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Racial and Socioeconomic Disparities in the Receipt of National Comprehensive Cancer Network (NCCN) Guideline Adherent Cancer Care in California

THESIS

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MASTER OF SCIENCE

in Biomedical and Translational Science

by

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This project is dedicated to the Black Lives Matter movement and to all patients and providers who have experienced racism in the healthcare setting.

ABSTRACT OF THE THESIS

Racial and Socioeconomic Disparities in the Receipt of National Comprehensive Cancer Network (NCCN) Guideline Adherent Cancer Care in California

By

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Master of Science in Translational and Basic Science

University of California, Irvine, 2020

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Background: Significant racial and socioeconomic disparities persist in the survival of patients with select cancers in California. There are a limited number of studies that have evaluated the association between National Comprehensive Cancer Network (NCCN) guideline adherent care and survival across different cancer types. We aim to assess the relationship between race/ethnicity, socioeconomic status (SES), insurance type and the likelihood of receiving NCCN guideline adherent care and its association with cancer-specific survival.

Objectives: To determine the relationship between NCCN guideline adherence and disease-specific survival across selected cancer types. Our secondary objective is to better understand the association of race/ethnicity, socioeconomic status, payer type, and disease characteristics with the receipt of NCCN guideline adherent care.

Methods: This was a retrospective population-based cohort study of patients with one of eight different types of invasive cancer using the California Cancer Registry. A total of

543,198 patients were identified with invasive cancer between 2004-2017 (breast, n=189,311; prostate, n=156,502; colon, n=80,102; rectal, n=30,118; liver, n=25,857; gastric, n=22,066; ovary, n=22,551; and cervix, n=16,691). Adherence with NCCN guideline care was defined by histology and stage-appropriate surgical procedures, radiation, and chemo- or hormonal therapies. Multivariate logistic regression was used to evaluate the relationship between the patient's race/ethnicity, SES, insurance type, and NCCN guideline adherence. Disease-specific survival analysis was performed using multivariate proportional hazards model.

Results: A total of 543,198 patients were identified with invasive cancer from 2004 to 2017 (cases by disease: breast 189,311, prostate 156,502, colon 80,102, rectal 30,118, liver 25,857, gastric 22,066, ovary 22,551, and cervix 16,691). Overall, less than half of patients (47.5%) received guideline-adherent care and this proportion varied by disease type (30-80%). Non-adherent treatment was associated with worse survival across all cancer types: breast (HR 1.28, 95%CI=1.23-1.33), prostate (HR 1.31, 95%CI=1.22-1.41), colon (HR 1.73, 95%CI=1.67 1.78), rectal (HR 1.52, 95%CI=1.41-1.63), liver (HR 2.52, 95%CI=2.42-2.63), ovary (HR 1.32, 95%CI=1.26-1.38), gastric (HR 2.38, 95%CI=2.28-2.49), and cervical cancer (HR 1.17, 95%CI=1.08-1.26). In multivariate models, Black patients were less likely to receive guideline adherent care for breast (OR 0.88, 95% CI 0.84-0.92), prostate (OR 0.90, 95% CI 0.86-0.93), colon (OR 0.86, 95% CI 0.80-0.92), and ovarian cancer (OR 0.71, 95% CI 0.62-0.82) compared to White patients. Hispanic patients were less likely to receive guideline-adherent care for breast (OR 0.91, 95%CI=0.88-0.93) and liver cancer (OR 0.86, 95%CI=0.80-0.91), compared to White patients. Medicaid payer status was also associated with lower guideline

adherence for breast (OR 0.81, 95% CI 0.78-0.84), prostate (OR 0.91, 95% CI 0.86-0.97), colon (OR 0.70, 95% CI 0.65-0.75), rectal (OR 0.91, 95% CI 0.83-0.99), gastric (OR 0.69, 95% CI 0.63-0.75), and liver cancer (OR 0.66, 95% CI 0.61-0.72), compared to managed care insurance type. Patients in the lowest socioeconomic group were less likely to receive guideline adherent care across all cancer types compared to the highest SES group (breast OR 0.77, 95%CI 0.74-0.80; prostate OR 0.86, 95%CI 0.82-0.89; colon OR 0.50, 95%CI 0.46-0.53; rectal OR 0.79, 95%CI 0.72-0.86; liver OR 0.61, 95%CI 0.55-0.67; gastric OR 0.54, 95%CI 0.48-0.59; ovary OR 0.60, 95%CI 0.54-0.67; cervix OR 0.86, 95%CI 0.77-0.97).

Conclusion: Less than half of cancer patients received NCCN guideline adherent care and non-adherence was associated with an increased disease-specific mortality. There was an incremental relationship observed between SES and the likelihood of receiving guideline adherent care. Individuals less likely to receive guideline adherent care also included patients of Black or Hispanic race and those with Medicaid or Medicare insurance coverage.

INTRODUCTION

It is predicted that cancer will be the leading cause of death in many regions of the United States as heart disease related deaths continue to decline[1]. In 2020, there will be an estimated 1,806,590 new cases of cancer diagnosed and 606,520 cancer related deaths[2]. While the cancer incidence rate has declined by 2% in men and has remained stable in women over the last 10 years, there remains a disproportionate burden of disease particularly for diverse populations[3,4].

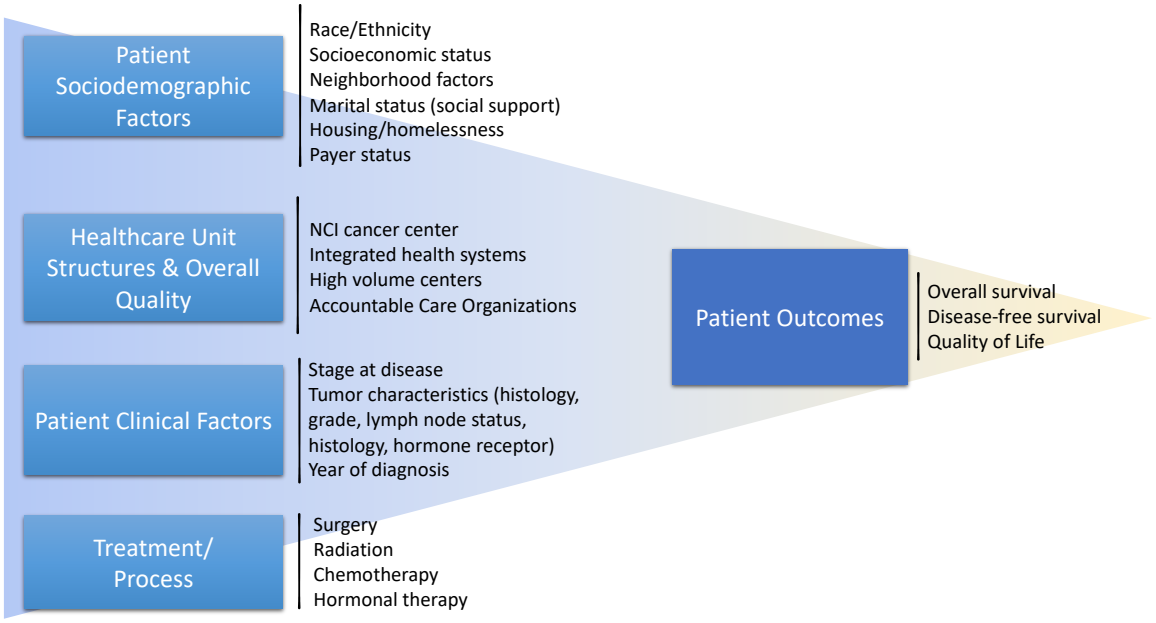
California remains one of the most racially and ethnically diverse states in the US, and its non-White population is projected to grow by 6.5 million over the next twenty years[5]. While the Hispanic/Latino population comprise 40 percent of the total population, California also has the largest Asian American population (14 percent) in the US. California cancer incidence rates continue to vary with racial/ethnic differences in breast, cervical, colorectal, and prostate cancer rates. Black patients experience the highest incidence rates of prostate and colorectal cancers, Hispanic patients have the highest rate of new cervical cancer rates, and White patients with the highest rate of new breast cancers. Despite the differences in cancer incidences, Black patients experienced the highest mortality rates for breast, colorectal, and prostate cancers in 2016[5].

