

# Racial and Ethnic Disparities in Cancer-Associated Thrombosis

Courtney Wiredu<sup>1</sup> Norrissa Haynes<sup>2,3</sup> Carmen Guerra<sup>3,4,5,6</sup> Bonnie Ky<sup>2,5,6</sup>

<sup>1</sup>Department of Molecular Biology, Princeton University, Princeton, New Jersey, United States

<sup>2</sup>Division of Cardiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, United States

<sup>3</sup>Leonard Davis Institute, University of Pennsylvania, Philadelphia, Pennsylvania, United States

<sup>4</sup>Division of Internal Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, United States

<sup>5</sup>Abramson Cancer Center, Philadelphia, Pennsylvania, United States

<sup>6</sup>Department of Epidemiology, Center for Clinical Epidemiology and Biostatistics, Philadelphia, Pennsylvania, United States

**Address for correspondence** Bonnie Ky, MD, MSCE, Smilow Center for Translational Research, Perelman School of Medicine at the University of Pennsylvania, 3400 Civic Center Boulevard, Philadelphia, PA 19104, United States (e-mail: bonnie.ky@pennmedicine.upenn.edu).

Thromb Haemost 2022;122:662–665.

## Abstract

### Keywords

- ▶ ethnic groups
- ▶ neoplasms
- ▶ race
- ▶ risk factors
- ▶ venous thromboembolism

Active malignancy increases the risk of developing venous thromboembolism (VTE) by four- to seven-fold. The risk of VTE, including deep vein thrombosis and pulmonary embolism, in patients with cancer varies based on several clinical factors, such as cancer stage and age. However, race and ethnicity are also associated with increased VTE risk. Black (African American) patients with cancer have a higher risk of developing VTE than White patients, while Asian/Pacific Islanders have a lower risk. Studies on cancer-associated thrombosis demonstrate a need to advance our understanding of both the biologic and sociologic underpinnings of the observed differences according to race. Addressing the causes of these disparities can better health outcomes for historically underserved patient populations.

## Introduction

Globally, there are approximately 10 million cases of venous thromboembolism (VTE) each year<sup>1</sup> and patients with cancer are a particularly high-risk subgroup with a four- to seven-fold increased risk of VTE.<sup>2</sup> Known risk factors for cancer-associated thrombosis (CT) include cancer type (brain, kidney, and pancreatic), cancer stage, age, sex, recent surgery, and limited mobility. Studies also suggest that race and ethnicity contribute to increased CT risk.<sup>3</sup> Black (African American) patients with cancer are three times more likely to develop CT compared with White patients with cancer, while Asian/Pacific Islanders have lower risk.

Moreover, there are racial disparities in CT management and outcomes. Black patients are less likely to be treated with direct oral anticoagulants (DOACs). CT mortality also differs

by race. A retrospective study of 1,015,598 patients with cancer reported a significantly higher CT mortality rate among Black (18.9%), Hispanic (19.1%), and Asian (20.5%) patients compared with White patients (15.4%;  $p < 0.0001$ ).<sup>4</sup>

Precisely *how* race and ethnicity may determine health disparities in CT remains incompletely understood. Here, using a detailed search strategy (**Supplementary File S1**, available in the online version), we review the literature on CT disparities, focusing on race and ethnicity. We highlight differences according to the epidemiology and management of CT and explore the potential biologic and structural basis of these disparities.

## Epidemiology

CT incidence rates vary across racial groups, with a higher incidence in Black patients and lower incidence in Asians.<sup>2</sup>

### received

August 29, 2021

### accepted after revision

October 18, 2021

### published online

October 20, 2021

© 2021. Thieme. All rights reserved.

Georg Thieme Verlag KG,  
Rüdigerstraße 14,  
70469 Stuttgart, Germany

DOI <https://doi.org/10.1055/a-1674-0259>.

ISSN 0340-6245.

An observational study of 16,498 patients determined that among certain cancer types, including lung, gastric, and colorectal cancers, the unadjusted incidence rate in Black patients was three-fold greater compared to Whites (1.8% vs. 0.6%;  $p < 0.001$ ).<sup>3</sup> Significantly higher rates of pulmonary embolism were reported in Black than White patients (27.6% vs. 14.4%;  $p < 0.0001$ ), while the converse was true for deep vein thrombosis (51.9% vs. 59.5%;  $p = 0.02$ ).<sup>5</sup> These data suggest that the social, environmental, and epigenetic factors represented by race may mediate and modify CT risk.

