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A Retrospective Pilot Study Suggesting an Increased Prevalence of Stroke in Patients with Breast Cancer in the Greater Cincinnati/Northern Kentucky Region

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Abstract

We identified a subset of 137 patients from the Greater Cincinnati/Northern Kentucky area (GCNK Region; Hamilton and Clermont counties in Ohio and Boone, Campbell, and Kenton counties in Kentucky) who had a diagnosis of cancer before a stroke. Then, further analysis was performed on the 98 patients within this population who had an ischemic stroke or TIA. This subset's most prevalent cancer type was breast (17.4%), followed by prostate (10.2%). A chi-square statistic was used to test the difference in cancer rates in this stroke database compared to a cancer only database from the University of Cincinnati Medical Center, with a 5% significance level. Interestingly, the prevalence of breast cancer in stroke patients was greater than that of the general cancer population (p=0.03). A retrospective chart review was conducted on the 17 patients with breast cancer documented before their ischemic stroke or TIA to identify potential etiologies in ischemic stroke/TIA incidence. This small dataset suggests breast cancer therapy may be associated with increased stroke incidence compared to several cancer subtypes. We recommend a large sample-size, extensive, prospective, well-designed registry with cancer patients to better control patient variables and determine if stroke is more prevalent in the breast cancer population compared to other cancer types. This prospective cohort may aid in identifying the potential risk factors that increase the risk of ischemic stroke in breast cancer patients.

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Introduction

Cancer is a common comorbidity of stroke [1] with a higher prevalence of ischemic and hemorrhagic stroke among cancer patients than in the general population [2-7]. The predominant theory is that cancers can contribute to stroke through primary mechanisms including tumor growth with subsequent artery compression, a hypercoagulable state, and secondarily through treatment-related side effects [1]. Post-surgical resection, oncology patients are commonly discharged on an anticoagulant for longer periods than other patients due to this fact. This hypercoagulable phenomenon is not novel, having first been described by Armand Trousseau in 1865 as migratory thrombophlebitis [8,9]. Despite over a century and a half passing, our understanding of the molecular underpinnings of the hypercoagulable state in cancer remains not well-understood.

Regarding the cancer-inherent mechanism, tumors often secrete Cancer Procoagulant (CP) and tissue factor, proteins that promote a hypercoagulable state which in turn increases the risk of ischemic stroke or TIA [1,10]. Brain tumors represent a unique subset of cancers with a link to Venous Thromboembolism (VTE) and stroke (i.e. arterial thromboembolism) given its localization within the brain parenchyma. In contemporary cohorts, Glioblastoma (GBM) has been associated with a 22%-30% incidence of symptomatic VTE [11]. Like metastatic tumors, brain tumors can have a compressive effect on intracranial vasculature reducing flow to critical areas of the brain.

Cancer also secondarily causes stroke through an immunocompromised state or the effects of radiation and/or chemotherapy. Many cancer patients are immunocompromised, putting them at greater risk of intracranial infection, abscess, and vasculitis. The immune response to these infections can further damage the inner cell lining of arteries and veins, increasing the risk of stroke [12]. Similarly, chemotherapy can cause damage to the endothelial lining of arteries and veins, increasing the risk of blood clotting and stroke [13]. In particular, platinum-based therapy and Vascular Endothelial Growth Factor (VEGF) inhibitors are associated with higher risks of ischemic strokes through the release of prothrombotic factors from apoptotic cancer cells and impairing cell regeneration [14-20]. However, a study by Du et al. found that the use of some chemotherapy agents, specifically colony-stimulating factors, and erythropoiesis-stimulating agents, were not significantly related to increased stroke risk [21]. This suggests there is nuance in specific-therapy type and stroke risk, a relationship which this study further explores. Lastly, radiation therapy can result in vascular wall fibrosis, providing a nidus for thrombus formation [16].

Patients with breast cancer have reported a higher incidence of stroke, though the exact mechanism(s) remain unknown [17]. Studies have shown that in post-menopausal women, the use of the estrogen receptor antagonist, tamoxifen, resulted in a significantly higher incidence of ischemic stroke than the use of the aromatase inhibitor, anastrozole [18]. Additionally, breast cancer patients have an 82% increased risk of ischemic stroke and a 29% increased risk of other stroke types when treated with tamoxifen, according to a meta-analysis conducted on breast cancer treatment clinical trials [19]. Overall, endocrine therapy may be a useful predictor in evaluating stroke risk in breast cancer patients [20].