Advancements in screening, genetic/molecular testing, and therapeutics have correlated with only modest improvements in the overall survival of patients from lower socioeconomic groups, racial/ethnic minority groups, and more rural geographic locations[6,7]. Even when tumor biology and stage-specific survival are controlled for, there remains a

considerable survival gap between racial/ethnic groups, suggestive of disparities in the receipt of quality cancer care[8-10].

There are four broad categories that contribute to the likelihood of a patient receiving quality cancer care: patient sociodemographic factors (social, geographic and economic determinants of health, race/ethnicity), health care systems (NCI designated cancer center, high volume, payer status), clinical factors (stage, histology, performance status), and the quality of treatment received (appropriate surgical, therapeutic or radiation therapies) (Figure 1). Patient decision making regarding treatments reflect not only their specific attitudes and/or beliefs but their ability to navigate the systemic and structural roadblocks starting from their neighborhood to the quality of treatment recommended.

Figure 1: Social, clinical, and systemic determinants of health outcomes for cancer patients.



Several studies have shown disparities in the survival of racial/ethnic groups after controlling for stage and co-morbidities. Specifically, Black race and hospital factors remain independent predictors of higher mortality rates among patients with colon cancer[9-11]. Reductions and even elimination of these disparities in cancer survival have been demonstrated when similar treatments are administered or when equal access to healthcare systems is protected [12-16]. As example, studies have shown an association with improvement in disease specific survival for ovarian cancer patients with increased adherence to NCCN guidelines [17,18]. Differences in the receipt of guideline-adherent treatment after diagnosis may strongly influence disparities in survival.

The National Comprehensive Cancer Network (NCCN) has developed clinical practice guidelines for 40 different cancer types to assist providers in the treatment and surveillance of patients. These evidence-based guidelines streamline multi-disciplinary treatment modalities that often include chemotherapy, radiation therapy, and surgery. There are a limited number of studies evaluating the association between NCCN guideline adherence and survival across different cancer types[19]. While differences in the receipt of guideline adherent care have been associated with insurance type, race/ethnicity, hospital volume, geographic location, and SES, the literature is not consistent, and results vary according to study methodology and the population under study. Our objective is to determine whether NCCN guideline adherence is associated with improved survival across selected cancer types. Our secondary objective is to better understand the association of sociodemographic status, payer type, and disease characteristics with NCCN guideline adherence.

