr Pharm Des 2006;12:1217–20.
27. Sabba C, Pasculli G, Lenato GM, Suppressa P, Lastella P, Memeo M, et al. Hereditary hemorrhagic telangiectasia: clinical features in ENG and ALK1 mutation carriers. J Thromb Haemost 2007;5:1149–57.
28. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000;91:66–7.
29. Zippin C, Lum D, Hankey BF. Completeness of hospital cancer case reporting from the SEER Program of the National Cancer Institute. Cancer 1995;76:2343–50.
30. Nattinger AB, McAuliffe TL, Schapira MM. Generalizability of the surveillance, epidemiology, and end results registry population: factors relevant to epidemiologic and health care research. J Clin Epidemiol 1997;50:939–45.
31. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care 2002;40:IV-3-18.
32. Klabunde CN, Warren JL, Legler JM. Assessing comorbidity using claims data: an overview. Med Care 2002;40:IV-26-35.
33. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–9.
34. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
35. van Gent MW, Velthuis S, Post MC, Snijder RJ, Westermann CJ, Letteboer TG, et al. Hereditary hemorrhagic telangiectasia: how accurate are the clinical criteria? Am J Med Genet A 2013;161:461–6.
36. Kaltenboeck A, Johnson SJ, Davis MR, Birnbaum HG, Carroll CA, Tarrants ML, et al. Direct costs and survival of medicare beneficiaries with early and advanced Parkinson's disease. Parkinsonism Relat Disord 2012;18:321–6.
37. Cox DR, Oakes D. Analysis of survival data. London: Chapman & Hall; 1984.
38. Collett D. Modelling survival data in medical research. London: Chapman & Hall; 1994.
39. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc 2009;172:137–59.
40. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. Stat Med 2003;22:2693–710.
41. Zarrabeitia R, Albinana V, Salcedo M, Senaris-Gonzalez B, Fernandez-Forcelledo JL, Botella LM. A review on clinical management and pharmacological therapy on hereditary haemorrhagic telangiectasia (HHT). Curr Vasc Pharmacol 2010;8:473–81.
42. Cole SG, Begbie ME, Wallace GM, Shovlin CL. A new locus for hereditary haemorrhagic telangiectasia (HHT3) maps to chromosome 5. J Med Genet 2005;42:577–82.
43. Harrell FE Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–87.
44. Casey TM, Eneman J, Crocker A, White J, Tessitore J, Stanley M, et al. Cancer associated fibroblasts stimulated by transforming growth factor-β1 (TGF-β1) increase invasion rate of tumor cells: a population study. Breast Cancer Res Treat 2008;110:39–49.

Correction

Cancer Epidemiology, Biomarkers & Prevention

Correction: Improved Survival Outcomes in Cancer Patients with Hereditary Hemorrhagic Telangiectasia

In this article (Cancer Epidemiol Biomarkers Prev 2014;23:117–25), which appeared in the January 2014 issue of *Cancer Epidemiology, Biomarkers & Prevention* (1), a source of grant support was not included in the grant support section of the article. The modified grant support section is included below. The authors regret this error.

Grant Support

This work was supported by The National Center for Research Resources (NCRR) grant P30RR030927/P30GM103392 (R. Friesel, PI); P. Brooks was supported by National Cancer Institute (NCI) grant R01 CA91645; and C.P.H. Vary was supported by National Heart, Lung, and Blood Institute (NHLBI) grant R01 HL083151 (of the NIH). All investigators gratefully acknowledge institutional support from the Maine Medical Center. This research is supported in part through the NIH National Institute of General Medical Sciences (NIH/NIGMS) COBRE in Stem Cell Biology and Regenerative Medicine (8P20GM103465).

Reference

1. Duarte CW, Murray K, Lucas FL, Fairfield K, Miller H, Brooks P, et al. Improved survival outcomes in cancer patients with hereditary hemorrhagic telangiectasia. Cancer Epidemiol Biomarkers Prev 2014;23:117–25.

Published online May 1, 2015.
doi: 10.1158/1055-9965.EPI-14-1404

AACR

Published OnlineFirst November 5, 2013; DOI: 10.1158/1055-9965.EPI-13-0665

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Improved Survival Outcomes in Cancer Patients with Hereditary Hemorrhagic Telangiectasia

Christine W. Duarte, Kimberly Murray, F. Lee Lucas, et al.

Cancer Epidemiol Biomarkers Prev 2014;23:117-125. Published OnlineFirst November 5, 2013.