In our study, we identified a group of stroke patients from the GCNK area and examined cancer as a comorbidity to address the gap in knowledge of which cancer types are more likely to precede stroke. Previous studies have looked at individual cancer types and future stroke risk. This study is novel in that a stroke database is analyzed for various cancers simultaneously. As such, this exploratory analysis is a preliminary step to systematically identify the relationship between multiple cancer subtypes and stroke.

Materials and Methods

Inclusion/Exclusion criteria

Inclusion criteria consist of the 137 patients treated for stroke in the Greater Cincinnati/Northern Kentucky (GCNK) Region in 2015 who were identified as having a diagnosis of any form or stage of cancer before their documented stroke event. The stroke data was gathered from all hospitalized and autopsied cases of stroke and Transient Ischemic Attack (TIA) treated at the University of Cincinnati Medical Center (UCMC). This patient population is derived from the 1.3 million inhabitants of a five-county region of Greater Cincinnati and Northern Kentucky (Hamilton and Clermont counties in Ohio and Boone, Campbell and Kenton counties in Kentucky) (Figure 1). The stroke database collects data every five years in a cross-sectional manner with 2015 being the most recently available dataset. The GCNK data were then grouped by primary cancer type to determine which type of cancer was most prevalent in those experiencing stroke. Data was also obtained for all cancer patients treated at the UCMC Barrett Cancer Center in 2015. The 2015 UCMC database served as a comparison group for the prevalence of select cancers in the general Cincinnati population. Exclusion criteria include patients who were diagnosed with cancer during a hospitalization for stroke to more definitively establish temporality between cancer and stroke incidence. Additionally, skin cancers were excluded as a cancer subcategory due to their numerous potential diagnoses.

The GCNK database is a well-published stroke datasets with experienced stroke nurses performing chart review. Furthermore, it has been NIH funded for over 30 years. The same team looked at cancer data as well. All the above factors support the validity of data acquisition.

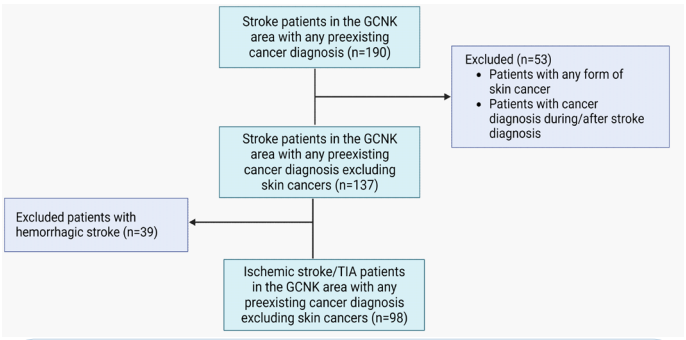

Figure 1: Inclusion and exclusion criteria for the GCNK stroke database.

Patients included in this study were residents of the GCNK area treated at UCMC with a preexisting cancer diagnosis at time of stroke diagnosis. Excluded patients were those with any form of skin cancer and those who were diagnosed with cancer after stroke. Further subgroup analysis was performed on patients only with ischemic stroke/TIA as the pathophsyiological mechanism differs from that of hemorrhagic stroke.

Statistical analysis

To determine if there was a statistically significant difference in cancer subtype prevalence amongst stroke patients com-

pared to a general cancer population, cancer rates between the 2015 GCNK Region stroke patients and all-cancer UCMC patients were compared using a chi-square or Fisher's exact test, as appropriate (SAS version 9.4; SAS Institute, Cary, NC). For breast cancer both an overall rate was compared and then the rate for females only. Breast cancer was diagnosed in only three male patients. In addition, for prostate cancer, overall rates were compared for consistency, but then rates were just compared for the males within each population. A p-value <0.05 was considered statistically significant.

Individual-level variables

Further retrospective chart review was conducted on the 24 stroke patients who were diagnosed with breast cancer which included patient data from our institution, UCMC. We collected sociodemographic data and medical comorbidities on this subset of patients. Briefly, data obtained included: Living status (date of death, if applicable), age, sex, ethnicity, race, zip code of residence, cancer stage, date of diagnosis, age at diagnosis, date of stroke, age at the time of stroke, type of stroke, which hormone therapy the patient was using, aspirin or statin use with dosage, whether antithrombotic medication were used before or after stroke event, changes in patients' antithrombotic medication, treatment information, comorbidities, d-dimer levels measured in ug/mL, and insurance providers.