METHODS

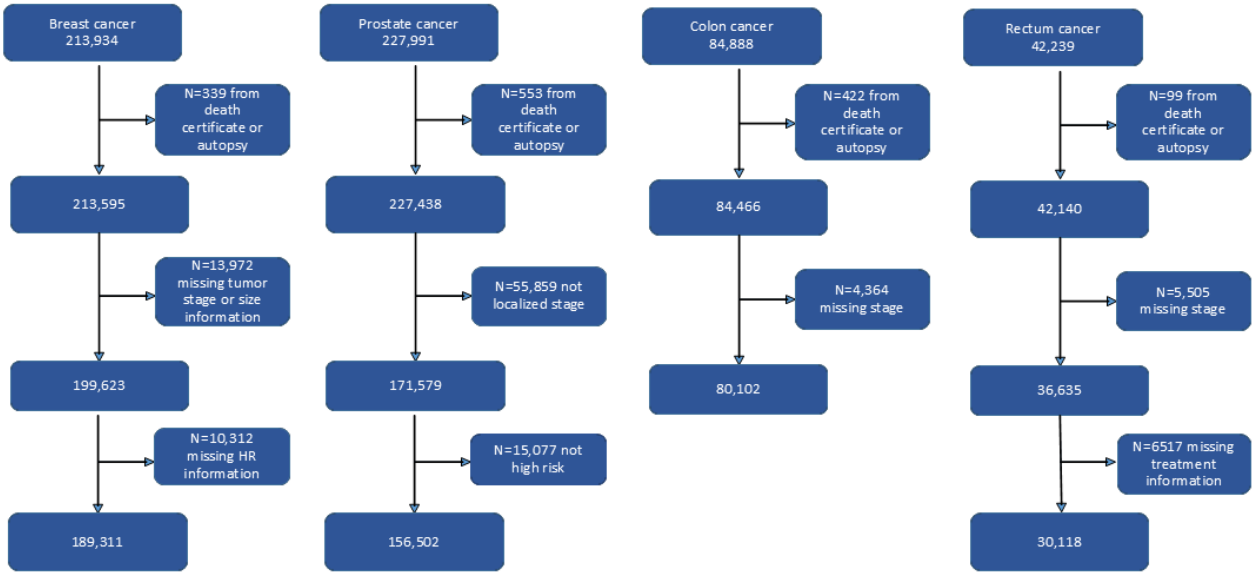
Disease Sites and Settings

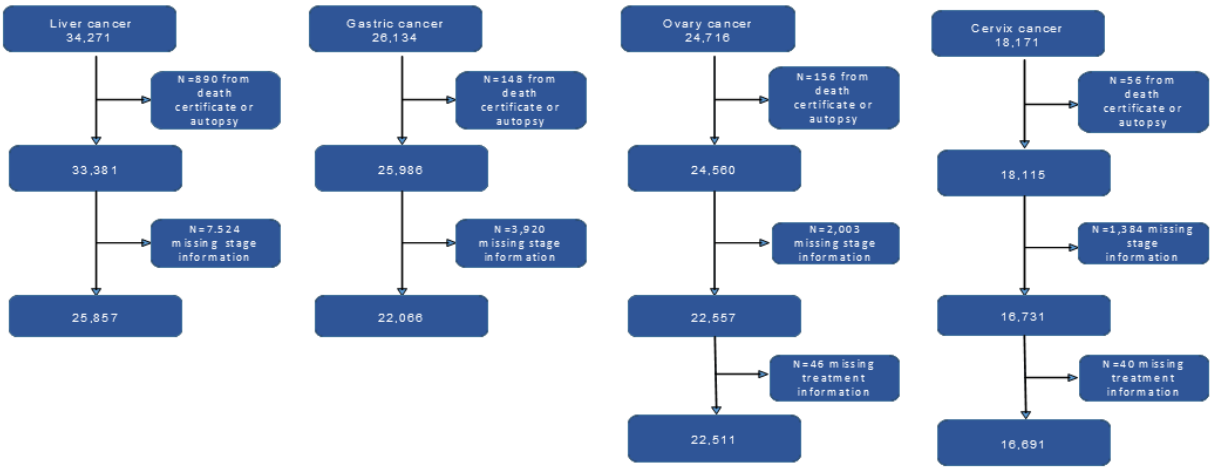
This was a retrospective cohort study of population-based invasive cancer cases diagnosed and reported to the California Cancer Registry (CCR) between 2004 and 2017 with follow up until 11/30/2018. CCR data include demographic information, socioeconomic status (SES), age at presentation, date of diagnosis, treatment information including surgery, chemotherapy, radiation and hormonal therapy, interval to definitive surgery, interval to initiation of chemotherapy, tumor characteristics including stage at presentation, tumor histology, tumor grade, follow-up information including vital status and cause of death. The exception was for breast cancer cases between 2004 and 2015 due to incomplete hormone receptor status in later years. Patient's socioeconomic status (SES) was stratified into quintiles using the Yost score for patients diagnosed prior to 2006 and the Yang index for those with diagnoses after 2006. Both Yost and Yang scores are composite indices of SES based on principal component analysis of block group level census variables such as education, income and occupation [20,21]. International Classification of Disease (ICD) Codes for Oncology based on World Health Organization's criteria were used for tumor histology. Cases were identified using Surveillance, Epidemiology, and Results (SEER) primary site codes. Cause of death was recorded according to ICD criteria. The study was approved by the institutional review board of the University of California, Irvine (HS#2018-4735) and the State of California Health and Human Services Agency Committee for the Protection of Human Subjects (19-03-0044).

Sample Design

Case selection criteria included age 18-79 years old diagnosed with first or only invasive cancer of breast (female), colon, prostate, rectal, ovarian, cervical, liver or gastric cancer. We then sequentially excluded cases that were identified from autopsy, death certificate, or were missing clinical or treatment information. A total of 543,198 patients were included in the study population (breast, n=189,311; prostate, n=156,502; colon, n=80,102; rectal, n=30,118; liver, n=25,857; gastric, n=22,066; ovary, n=22,551; and cervix, n=16,691). CONSORT diagrams for each disease type are listed in Figure 2.

Figure 2: CONSORT diagram illustrating inclusions and exclusions to arrive at the final cohort.





Age at diagnosis was treated as either a continuous or categorical variable with four groups (younger than 45 years, 45-54 years, 55-64 years, and older than 65 years). Tumor characteristics included American Joint Commission on Cancer stage, tumor grade, and histology. We categorized insurance type as managed care (including managed care, HMO and PPO), Medicare, Medicaid, other, or uninsured/unknown. Other insurance types included TriCare, VA, fee-for-service plans (FFS), and insurance not otherwise specified.

Key Study Measures

The NCCN guideline consensus statements define the most current and accepted standards for cancer treatment. For each cancer site, a group of experienced physicians were consulted to develop cancer-specific algorithms of treatment adherence with NCCN guidelines (

Figure 3). For each cancer site of interest, a rigorous review of the NCCN guidelines was performed with nuanced input from sub-specialists on the most clinically significant components of treatment guidelines. Based on the expert input, guideline review, and CCR variables, disease-based treatment algorithms were designed after several iterations. Based upon specific treatments for each cancer site, indicators were created for adherence with surgical, chemotherapy, radiation and hormonal therapy guidelines and the overall treatment plan. Adherence was then determined if a patient received all of the guideline-based therapies across treatment modalities (surgery, chemotherapy and/or radiation therapy). Please see Appendix 1 for each disease-based treatment algorithms that were adapted from NCCN guidelines using CCR treatment variables.

Univariate logistic regression was used to determine the effect of race/ethnicity, SES, payer status on NCCN guideline indicators respectively. A multivariate logistic regression model was developed to assess the effect of each variable on the likelihood of receiving NCCN guideline adherent care. Besides race/ethnicity, insurance type and SES, the multivariate model controls for age at diagnosis, year of diagnosis, marital status, tumor stage and grade. Multivariate logistic regression analyses were used to determine the effect of socio-demographic variables that were significant in univariate analysis on NCCN guideline indicators, with persistent disparities indicative of potential biases in treatment administration and/or patient preference.

Figure 3: Example of treatment algorithm based on the NCCN Breast Cancer guideline.