The Khorana risk score, a commonly used CT risk calculator, uses five variables—cancer site, pre-chemotherapy platelet count, hemoglobin levels or use of red cell growth factors, leukocyte count, and body mass index (BMI).<sup>4</sup> Data suggest that the Khorana score does not accurately predict CT risk in Black patients as predicted estimates are similar between Blacks and Whites despite a greater incidence in Blacks.<sup>3</sup> These findings underscore a need for patient- and race-specific metrics to improve risk prediction across diverse populations.

### Biologic Mechanisms

One fundamental question regarding the observed racial differences in CT risk is how much of the increased risk is explained by genetic and biologic variation. Factor VIII (FVIII) levels, which increase thrombotic risk in a dose-dependent fashion, differ by race. In a study of 6,814 individuals, FVIII levels were significantly higher in Black Americans than in White, Chinese, and Hispanic Americans ( $p < 0.0001$ ).<sup>6</sup> FVIII levels are also higher in sickle cell, a prothrombotic disease, which is significantly more common among Blacks compared with Whites.<sup>7</sup> In contrast, the factor V Leiden polymorphism and prothrombin gene G20210A variant are more prevalent among Northern and Southern Europeans, and are each associated with an increased odds of VTE (factor V Leiden VTE odds ratio [OR] 4.9; 1.1–7.3% minor allele frequency [MAF]; prothrombin gene G20210A VTE OR 3.1; 1.1–4.0% MAF, respectively).<sup>8</sup> Protein C and protein S gene mutations increase VTE odds among Chinese (OR 6.4; 0.04–1.2% MAF) and Japanese populations (OR 5.2; 0.9% MAF).<sup>8</sup> In contrast, protein C and S mutations, antiphospholipid syndrome, and antithrombin deficiency have similar prevalence among Blacks and Whites.<sup>9</sup>

Race-based differences in circulating inflammatory markers, which may contribute to CT risk, have also been noted.<sup>10</sup> A study of 508 participants showed that Black individuals have significantly higher levels of inflammatory markers C-reactive protein ( $p = 0.010$ ), interleukin-6 ( $p < 0.001$ ), and D-dimer levels compared with Whites, even when controlling for age, sex, socioeconomic status (SES), exercise, diet, BMI, and inflammatory diseases.<sup>11</sup>

### Sociologic Mechanisms

Environmental factors and comorbidities influenced by social determinants of health (SDOH) contribute significantly to CT risk. Obesity, an established risk factor for CT, is more common among non-Hispanic Black adults and Hispanic adults, and is strongly influenced by social and environmen-

tal factors such as SES. In the United States, SES is one of the most powerful predictors of obesity and overall health.<sup>12</sup> Childhood poverty rates demonstrate significant disparities with 30%, 31%, and 23% of American Indian, Black, and Hispanic children being born into poverty compared with 10% of Asian and non-Hispanic White children.<sup>13</sup> Low childhood SES is associated with an increased risk of cardiovascular disease and obesity as adults.<sup>12</sup> Other important factors that contribute to disparities in obesity rates include geography, nutritional food availability, and neighborhood safety, which can influence physical activity.<sup>12</sup>

As noted above, inflammation is associated with increased CT risk. Related to this, weathering and allostatic load characterize the “wear and tear” of discrimination, racism, chronic stress, and adversity. Studies have found a correlation between early life adversity and increased inflammation.<sup>14</sup> A study of stress levels among 25,335 participants reported that the majority of participants with the highest stress scores were Black.<sup>15</sup> Evidence suggests that neighborhood quality impacts stress levels and overall health outcomes.<sup>16</sup> Residential segregation, a consequence of discriminatory housing policies, persists and minority neighborhoods tend to have a higher density of food deserts, lower air quality, and higher violence and poverty indices.<sup>17</sup>

Additionally, limited access to health care increases the risk for poor CT outcomes.<sup>5</sup> White Americans are more likely to be insured and to have private insurance than Black Americans.<sup>18</sup> Insurance status and proximity to well-resourced hospital systems have an impact on the treatment that patients receive and health outcomes<sup>19,20</sup>

### Treatment

DOACs are standard care for CT treatment.<sup>2</sup> A retrospective analysis of 14,140 VTE patients found that Black patients are less likely to receive DOACs than White patients (OR 0.86; 95% confidence interval [CI] 0.77–0.97;  $p = 0.02$ ); however, there were no significant differences in DOAC usage for Asian (OR 1.06; 95% CI 0.75–1.49;  $p = 0.74$ ) or Hispanic patients (OR 1.04; 95% CI 0.88–1.22;  $p = 0.66$ ) compared with White patients.<sup>21</sup> Thromboprophylaxis usage may also be lower in Black patients; a retrospective study of 3,719 patients found that Black patients made up a larger proportion of patients who did not receive enoxaparin thromboprophylaxis compared with those who did (10.5% vs. 1.9%), while the opposite was true for White patients (85.0% vs. 94.4%).<sup>22</sup> Potential explanations include reduced access to specialty providers, insurance coverage differences, lower SES, and provider implicit bias.