Results

There was a total of 137 total stroke patients in the GCNK Region that also had cancer. Breast cancer and prostate cancer were the two most prevalent cancer types in surveyed stroke patients with 24 (17.5%) and 15 patients (10.9%), respectively. Table 1 shows the breakdown for the number of patients per cancer type for the seven most common cancers in the GCNK Region stroke cohort. This data includes both hemorrhagic and ischemic stroke/TIA. The accompanying patient numbers for those seven cancer types in the UCMC 2015 all-cancer data are included (*n* = 2,488). The most common cancer type in the UCMC data set was lung, followed by breast cancer. The rates and respective p-values are reported for each cancer type in Table 1. Breast cancer (p=0.009), prostate cancer (p<.0001), and bladder cancer (p=0.04) were all significantly higher in the all-stroke population than in the all-cancer population of UCMC. Lung cancer (p=0.02) was significantly lower in the all-stroke population than in the UCMC cancer population.

Table 1: Breakdown of number and percentage of patients affected by the seven most common primary cancers in the GCNK Region.

Type of Cancer	GCNK Region All-stroke 2015 (*n* = 137)	UCMC 2015 All-cancer (*n* = 2448)	p-value GCNK Region vs UCMC
Breast Females only	**24 (17.5%)** 24/75 (32.0%)*	**254 (10.4%)** 251/1121 (22.4%)*	**0.009** 0.055
Prostate Males only	15 (10.9%) **15/62 (24.2%)***	171 (7.0%) **171/1327 (12.9%)***	0.08 **<.0001**
Colorectal	9 (6.6%)	101 (4.1%)	0.19†
Brain	8 (5.8%)	103 (4.2%)	0.38†
Bladder	**7 (5.1%)**	**53 (2.2%)**	**0.04†**
Lung	**7 (5.1%)**	**279 (11.4%)**	**0.02†**
Gynecological Females only	5 (3.6%) 5/75 (6.7%)	127 (5.2%) 127/1121 (11.3%)	0.55† 0.21

*Denominator of just females used for breast cancer (3 males in the UCMC database had primary breast cancer); just males for prostate cancer. Chi-square used to compare populations except for † where Fisher's exact test was used.

Further analysis revealed that 98 of the 137 GCNK Region patients (71.53%) had an ischemic stroke or TIA. Among the patients in the GCNK Region who were admitted to UCMC with ischemic stroke or TIA, the most prevalent form of primary cancer was breast with 17 patients (17.4%). At UCMC in 2015, there were 2,448 total cancer patients. 254 patients had breast cancer (10.4%) and 171 (7.0%) had prostate cancer. When compared to the general population of cancer patients from our institution, there was a significantly higher rate of breast cancer amongst ischemic stroke or TIA patients than amongst the general population of cancer patients. There were no other statistically significant differences between the rate of cancer within the ischemic stroke/TIA population and the UCMC cancer population. The p-value for the difference in the rate of breast cancer for the two populations, including both males and females was significant at p=0.03**.** When this analysis was limited to females diagnosed with breast cancer, this analysis was not significant at p = 0.08.

Table 2 shows the breakdown for the number of patients by cancer type for the seven most common cancers in the GCNK Region, along with the respective patient numbers from the UCMC 2015 site distribution.

Table 3 provides a demographic breakdown for both the GCNK Region dataset, both "all-stroke" and "ischemic/TIA", and the UCMC 2015 all-cancer data.

Table 2: Breakdown of number of patients and percentage of patients affected by the seven most common primary cancers in the GCNK Region.