Subtype				Adherent treatment				
HR	HER2	Lymph node	Tumor size	Surgery and radiation therapy	Lymph node surgery - Sentinel	Lymph node surgery - Axillary	Chemo therapy	Hormone therapy
Stage I, II, IIIA with N1								
HR+	HER2+	N0	<=5mm	Total mastectomy or BCS + radiation	Yes			
HR+	HER2+	N0	6-10mm	Total mastectomy or BCS + radiation	Yes			Yes
HR+	HER2+	N0	>10mm	Total mastectomy or BCS + radiation	Yes		Yes	Yes
HR+	HER2+	N1mi	<=5mm	Total mastectomy or BCS + radiation	Yes			Yes
HR+	HER2+	N1mi	6-10mm	Total mastectomy or BCS + radiation	Yes			Yes
HR+	HER2+	N1mi	>10mm	Total mastectomy or BCS + radiation	Yes		Yes	Yes
HR+	HER2+	Positive	Any	Total mastectomy or BCS + radiation	Yes		Yes	Yes
HR+	HER2-	N0	<=5mm	Total mastectomy or BCS + radiation	Yes			
HR+	HER2-	N0	>5mm	Total mastectomy or BCS + radiation	Yes			Yes
HR+	HER2-	N1mi	<=5mm	Total mastectomy or BCS + radiation	Yes			Yes
HR+	HER2-	N1mi	>5mm	Total mastectomy or BCS + radiation	Yes			Yes
HR+	HER2-	Positive	Any	Total mastectomy or BCS + radiation	Yes		Yes	Yes
HR+	Unknown	N0	<=5mm	Total mastectomy or BCS + radiation	Yes			
HR+	Unknown	N0	>5mm	Total mastectomy or BCS + radiation	Yes			Yes
HR+	Unknown	N1mi	<=5mm	Total mastectomy or BCS + radiation	Yes			Yes
HR+	Unknown	N1mi	>5mm	Total mastectomy or BCS + radiation	Yes			Yes
HR+	Unknown	Positive	Any	Total mastectomy or BCS + radiation	Yes		Yes	Yes
HR-	HER2+	N0	<=5mm	Total mastectomy or BCS + radiation	Yes			
HR-	HER2+	N0	6-10mm	Total mastectomy or BCS + radiation	Yes			
HR-	HER2+	N0	>10mm	Total mastectomy or BCS + radiation	Yes		Yes	
HR-	HER2+	N1mi	<=5mm	Total mastectomy or BCS + radiation	Yes			
HR-	HER2+	N1mi	6-10mm	Total mastectomy or BCS + radiation	Yes			
HR-	HER2+	N1mi	>10mm	Total mastectomy or BCS + radiation	Yes		Yes	
HR-	HER2+	Positive	Any	Total mastectomy or BCS + radiation	Yes		Yes	
HR-	HER2-	N0	<=10mm	Total mastectomy or BCS + radiation	Yes			
HR-	HER2-	N0	>10mm	Total mastectomy or BCS + radiation	Yes		Yes	
HR-	HER2-	N1mi	<=10mm	Total mastectomy or BCS + radiation	Yes			
HR-	HER2-	N1mi	>10mm	Total mastectomy or BCS + radiation	Yes		Yes	
HR-	HER2-	Positive	Any	Total mastectomy or BCS + radiation	Yes		Yes	
HR-	Unknown	N0	<=10mm	Total mastectomy or BCS + radiation	Yes			
HR-	Unknown	N0	>10mm	Total mastectomy or BCS + radiation	Yes		Yes	
HR-	Unknown	N1mi	<=10mm	Total mastectomy or BCS + radiation	Yes			
HR-	Unknown	N1mi	>10mm	Total mastectomy or BCS + radiation	Yes		Yes	
HR-	Unknown	Positive	Any	Total mastectomy or BCS + radiation	Yes		Yes	
Stage IIIA with N2+, IIIB, IIIC								
HR+	HER2+	Any	Any	Total mastectomy + radiation or BCS + radiation		Yes	Yes	Yes
HR+	HER2-	Any	Any	Total mastectomy + radiation or BCS + radiation		Yes	Yes	Yes
HR+	Unknown	Any	Any	Total mastectomy + radiation or BCS + radiation		Yes	Yes	Yes
HR-	HER2+	Any	Any	Total mastectomy + radiation or BCS + radiation		Yes	Yes	
HR-	HER2-	Any	Any	Total mastectomy + radiation or BCS + radiation		Yes	Yes	
HR-	Unknown	Any	Any	Total mastectomy + radiation or BCS + radiation		Yes	Yes	
Stage IV								
Any	Any	Any	Any				Yes	

Abbreviation: HR: Hormone receptor; HER2:human epidermal growth factor receptor 2; BCS: Breast conserving surgery

Statistical Analysis

Survival analysis was conducted using disease-specific survival as the outcome. Cancer-specific mortality was defined as death caused by the specific cancer. Patients who died from other causes or alive until end of follow up on November 30, 2018 were treated as censored events. Multivariate survival analysis was performed using the Cox proportional hazards model controlling for patients' sociodemographic characteristics (age, year of diagnosis, sex, race/ethnicity, SES, payer type) and tumor characteristics (stage and grade). Adjusted hazard ratios and 95% confidence intervals were generated. All statistical analyses were performed on SAS 9.4 (SAS Institute Cary, NC.). Statistical significance was set at $P<0.05$, using 2-tailed tests.

RESULTS

A total of 543,198 patients were identified for study inclusion. Age at diagnosis ranged from 18-79, with 58.3% of patients being younger than 65 years old (Overall, 47.5% of patients received NCCN guideline-adherent care as detailed in Table 2. There were

several statistically significant differences between the patient and tumor characteristics for patients who received guideline-adherent care compared to those who received non-adherent care.

Table). The highest proportion of incident cancer cases were breast (34.8%), prostate (28.8%), and colon cancer (14.7%). The majority of all cancers were diagnosed with stage I disease and only 14.5% diagnosed at stage IV disease. The largest racial/ethnic group was non-Hispanic White (56.4%), followed by Hispanic (20.9%), Asian/Pacific Islander (12.7%), Black (7.6%), and other/unknown (2.3%).

Table 1: Distribution of patient and disease characteristics.

	Total (%)
Total cases	543,158 (100.0)
Tumor site	
Female breast	189,311 (34.9)
Prostate	156,502 (28.8)
Colon	80,102 (14.7)
Rectum	30,118 (5.5)
Liver	25,857 (4.8)
Gastric	22,066 (4.1)
Ovary	22,511 (4.1)
Cervix	16,691 (3.1)
Age at diagnosis (years)	
18-44	50,165 (9.2)
45-54	102,967 (19.0)
55-64	163,694 (30.1)
65+	226,332 (41.7)
Race/ethnicity	
NH White	306,263 (56.4)
NH Black	41,354 (7.6)
Hispanic	113,652 (20.9)
Asian	69,243 (12.7)
Others/Unknown	12,646 (2.3)
Payer Status	
Managed care	265,375 (48.9)
Medicare	126,328 (23.3)
Medicaid	47,950 (8.8)
Other Insurance	80,780 (14.9)
Not insured	22,725 (4.2)
Socioeconomic Status (SES)	
Highest	133,299 (24.5)
Higher-middle	122,618 (22.6)
Middle	110,427 (20.3)
Lower-middle	98,624 (18.2)
Lowest	78,190 (14.4)
Gender	
Male	248,717 (45.8)
Female	294,387 (54.2)
Marital Status	
Single	217,140 (40.0)
Married	326,018 (60.0)
Tumor stage	
I	148,986 (38.5)
II	107,296 (27.7)
III	74,162 (19.2)
IV	56,212 (14.5)
Tumor Grade	
I	61,051 (15.8)
II	162,415 (42.0)
III	103,175 (26.7)
IV	9,152 (2.4)
Not stated	50,863 (13.2)

Overall, 47.5% of patients received NCCN guideline-adherent care as detailed in Table 2. There were several statistically significant differences between the patient and tumor characteristics for patients who received guideline-adherent care compared to those who received non-adherent care.

Table 2: Distribution of patient characteristics by status of treatment.