### Call to Action

Racial disparities in cancer and cardiovascular disease lead to worse outcomes among historically marginalized racial groups (→ Fig. 1). As highlighted, the mechanisms of increased CT risk among Black individuals are multifactorial and incompletely understood. To address CT disparities, there first needs to be a greater understanding of the role of ancestry, as well as gene × environment interactions.

Racial and Ethnic Disparities of Cancer Associated Thrombosis (CT)			
Epidemiology	Biologic Mechanisms	Sociologic Mechanisms	Treatment
<ul style="list-style-type: none"> <li>• Higher VTE incidence rate among Black cancer patients than White</li> <li>• Lower VTE incidence rate among Asian cancer patients</li> <li>• Lack of SDOH and ethnicity-sensitive risk scores</li> </ul>	<ul style="list-style-type: none"> <li>• Factor V Leiden associated with greater VTE risk among Whites</li> <li>• Sickle cell and high Factor VIII with greater VTE risk among Blacks</li> <li>• Inflammation increases CT risk</li> </ul>	<ul style="list-style-type: none"> <li>• Adversity and poor health outcomes increase CT risk</li> <li>• Obesity more common among minorities</li> <li>• Black cancer patients commonly with lower SES</li> </ul>	<ul style="list-style-type: none"> <li>• Black patients less likely to receive DOACs and prophylaxis than White patients</li> </ul>
Strategies to Overcome CT Disparities			
<ul style="list-style-type: none"> <li>• Conduct research on how to best characterize genetic predisposition based on race</li> <li>• Phenotype the social determinants of health among patients who develop CT</li> <li>• Standardize recording of race/ethnicity in health records</li> <li>• Reform CT predictive models</li> <li>• Personalize treatment strategies</li> <li>• Pursue economic and healthcare reform</li> </ul>			

**Fig. 1** Contributors to racial and ethnic disparities in cancer-associated thrombosis (CT) and strategies to overcome disparities. A summary of the epidemiology, potential biologic, and social mechanisms of racial and ethnic disparities in CT is provided, as well as treatment delivery in venous thromboembolism (VTE). Potential strategies to overcome disparities are also highlighted.<sup>23</sup>

Robust, international, population-based genetic analyses are needed to better characterize genetic predisposition according to race.<sup>9</sup> Furthermore, deep phenotyping of environmental factors and SDOH among individuals at increased CT risk are necessary to define the associations between SDOH and CT risk. In all clinical studies, there needs to be standardized reporting of race and ethnicity in health records and greater inclusivity of racially and ethnically diverse populations.<sup>23</sup> Personalized strategies to mitigate VTE risk among historically marginalized populations need to be developed and tested. Societal level changes, such as improved health and economic policy reform, cancer screening, preventative medicine, and health care access,<sup>24</sup> are needed to mitigate health disparities and achieve health equity.

Ultimately, health care and economic reform will be necessary to address SDOH associated with increased VTE and CT risk.

## Conclusions and Recommendations

Health disparities on the basis of race/ethnicity exist in CT. In comparison to White patients with cancer, Black patients with cancer have a higher risk of developing CT, While Asian/Pacific Islanders may have a lower risk. Research focused on understanding and mitigating racial/ethnic disparities in CT are needed to provide equitable health care and to improve overall outcomes across all populations.

### Funding

C.W. was supported by a Penn Access Summer Scholars Program. B.K. is supported in part by an American Heart Association Award Strategically Focused Research Network Award in Cardio-Oncology Disparities.

## Conflict of Interest

None declared.