Type of Cancer	GCNK Region Ischemic/TIA only 2015 (*n* = 98)	UCMC 2015 All-cancer (*n* = 2448)	p-value GCNK Region vs UCMC
Breast Females only	**17 (17.4%)** 17/52 (32.7%)*	**254 (10.4%)** 251/1121 (22.4%)*	**0.03** 0.08
Prostate Males only	10 (10.2%) 10/46 (21.7%)*	171 (7.0%) 171/1327 (12.9%)*	0.22 0.08
Brain	7 (7.1%)	103 (4.2%)	0.20†
Colorectal	6 (6.1%)	101 (4.1%)	0.30†
Lung	6 (6.1%)	279 (11.4%)	0.14†
Bladder	4 (4.1%)	53 (2.2%)	0.28†
Gynecological Females only	4 (4.1%) 4/52 (7.7%)	127 (5.2%) 127/1121 (11.3%)	0.82† 0.42

*Denominator of just females used for breast cancer (3 males in the UCMC database had primary breast cancer); just males for prostate cancer. Chi-square used to compare populations except for † where Fisher's exact test was used.

Timing of medical events

Amongst the 17 breast cancer patients in the subset of patients who went on to suffer from an ischemic stroke or TIA; eight (47.06%) are now deceased and nine (52.94%) are living as of January 2023, 11 (64.71%) identified as non-Hispanic Caucasians and 6 (35.29%) identified as non-Hispanic African Americans, 13 (76.47%) of the patients resided in the city of Cincinnati, one (5.88%) of them resided in townships in the greater Cincinnati area, and three (17.65%) of them resided in the cities

of Northern Kentucky (Tables S1 and S2). The age of patients at the time of their breast cancer diagnosis was younger than 40 (5.9%), 40-49 years old (11.8%), 50-59 years old (11.8%), 60-69 years old (35.3%), and 70-79 years old (23.5%), two patients had unknown age at diagnosis because data reflects their cancer initiated within the decade of 1990; therefore, no specific date of diagnosis within their electronic medical record is available for calculation. The mean age of all patients at the time of their ischemic stroke or TIA was 71.5 years.

The timeframe between breast cancer diagnosis and subsequent ischemic stroke/TIA was 0-4 years (41.2%), 5-9 years (11.8%), 10-14 years (11.8%), 15-19 years (17.6%), and 42 years (5.9%). Seven of the ischemic stroke/TIA patients (41.18%) were undergoing active treatment for breast cancer at the time of stroke. Six were receiving some form of immuno- or chemotherapy; one was undergoing radiotherapy.

Breast cancer staging

One of the ischemic stroke patients (5.9%) was diagnosed with Stage 0 breast cancer. Five patients (29.4%) had Stage 1, three (17.6%) had Stage 2, and two (11.8%) had Stage 3 disease (Table 4). The remaining six patients (35.3%) were either listed as unstaged or unknown. Of the seven hemorrhagic stroke patients, one had stage 1, one had stage 2 and for five the stage was unknown.

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Table 3: Breakdown of number and percentage of patients of each demographic in the GCNK Region population with cancer in 2015 and for those in the UCMC site treated for cancer in 2015. *This does not include those outside of the GCNK Region.

	GCNK Region 2015 All-stroke (*n* = 137)	GCNK Region 2015 Ischemic/TIA (*n* = 98)	UCMC 2015 All-cancer (*n* = 2448)	p-value All strokes vs UCMC	p-value Ischemic/TIA vs UCMC
Sex				**0.04**	0.16
Female	**75 (54.7%)**	52 (53.1%)	**1121 (45.8%)**		
Male	**62 (45.3%)**	46 (46.9%)	**1327 (54.2%)**		
Race				0.21	0.28
Non-Hispanic Caucasian	108 (78.8%)	75 (76.5%)	1920 (78.4%)		
Non-Hispanic African American	28 (20.4%)	22 (22.4%)	446 (18.2%)		
Other	1 (0.7%)	1 (1.0%)	82 (3.4%)		
Area of residence				0.10*	0.13*
City of Cincinnati	99 (72.3%)	73 (74.5%)	1093 (71.2%)		
Greater Cincinnati Area	13 (9.5%)	8 (8.2%)	231 (15.1%)		
Northern Kentucky	25 (18.2%)	17 (17.4%)	210 (13.7%)		
Outside of GCNK Region	0	0	925		
Type of stroke					
Hemorrhagic	39 (28.5%)				
Ischemic	78 (56.9%)	78 (79.6%)			
TIA	20 (14.6%)	20 (20.4%)			
Age at Time of Stroke (years), mean (standard deviation)	71.6 (12.0)	71.1 (12.1)			

Table 4: Breakdown of the number of patients by current AJCC breast cancer staging by population.