	Total (%)	Adherent care (%)	Non-adherent care (%)	P-Value
Total	543,158 (100.0)	258,213 (47.5)	284,945 (52.5)	
Tumor site				<0.001
Female breast	189,311 (34.9)	57,784 (30.5)	131,527 (69.5)	
Prostate	156,502 (28.8)	79,904 (51.1)	76,598 (48.9)	
Colon	80,102 (14.7)	64,677 (80.7)	15,425 (19.3)	
Rectum	30,118 (5.5)	13,676 (45.4)	16,442 (54.6)	
Liver	25,857 (4.8)	11,295 (43.7)	14,562 (56.3)	
Gastric	22,066 (4.1)	14,271 (64.7)	7,795 (35.3)	
Ovary	22,511 (4.1)	9,345 (41.5)	13,166 (58.5)	
Cervix	16,691 (3.1)	7,261 (43.5)	9,430 (56.5)	
Age at diagnosis (years)				<0.001
18-44	50,165 (9.2)	21,661 (43.2)	28,504 (56.8)	
45-54	102,967 (19.0)	47,995 (46.6)	54,972 (53.4)	
55-64	163,694 (30.1)	79,114 (48.3)	84,580 (51.7)	
65+	226,332 (41.7)	109,443 (48.4)	116,889 (51.6)	
Race/ethnicity				<0.001
Non-Hispanic white	306,263 (56.4)	146930 (48.0)	159333(52.0)	
Non-Hispanic black	41,354 (7.6)	18661 (45.1)	22693 (54.9)	
Hispanic	113,652 (20.9)	52889 (46.5)	60763 (53.5)	
Asian/Pacific Islander	69,243 (12.7)	34593 (50.0)	34650 (50.0)	
Others/Unknown	12,646 (2.3)	5140 (40.6)	7506 (59.4)	
Insurance				<0.001
Managed care	265,375 (48.9)	129077 (48.6)	136298 (51.4)	
Medicare	126,328 (23.3)	60878 (48.2)	65450 (51.8)	
Medicaid	47,950 (8.8)	19905 (41.5)	28045 (58.5)	
Other Insurance	80,780 (14.9)	39436 (48.8)	41344 (51.2)	
Not insured	22,725 (4.2)	8917 (39.2)	13808 (60.8)	
Socioeconomic Status (SES)				<0.001
Highest	133,299 (24.5)	66625 (50.0)	66674 (50.0)	
Higher-middle	122,618 (22.6)	59360 (48.4)	63258 (51.6)	
Middle	110,427 (20.3)	52207 (47.3)	58220 (52.7)	
Lower-middle	98,624 (18.2)	45444 (46.1)	53180 (53.9)	
Lowest	78,190 (14.4)	34577 (44.2)	43613 (55.8)	
Tumor stage				<0.001
I	148,986 (38.5)	73736 (49.5)	75250 (50.5)	
II	107,296 (27.7)	39413 (36.7)	67883 (63.3)	
III	74,162 (19.2)	33224 (44.8)	40938 (55.2)	
IV	56,212 (14.5)	31936 (56.8)	24276 (43.2)	

*Using chi square test to assess differences between guideline non-adherent group and adherent group.

NCCN Guideline Adherence

Compared to the highest SES, the lowest SES quintile were less likely to receive guideline adherent care across all cancer types. There was gradient observed between the odds of receiving adherent care and SES status, with increasing odds as SES improved (Table 3).

Table 3: Adjusted Odds Ratio of NCCN guideline adherent care by SES. (Red highlight denotes statistically significant, p<0.05)

Cancer Type	Highest n=133,299	Higher-Middle n=122,618	Middle n=47,950	Lower-Middle n=98,624	Lowest n=78,190
	OR (95%CI)				
Breast	Ref	0.94 (0.91,0.97)	0.89 (0.86,0.92)	0.82 (0.79,0.85)	0.77 (0.74,0.80)
Prostate	Ref	0.93 (0.90,0.96)	0.91 (0.88,0.94)	0.90 (0.87,0.93)	0.86 (0.82,0.89)
Colon	Ref	0.80 (0.75,0.86)	0.67 (0.63,0.72)	0.61 (0.57,0.65)	0.50 (0.46,0.53)
Rectum	Ref	0.97 (0.91,1.05)	0.88 (0.81,0.94)	0.79 (0.73,0.85)	0.79 (0.72,0.86)
Liver	Ref	0.88 (0.81,0.97)	0.76 (0.65,0.79)	0.72 (0.66,0.79)	0.61 (0.55,0.67)
Gastric	Ref	0.85 (0.77,0.94)	0.71 (0.65,0.79)	0.62 (0.56,0.68)	0.54 (0.48,0.59)
Ovary	Ref	0.92 (0.84,0.99)	0.85 (0.78,0.92)	0.74 (0.67,0.81)	0.60 (0.54,0.67)
Cervix	Ref	0.89 (0.79,1.00)	0.93 (0.83,1.04)	0.87 (0.77,0.97)	0.86 (0.77,0.97)

*Multivariate logistic regression model for each tumor site also controlled for patient's age at diagnosis, year of diagnosis, sex (except for breast, prostate, ovary and cervix), race/ethnicity, payer status, and tumor stage (except for prostate cancer) and grade.

Compared to non-Hispanic whites (NHWs), Blacks were less likely to receive NCCN adherent care for breast (OR 0.88, 95%CI 0.84-0.92, p<0.0001), prostate (OR 0.90, 95%CI 0.86-0.93, p<0.0001)), colon (OR 0.85, 95%CI 0.79-0.92, p<0.0001), and ovarian cancer (OR 0.71, 95%CI 0.62-0.82, p<0.0001) (Table 3). Patients of Hispanic race/ethnicity were less likely to receive guideline adherent care for breast (OR 0.91, 95%CI 0.88-0.93, p<0.0001), liver cancer (OR 0.86, 95%CI 0.80-0.91, p<0.0001), and gastric cancer (OR 0.92, 95%CI 0.85-0.99),

p= 0.0235). Asian/Pacific Islanders were more likely to receive guideline adherent care compared NHWs for breast cancer (OR 1.07, 95%CI 1.04-1.10, p<0.0001) and rectal cancer (OR 1.15, 95%CI 1.07-1.23, p=0.0001).

Analysis of disaggregated Asian American sub-ethnic groups revealed significant differences across different cancers (Table 4). Chinese and Korean patients were less likely to receive adherent care for colon cancers compared to non-Hispanic White (OR 0.86, 95%CI 0.77-0.96, p<0.05 and OR 0.80, 95%CI 0.68-0.95, p<0.05, respectively). Vietnamese patients were less likely to receive adherent care for gastric cancer (OR 0.84, 95%CI 0.73-0.96, p<0.05). Filipino and East Indian patients were more likely to receive NCCN guideline care compared to NHW patients for breast and rectal cancers.