## References

- 1 Jha AK, Larizgoitia I, Audera-Lopez C, Prasopa-Plaizier N, Waters H, Bates DW. The global burden of unsafe medical care: analytic modeling of observational studies. *BMJ Qual Saf* 2013;22(10):809–815
- 2 Gervaso L, Dave H, Khorana AA. Venous and arterial thromboembolism in patients with cancer: *JACC: CardioOncology* state-of-the-art review. *JACC CardioOncol* 2021;3(02):173–190
- 3 Addo-Tabiri NO, Chudasama R, Vasudeva R, et al. Black patients experience highest rates of cancer-associated venous thromboembolism. *Am J Clin Oncol* 2020;43(02):94–100
- 4 Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. *Cancer* 2007;110(10):2339–2346
- 5 Heit JA, Beckman MG, Bockenstedt PL, et al; CDC Thrombosis and Hemostasis Centers Research and Prevention Network. Comparison of characteristics from White- and Black-Americans with venous thromboembolism: a cross-sectional study. *Am J Hematol* 2010;85(07):467–471
- 6 Lutsey PL, Cushman M, Steffen LM, et al. Plasma hemostatic factors and endothelial markers in four racial/ethnic groups: the MESA study. *J Thromb Haemost* 2006;4(12):2629–2635
- 7 Chekkal M, Rahal MCA, Moulasserdoun K, Seghier F. Increased level of factor VIII and physiological inhibitors of coagulation in patients with sickle cell disease. *Indian J Hematol Blood Transfus* 2017;33(02):235–238
- 8 Tang L, Hu Y. Ethnic diversity in the genetics of venous thromboembolism. *Thromb Haemost* 2015;114(05):901–909
- 9 Goldhaber SZ. Race and venous thromboembolism: nature or nurture? *Circulation* 2014;129(14):1463–1465
- 10 Branchford BR, Carpenter SL. The role of inflammation in venous thromboembolism. *Front Pediatr* 2018;6:142
- 11 Paalani M, Lee JW, Haddad E, Tonstad S. Determinants of inflammatory markers in a bi-ethnic population. *Ethn Dis* 2011;21(02):142–149
- 12 Lee A, Cardel M, Donahoo WT. Social and environmental factors influencing obesity. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Grossman A, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, McGee EA, McLachlan R, et al., eds. *Endotext*. South Dartmouth, MA: MDText.com, Inc.; 2000
- 13 C17001. Poverty Status in the Past 12 Months by Sex by Age [19] - American Community Survey Tables: 2009 – 2011 (3-Year Estimates) (ACS2011\_3yr) - ACS 2011 (3-Year Estimates). *Social Explorer*.
- 14 Slopen N, Lewis TT, Gruenewald TL, et al. Early life adversity and inflammation in African Americans and Whites in the midlife in the United States survey. *Psychosom Med* 2010;72(07):694–701
- 15 Albert MA, Durazo EM, Slopen N, et al. Cumulative psychological stress and cardiovascular disease risk in middle aged and older women: rationale, design, and baseline characteristics. *Am Heart J* 2017;192:1–12
- 16 Bird CE, Seeman T, Escarce JJ, et al. Neighbourhood socioeconomic status and biological 'wear and tear' in a nationally representative sample of US adults. *J Epidemiol Community Health* 2010;64(10):860–865
- 17 National Academies of Sciences, Engineering, and Medicine. *The Root Causes of Health Inequity. Communities in Action: Pathways to Health Equity* 500 Fifth Street, NW Washington, DC 20001: The National Academies Press;2017:99–185
- 18 Artiga S, Hill L, Orgera K, Damico A. *Health Coverage by Race and Ethnicity, 2010–2019*. KFF; 2021
- 19 *Effects of Health Insurance on Health. Care Without Coverage: Too Little, Too Late*. National Academies Press (US); 2002
- 20 Akinleye DD, McNutt L-A, Lazariu V, McLaughlin CC. Correlation between hospital finances and quality and safety of patient care. *PLoS One* 2019;14(08):e0219124
- 21 Nathan AS, Geng Z, Dayoub EJ, et al. Racial, ethnic, and socioeconomic inequities in the prescription of direct oral anticoagulants in patients with venous thromboembolism in the United States. *Circ Cardiovasc Qual Outcomes* 2019;12(04):e005600
- 22 McGarry LJ, Thompson D. Retrospective database analysis of the prevention of venous thromboembolism with low-molecular-weight heparin in acutely ill medical inpatients in community practice. *Clin Ther* 2004;26:419–430
- 23 Fazal M, Malisa J, Rhee J-W, Witteles RM, Rodriguez F. Racial and ethnic disparities in cardio-oncology: a call to action. *JACC CardioOncol* 2021;3(02):201–204
- 24 Thorlu -Bangura Z, Manisty C, Banerjee A. Understanding race and ethnicity in cancer and CV disease. *JACC CardioOncology* 2021; 3:335–337