	GCNK Region 2015 (All-stroke) (*n* = 24)	GCNK Region 2015 (Ischemic/TIA only) (*n* = 17)	UCMC 2015 (*n* = 243)
0	1 (4.2%)	1 (5.9%)	28 (11.5%)
I	6 (25.0%)	5 (29.4%)	107 (44.0%)
II	4 (16.7%)	3 (17.6%)	35 (14.4%)
III	2 (8.3%)	2 (11.8%)	13 (5.3%)
IV	0 (0%)	0 (0%)	28 (11.5%)
Unknown	1 (25.0%)	1 (5.9%)	28 (11.5%)
N/A	10 (20.8%)	5 (29.4%)	4 (1.6%)

Cancer treatment information

All the ischemic stroke or TIA patients underwent one or more forms of treatment for their breast cancer (Table 5). Eight patients were confirmed to have received some form of hormone therapy while six patients received some form of chemotherapy or hormone therapy as part of their treatment regimen. These drugs included: anastrozole, exemestane, tamoxifen, letrozole, trastuzumab, fluorouracil, doxorubicin, cyclophosphamide, paclitaxel, carboplatin, and docetaxel. Eight patients received radiotherapy for their breast cancer diagnosis. Dosages ranged from 42.56 to 50.4 Gy. Fifteen patients had surgery following their diagnosis. Common interventions included biopsies, fine needle aspiration, lumpectomy, and mastectomy. Patients ranged from having only one treatment modality, to a combination of any of the three.

Table 5: Breakdown of each cancer treatment modality in the GCNK Region breast cancer patients who had an ischemic stroke or TIA. Note: Some patients could be treated by more than one modality.

	GCNK Region Ischemic/TIA only (*n* = 17)
Hormone Therapy	
Yes	8 (47.1%)
No	4 (23.5%)
Unknown	5 (29.4%)
Chemotherapy	
Yes	6 (35.3%)
No	7 (41.2%)
Unknown	4 (23.5%)
Radiation	
Yes	8 (47.1%)
No	5 (29.4%)
Unknown	4 (23.5%)
Surgical Intervention	
Yes	15 (88.2%)
No	2 (11.8%)

Aspirin/Statin use

Ten of the 17 TIA/stroke patients with concurrent breast cancer (58.8%) were prescribed antiplatelet medications (aspirin or clopidogrel) before their stroke event. Of the ten patients on antiplatelet medication, five patients (50%) continued the same medicine and dosage following their stroke event, while the other five patients (50%) were prescribed an additional antithrombic medication or changed dosages of the medication they were taking prior to their stroke. Additionally, nine patients (52.9%) were using statin medications before having a stroke. Common statin drugs included atorvastatin (ranging doses from 20-80mg), rosuvastatin (40mg), and pravastatin (40mg). Exact medication start dates and/or dose changes were not recorded in the chart review.

Comorbidities

The most common comorbidity amongst our ischemic stroke patients with breast cancer was hypertension (16 patients, 94.3%). Eight patients (47.1%) had a history of diabetes mellitus, and 13 patients (76.5%) had a history of hyperlipidemia (Table 8). Additionally, eight patients (47.1%) had a history of smoking, with two of those patients (11.8%) reporting they were currently smoking at the time of their ischemic stroke event. Other comorbidities in this population include heart failure or other heart conditions, COPD or other respiratory ailments, chronic kidney disease, epilepsy, and other cancers. One patient was confirmed to have brain metastasis originating from her breast cancer diagnosis and another patient was suspected to have brain metastasis, however, imaging was not obtained to confirm before hospice care was initiated. Two patients (8%) had documented leptomeningeal disease.

Table 6: Breakdown of variables analyzed as potential risk factors for stroke in breast cancer patients only and the respective patient numbers from the GCNK Region stroke cohort for each variable.