Table 1: Adjusted Odds Ratio of NCCN guideline adherent care by race/ethnicity. (Red and green highlights denote statistically significant, p<0.05; Red correlates with OR <1.0 and Green is OR >1.0).

Cancer Type	NH White n=306,263	NH Black n=41,354	Hispanic n=113,652	Asian n=69,243	Other/Unknown n=12,646
	OR (95%CI)				
Breast	Ref	0.88 (0.84,0.92)	0.91 (0.88,0.93)	1.07 (1.04,1.10)	0.88 (0.81,0.96)
Prostate	Ref	0.90 (0.86,0.93)	1.15 (1.12,1.19)	1.01 (0.97,1.05)	0.63 (0.59,0.66)
Colon	Ref	0.85 (0.79,0.92)	1.02 (0.97,1.08)	0.95 (0.89,1.01)	0.72 (0.61,0.85)
Rectum	Ref	0.98 (0.88,1.09)	1.09 (1.02,1.17)	1.15 (1.07,1.23)	1.55 (1.31,1.85)
Liver	Ref	0.92 (0.83,1.02)	0.86 (0.80,0.91)	1.25 (1.17,1.34)	0.94 (0.78,1.13)
Gastric	Ref	0.89 (0.79,1.01)	0.92 (0.85,0.99)	1.07 (0.98,1.16)	0.68 (0.53,0.86)
Ovary	Ref	0.71 (0.62,0.82)	0.95 (0.88,1.03)	1.00 (0.91,1.09)	0.79 (0.61,1.01)
Cervix	Ref	1.04 (0.89, 1.20)	0.97 (0.89,1.05)	1.06 (0.96,1.18)	0.81 (0.65,1.02)

*Multivariate logistic regression model for each tumor site also controlled for patient's age at diagnosis, year of diagnosis, sex (except for breast, prostate, ovary and cervix), SES, payer status, and tumor stage (except for prostate cancer) and grade.

Table 2: Adjusted Odds Ratio of NCCN guideline adherent care by Asian sub-ethnic groups.

Cancer Type	NHW	Chinese	Japanese	Filipino	Korean	Vietnamese	Asian Indian	Others/ Unknown
	OR (95%CI)							
Breast	Ref	1.04 (0.98,1.10)	1.04 (0.94,1.15)	1.18 (1.12,1.25)	0.91 (0.81,1.02)	1.01 (0.95,1.07)	1.12 (1.02,1.24)	0.88 (0.81,0.86)
Prostate	Ref	1.09 (1.01,1.18)	1.11 (0.97,1.27)	0.96 (0.89,1.02)	1.03 (0.86,1.22)	0.96 (0.89,1.04)	1.03 (0.91,1.17)	0.63 (0.59,0.66)
Colon	Ref	0.86 (0.77,0.96)	1.01 (0.84,1.21)	1.14 (1.01,1.29)	0.80 (0.68,0.95)	0.92 (0.83,1.03)	1.22 (0.93,1.59)	0.72 (0.61,0.85)
Rectum	Ref	1.13 (1.00,1.29)	1.01 (0.82,1.25)	1.19 (1.05,1.36)	1.04 (0.86,1.27)	1.13 (1.01,1.27)	1.56 (1.19,2.04)	1.55 (1.33,1.84)
Liver	Ref	1.45 (1.29,1.63)	1.43 (1.10,1.86)	0.97 (0.84,1.12)	1.31 (1.09,1.56)	1.25 (1.14,1.38)	1.22 (0.89,1.66)	0.94 (0.78,1.13)
Gastric	Ref	1.08 (0.94,1.25)	1.13 (0.92,1.40)	1.17 (0.97,1.41)	1.24 (1.07,1.44)	0.84 (0.73,0.96)	1.42 (1.00,2.02)	0.68 (0.53,0.86)
Ovary	Ref	1.09 (0.92,1.29)	0.93 (0.66,1.29)	1.09 (0.94,1.27)	0.81 (0.61,1.07)	0.90 (0.77,1.05)	1.06 (0.82,1.38)	0.79 (0.61,1.01)
Cervix	Ref	1.04 (0.84,1.28)	0.96 (0.66,1.39)	1.09 (0.91,1.30)	1.00 (0.74,1.36)	1.09 (0.93,1.27)	1.04 (0.68,1.59)	0.81 (0.65,1.02)

*Multivariate logistic regression model for each tumor site also controlled for patient's age at diagnosis, year of diagnosis, sex (except for breast, prostate, ovary and cervix), SES, payer status, and tumor stage (except for prostate cancer) and grade.

Compared to Managed care insurance patients, independent of race/ethnicity and SES, Medicaid payer status was also associated with lower guideline adherent care for breast (OR 0.81, 95%CI 0.78-0.84), prostate (OR 0.91, 95%CI 0.86-0.97), colon (OR 0.70, 95%CI 0.65-0.75), rectal (OR 0.91, 95%CI 0.83-0.99), gastric (OR 0.69, 95%CI 0.63-0.75), and liver cancer (OR 0.66, 95%CI 0.61-0.72) (Table 5). Other insurance types including Fee-for-service and the Veteran's Affairs (VA) were associated with better guideline adherence compared to Managed care patients for prostate (OR 1.33, 95%CI 1.28-1.37), liver (OR 1.12, 95% CI 1.02-1.23), and gastric cancers (OR 1.13, 95%CI 1.02-1.26). Additionally, married patients across all cancer types (except cervical cancer) were more likely to receive NCCN guideline adherent

care (Table 6). Female gender, independent of race/ethnicity, SES, payer status, and tumor stage or grade, was found to be associated with increased likelihood of guideline-based care for colon (OR 1.13, 95%CI 1.08-1.18) and liver cancer (OR 1.11, 95%CI 1.04-1.18), while males were more likely for rectal cancer (OR 0.94, 95%CI 0.90-0.99).

Table 5: Adjusted odds ratio (OR) of NCCN guideline adherent care by Payer Status.

Cancer Type	Managed Care n=265,375	Medicare n=126,328	Medicaid n=47,950	Other Insurance (FFS, Tricare, VA) n=80,780	Uninsured or Unknown n=22,725
	OR (95%CI)				
Breast	Ref	0.83 (0.80,0.85)	0.81 (0.78,0.84)	0.88 (0.85,0.90)	0.83 (0.78,0.88)
Prostate	Ref	0.95 (0.93,0.98)	0.91 (0.86,0.97)	1.33 (1.28,1.37)	0.62 (0.59,0.65)
Colon	Ref	0.83 (0.79,0.88)	0.70 (0.65,0.75)	0.92 (0.86,0.99)	0.46 (0.42,0.51)
Rectum	Ref	0.92 (0.86,0.98)	0.91 (0.83,0.99)	1.00 (0.93,1.07)	0.84 (0.75,0.95)
Liver	Ref	1.07 (1.00,1.14)	0.66 (0.61,0.72)	1.12 (1.02,1.23)	0.47 (0.41,0.54)
Gastric	Ref	1.00 (0.93,1.08)	0.69 (0.63,0.75)	1.13 (1.02,1.26)	0.43 (0.37,0.49)
Ovary	Ref	0.80 (0.73,0.86)	0.91 (0.82,1.01)	1.02 (0.94,1.11)	0.67 (0.58,0.78)
Cervix	Ref	0.92 (0.81,1.05)	1.07 (0.98,1.16)	1.07 (0.97,1.19)	0.69 (0.59,0.80)

*Multivariate logistic regression model for each tumor site also controlled for patient's age at diagnosis, year of diagnosis, sex (except for breast, prostate, ovary and cervix), race/ethnicity, SES, and tumor stage (except for prostate cancer) and grade.

Table 6: Likelihood of receiving NCCN adherent care by Marital status and Gender.

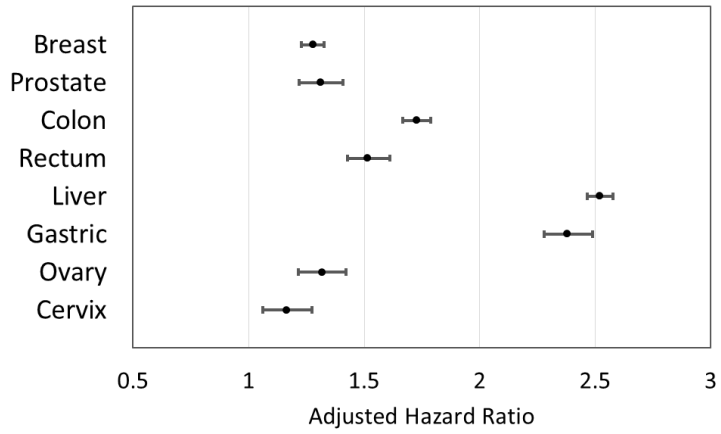
Cancer Type	Unmarried or widowed n=217,140	Married n=326,018	Male	Female
	OR (95%CI)			
Breast	Ref	1.12 (1.09,1.14)	-	-
Prostate	Ref	1.50 (1.46,1.53)	-	-
Colon	Ref	1.49 (1.43,1.55)	Ref	1.13 (1.08,1.18)
Rectum	Ref	1.17 (1.12,1.23)	Ref	0.94 (0.90,0.99)
Liver	Ref	1.40 (1.33,1.48)	Ref	1.11 (1.04,1.18)
Gastric	Ref	1.48 (1.39,1.58)	Ref	1.01 (0.95,1.07)
Ovary	Ref	1.15 (1.09,1.22)	-	-
Cervix	Ref	1.05 (0.98,1.12)	-	-

*Multivariate logistic regression model for each tumor site also controlled for patient's age at diagnosis, year of diagnosis, sex (except for breast, prostate, ovary and cervix), race/ethnicity, SES, payer status, and tumor stage (except for prostate cancer) and grade.

Survival Analysis

In multivariate survival analysis, after controlling for age at diagnosis, race/ethnicity, insurance type, SES, marital status, tumor stage and grade, NCCN guideline adherence was associated with a statistically significant improvement in disease-specific survival compared to non-adherent care across all cancer types. The multivariate Cox proportional hazards model revealed an increased risk of disease-related death in patients who did not receive NCCN guideline-adherent care (Figure 4). This finding was consistent across all cancer types: breast (HR 1.28, 95%CI 1.23-1.33, p<0.0001), prostate (HR 1.31, 95%CI 1.22-1.41, p<0.0001), colon (HR 1.73, 95%CI 1.67-1.78, p<0.0001), rectal (HR 1.51, 95%CI 1.41-1.63, p<0.0001), liver (HR 2.52, 95%CI 2.42-2.63, p<0.0001), ovary (HR 1.32, 95%CI 1.26-1.38, p<0.0001), gastric (HR 2.38, 95%CI 2.28-2.49, p<0.0001), and cervix (HR 1.17, 95%CI 1.08-1.26, p<0.0001). Disease-specific survival 5-year survival was consistently lower for non-adherent patients with GI cancers: colon, rectal, liver and gastric cancers (Log rank test, p<0.001) (Figure 5).

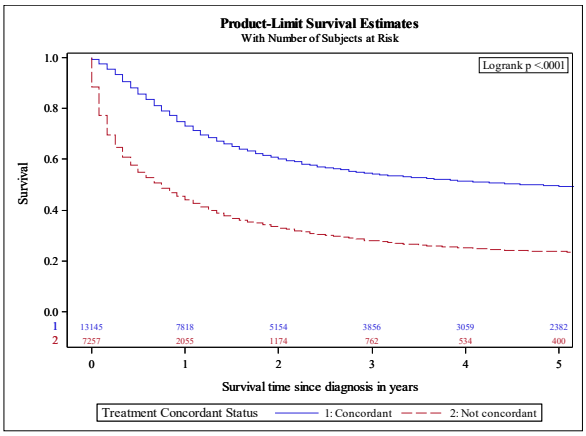
Figure 4: Adjusted hazard ratio (HR) for disease-specific survival with non-adherent care.



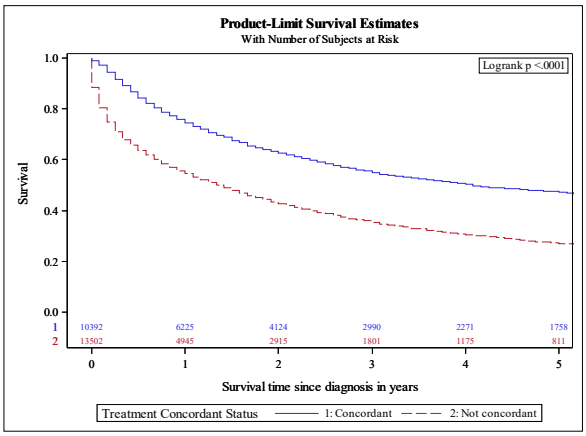
*Cox proportional hazards models for disease-specific survival controlled for age, year, race/ethnicity, insurance type, SES, marital status, sex, and tumor stage and grade.

Figure 5: Kaplan-Meier curves for disease-specific survival differences between concordant (NCCN guideline-adherent) and non-concordant (or non-adherent) patients with GI cancers (colorectal, liver, and gastric cancers).