Variable	GCNK Region All-stroke (*n* = 24)	GCNK Region Ischemic/TIA only (*n* =17)
Sex – Female	24 (100%)	17(100%)
Race/ethnicity		
Non-Hispanic Caucasian	15 (62.5%)	11 (64.7%)
Non-Hispanic African American	9 (37.5%)	6 (35.3%)
Age at stroke (years)		
Mean (standard deviation)	73.4 (13.2)	71.5 (13.6)
Insurance		
Medicare	12 (50%)	8 (47.1%)
Medicaid	2 (8.3%)	1 (5.9%)
Medicare & Medicaid	6 (25%)	5 (29.4%)
Private	4 (16.7%)	3 (17.6%)
History of Hypertension	23 (95.8%)	16 (94.1%)
History of Diabetes	9 (37.5%)	8 (47.1%)
History of Hyperlipidemia	16 (66.7%)	13 (76.5%)
Smoking status		
Current	2 (8.3%)	2 (11.8%)
Past	8 (33.3%)	6 (35.3%)
Never	14 (58.3%)	9 (52.9%)

Thromboembolic events

Five patients (29.41%) had thromboembolic events noted within their medical records. The most common events included pulmonary embolism and deep vein thrombosis. Two of the 12 patients with ischemic strokes only (not including TIA) were given tPA. The etiology of the ischemic strokes/TIAs were small vessel (11.8%), cardioembolic (23.53%), large vessel (5.88%),

and one classified as "other" (5.88%). 9 patients (52.94%) did not have known etiology for their stroke.

Insurance coverage

The types of insurance coverage in the ischemic stroke population with breast cancer varied, with most having Medicare or Medicaid (Table 6). Eight patients (47.1%) listed Medicare as their primary insurance provider, whether it was government-based directly or through another insurance company. Three patients (17.6%) had private insurance. One patient (5.9%) was covered by Medicaid through an insurance provider, and five patients (29.4%) had combined Medicare and Medicaid.

Discussion

In this retrospective study, the prevalence of various cancer subtypes within a stroke database was compared to the prevalence of these same cancer subtypes within all cancer patients treated at UCMC in 2015. Only the rate of breast cancer prevalence in the ischemic stroke/TIA population was found to be significantly higher (p=0.03) than in the overall cancer population. This suggests that there is a correlation between breast cancer and subsequent stroke that is worth further exploration. However, it must be noted that this relationship was not significant (p=0.08) when analysis was restricted to females only. The loss of significance is likely due to a combination of the small sample size of the study and the rarity of male breast cancer. Ischemic stroke events were detected in breast cancer patients in stages 0-4, with most patients experiencing stage 1 disease. Notably, 53% of patients included in this study experienced a stroke up to nine years following their breast cancer diagnosis. This may be due to the high survival rate of individuals diagnosed with breast cancer. The American Cancer Society reports that women who have breast cancer have a 5-year relative survival rate of 91% using data gathered from 2012-2018 [22]. As breast cancer patients live longer compared to brain and lung cancers, it is possible we may see an increase in ischemic stroke in this population.

Additionally, breast cancer is often treated with long-term hormone therapy and chemotherapy regimens, which have been shown to increase the likelihood of ischemic stroke [23]. Table 5 demonstrates the treatment regimens that patients in this study received for their cancers. In our study population, nearly half of the patients who had an ischemic stroke had documented use of hormone therapies. This may be a potential mechanism for ischemic stroke in this population and suggest that cancer patients who receive therapy are more likely to be hypercoagulable at the beginning of their systemic treatment [3]. Understanding the distribution of cancer and stroke in patients is extremely important when weighing their long-term health outcomes and providing care to this vulnerable population.

Insurance coverage was analyzed in this data set as a potential surrogate for patient socioeconomic status. Although Medicare is not need-based like Medicaid, it may be a proxy for socioeconomic status because it serves population older than 65. The co-payments required by this insurance may predict available income, as many are no longer working and live off social security or other retirement measures [24,25]. Patients on private insurance plans can likely afford healthcare, whereas this population of patients may not. Medicare patients are also typically elderly, which is a known risk factor for stroke. A total of 82.4% of patients had Medicare or Medicaid coverage, indicating that ischemic stroke or TIA in breast cancer patients could be linked with healthcare disparities such as access to care, available treatment options, and affordability of care which could contribute to ways in which women are not receiving effective care.

There was also a relatively low rate of antiplatelet medication (58.8%) and statin (52.9%) usage in the breast cancer population before an ischemic stroke/TIA. Furthermore, many of the breast cancer patients had significant comorbidities such as hyperlipidemia, hypertension, and diabetes which further supports the need for prophylactic medication for atherosclerosis and subsequent stroke. Perhaps increasing the rate of antiplatelet and statin adherence in this population would lead to decreasing stroke incidence. Future study should also focus on optimal medication dose and duration for stroke prophylaxis in breast cancer patients.

Initial analysis on all stroke patients, including hemorrhagic stroke, indicates several cancer types may confer significantly higher risk of stroke including breast, prostate, and bladder cancer (Table 1). We restricted most of our analysis to ischemic stroke/TIA as hemorrhagic stroke can be caused by trauma, metastasis, bleeding disorders, or vascular trauma secondary to cancer. As such, it is more difficult to identify possible associations between cancer pathogenesis and hemorrhagic stroke given these diverse etiologies. Future study may be helpful in identifying other correlations between cancer and hemorrhagic stroke.

Interestingly, data analysis did not reveal an increased incidence of stroke in the brain cancer subset (p=0.38). Given the intraparenchymal localization of primary brain tumor, we suspected this would inherently predispose this cancer subtype to both stroke subtypes. Chen et al. found an increased risk of ischemic stroke in glioma patients compared to a general population [26]. This may be a product of using all-cancer data from a highly specialized academic center in the area which will increase the number of brain tumor presentations. In fact, 4.2% of all cancers at UCMC in 2015 were brain tumors whereas the national percentage of new cancer diagnoses that are brain tumors was only 1.3% [27]. The sample size is small, and this finding could simply be due to statistical chance.

A limitation of this study is that it describes patient demographics from only one health system. This limited analysis to 24 patients available, making a case for larger future studies, especially in breast cancer patients. The selected GCNK Region stroke patients treated at our institution are not necessarily representative of the greater United States. However, the all-cancer UCMC data is fairly representative of larger, national cohorts for the most prevalent types of cancer (lung, breast) as the UCMC all-cancer data reflected national cancer prevalence accurately [28]. Additional limitations include unavailable patient data, including treatment or staging information, the very high rate of comorbidities within our sample population, and the inability to control for these factors given the retrospective design. The high rates of comorbidities, specifically the rate of hypertension and hyperlipidemia within the patient population, could be key contributing factors to ischemic stroke in addition to other history of cardiac events.

Conclusions

Due to the limitations discussed above, we believe that breast cancer treatments, healthcare disparities, and social de-

terminants should be taken into consideration in future studies as they may play a role in increasing the risk of stroke. We recommend that a larger prospective study be done to compare the number of breast cancer patients suffering from strokes with the general population of breast cancer patients to explore whether similar trends are identified in these larger groups and potentially identify other factors within the susceptible group that puts them at risk for stroke. For example, there could be shared risk factors such as smoking, alcohol consumption, and other lifestyle factors which would need to be controlled for more effective analysis. This should include a patient population representative of the entire GCNK Region, as opposed to our sample within our healthcare system, to obtain a thorough analysis, and decrease biases of a single institution. Additionally, comparing rates of breast cancer and stroke within national databases may prove useful in studying this phenomenon on a larger scale.

Eventually, a prospective study, including breast cancer patients in the United States with documented stroke incidence is warranted. Data from a larger population may identify what, if any, underlying mechanisms are involved in stroke following a breast cancer diagnosis, including the possibility of treatments predisposing to stroke risk. Additionally, obtaining patient samples such as serum and cerebrospinal fluid may prove useful in identifying molecular pathways associated with increased ischemic stroke risk in this patient population. Another interesting connection is the interplay of psychosocial factors, cancer, and stroke. There is data published on the adverse psychological effects of a breast cancer diagnosis on patients [29]. This could potentially lead to decreased adherence with medication regimens and participation in further studies [30,31]. It would be relevant to identify whether the negative psychosocial effect of cancer has an impact on stroke incidence in future prospective studies. Future data gathered from a prospective study may elucidate potential mechanisms between stroke and cancer. With this information, clinicians can identify gold standards in anticoagulation/antiplatelet dose and duration following cancer diagnosis to best prevent stroke.

Author contributions

Conceptualization, Stacie Demel and Soma Sengupta; Formal analysis, Jane Khoury; Investigation, Abigail Koehler; Methodology, Stacie Demel and Soma Sengupta; Supervision, Stacie Demel and Soma Sengupta; Writing-original draft, Abigail Koehler, Jane Khoury and Kiran Desai; Writing-review & editing, Rohan Rao, Abigail Koehler, Jane Khoury, Yehudit Rothman, Lalanthica Yogendran, Kathleen Alwell, Elizabeth Shaughnessy, Wuwei Feng, Stacie Demel and Soma Sengupta.

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Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of the University of Cincinnati (IRB 2013-3959). Additional IRB approvals awarded through participating hospitals.

Informed consent statement

Patient consent was waived due to this being a retrospective study without the use of any patient identifiers and the data being remote in time.

Data availability statement

Data is contained within the article or supplementary material.

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Conflicts of interest

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table S1: Demographic information for GCNK Region female patients who had breast cancer and for the male patients with prostate cancer who went on to suffer an ischemic stroke, hemorrhagic stroke, or TIA in 2015, and for the female patients with breast cancer and the male with prostate cancer at UCMC in 2015. *This does not include those outside of the GCNK Region. † Females only.

	Breast Cancer			Prostate Cancer		
	GCNK Region All- stroke (*n* = 24)	UCMC† (*n* = 254)	p-value	GCNK Region All-stroke (*n* = 15)	UCMC (*n* = 171)	p-value
Sex			1.00			NA
Female	24 (100%)	251 (98.8%)		0 (0%)	0 (0%)	
Male	0 (0%)	3 (1.2%)		15 (100%)	171 (100%)	
Race			0.41			0.56
Non-Hispanic Caucasian	15 (62.5%)	167 (65.8%)		12 (80.0%)	116 (67.8%)	
Non-Hispanic African American	9 (37.5%)	74 (29.1%)		3 (20.0%)	50 (29.2%)	
Other	0 (0%)	13 (5.1%)		0 (0%)	5 (2.9%)	
Area of residence			0.33*			0.09*
City of Cincinnati	19 (79.2%)	146 (82.0%)		11 (73.3%)	101 (76.5%)	
Greater Cincinnati Area	1 (4.2%)	16 (9.0%)		0 (0%)	17 (12.9%)	
Northern Kentucky	4 (16.7%)	16 (9.0%)		4 (26.7%)	14 (10.6%)	
Outside of GCNK Region	0	76		0	39	
Type of stroke						
Hemorrhagic	7 (29.2%)			5 (33.3%)		
Ischemic	12 (50.0%)			9 (60.0%)		
TIA	5 (20.8%)			1 (6.7%)		
Age at Time of Stroke (years), mean (SD)	73.4 (13.2)			74.5 (12.3)		
Age at Time of Cancer Diagnosis (years), mean (SD)	62.1 (12.6)					

Table S2: Demographic information for GCNK Region female patients who had breast cancer and for the male patients with prostate cancer who went on to suffer an ischemic stroke or TIA in 2015, and for the female patients with breast cancer and the male with prostate cancer at UCMC in 2015. *This does not include those outside of the GCNK Region. † Females only.

	Breast Cancer			Prostate Cancer		
	GCNK Region Ischemic Stroke/ TIA (n=17)	UCMC† (n=254)	p-value	GCNK Region Ischemic Stroke/ TIA (n=10)	UCMC (n=171)	p-value
Sex			1.00			NA
Female	17 (100%)	251 (98.8%)		0 (0%)	0 (0%)	
Male	0 (0%)	3 (1.2%)		10 (100%)	171 (100%)	
Race			0.58			0.86
Non-Hispanic Caucasian	11 (64.7%)	167 (65.8%)		7 (70.0%)	116 (67.8%)	
Non-Hispanic African American	6 (35.3%)	74 (29.1%)		3 (30.0%)	50 (29.2%)	
Other	0 (0%)	13 (5.1%)		0 (0%)	5 (2.9%)	
Area of residence			0.42*			0.47*
City of Cincinnati	13 (76.5%)	146 (82.0%)		9 (90.0%)	101 (76.5%)	
Greater Cincinnati Area	1 (5.9%)	16 (9.0%)		0 (0%)	17 (12.9%)	
Northern Kentucky	3 (17.6%)	16 (9.0%)		1 (10.0%)	14 (10.6%)	
Outside of GCNK Region	0	76		0	39	
Type of stroke						
Ischemic	12 (50.0%)			9 (60.0%)		
TIA	5 (20.8%)			1 (6.7%)		
Age at Time of Stroke (years), mean (SD)	71.5 (13.6)			73.4 (13.3)		
Age at Time of Cancer Diagnosis (years), mean (SD)	61.1 (12.1)					