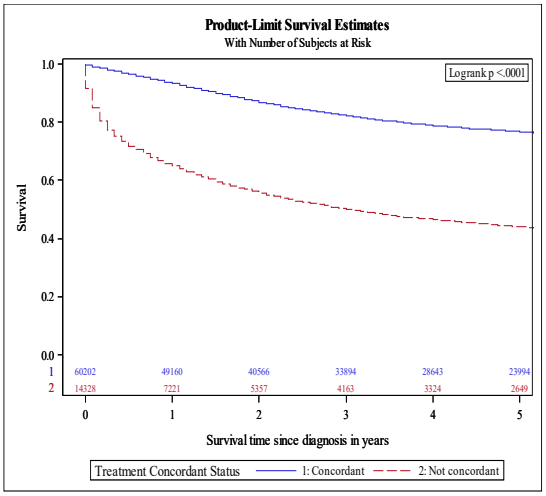
A. Gastric Cancer:



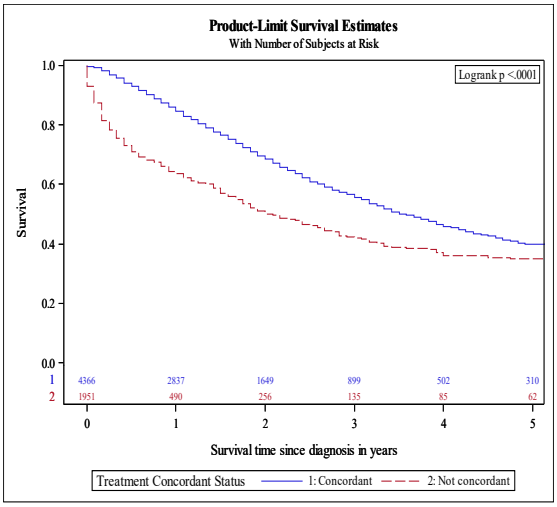
B. Liver Cancer:



C. Colon Cancer



D. Rectal Cancer (Stage IV)



DISCUSSION

Disparities in cancer survival are multifactorial, with structural barriers (insurance type, hospital location, geography/neighborhood), clinical factors (guideline adherence, quality of surgical treatment, physician perceptions/bias, stage/tumor biology), and patient decisions (cultural and economic factors) all contributing in varying degrees [11,19,22]. Recently, Ellis et al. found that stage had the largest effect on racial/ethnic disparities in survival for breast, prostate, and colorectal cancers [22]. While cancer stage itself is influenced by a similar set of factors (SES, insurance type, screening uptake, and access to health care), early cancer detection leading to an earlier stage at diagnosis is not sufficient in eliminating racial/ethnic disparities. One major shortcoming is the limited study of the impact of guideline-adherent treatment on survival across racial/ethnic groups controlling for tumor stage/grade, SES, and payer type. In our study, we observe significant racial/ethnic disparities in the receipt of quality of cancer treatment as defined by the receipt of NCCN guideline-adherent care. Even after controlling for socioeconomic status and payer type, persistent differences were observed by race/ethnicity across cancer types.

Using population-based cancer registry data for over 500,000 patients with new cancer diagnoses in California, we found an association between disease-specific survival and the likelihood of receiving NCCN guideline-adherent care. Significant disparities by race/ethnicity, socioeconomic status, and insurance type were also found in the likelihood of receiving NCCN guideline-adherent care. We observed that over half (52.5%) of patients did not receive NCCN guideline-adherent cancer care across all cancer types. While the difference in survival between guideline-adherent and non-adherent patients was statistically

significant across all cancer types, the degree of improvement in disease-specific five-year mortality also varied by disease type.

Our model demonstrates a consistent pattern in the relationship between NCCN guideline-adherence and improved survival across eight different cancer types. Most strikingly, our model demonstrates a consistent gradient across SES groups when comparing the likelihood of receiving guideline-adherent care within each specific cancer type. We identify the lower and lowest- socioeconomic groups as being the most disadvantaged in their likelihood of receiving guideline-adherent cancer care, thus, significantly impacting their disease-specific survival. This pattern for non-adherent care suggests systemic barriers or limitations in the delivery of high-quality cancer care to lower SES patients. While the most disadvantaged socioeconomic groups are identified within our study, further analysis is needed to obtain a more granular understanding of what aspects of treatment caused deviation from guideline-adherent care. For example, are there specific modalities (chemotherapy vs surgery vs radiation therapy) that were more likely to deviate, was there a lack of initiation of treatment or increased likelihood of incomplete treatment, was there over- or under-treatment? These are all important considerations that need to be investigated in further detail to understand the nuances in clinical and patient decision making that may be contributing to non-adherence.

Black patients were less likely to receive guideline-adherent care across several cancer types (breast, ovarian, prostate, and colon cancer) as compared to White patients. Even after controlling for SES, payer type, age, gender, tumor stage and grade, there were still persistent differences between these two groups. The patterns of guideline non-adherent

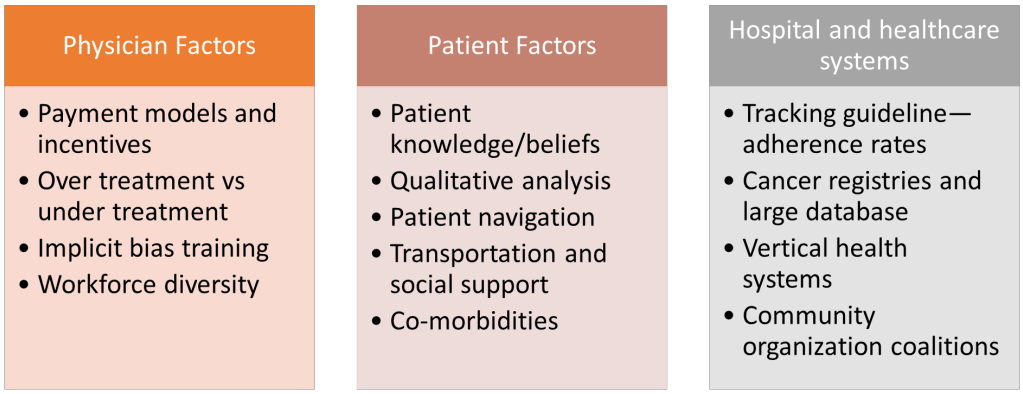
care for Black patients across different cancer types warrants further attention and are concerning for underlying systemic bias and/or racism within oncologic care. In our study, by controlling for tumor stage/grade and patient characteristics (age, gender, SES, insurance), we present evidence on the likelihood of receiving NCCN guideline adherent care by race/ethnicity. Based on the decreased likelihood of Black and Hispanic patients to receive NCCN guideline adherent care and the consistent relationship between NCCN guideline adherence and disease-specific survival across cancer types, it becomes imperative to understand and correct the systemic and provider level biases that are contributing to these differences. In order to address disparities in cancer survival, further research on the systemic discrimination experienced by specific racial/ethnic groups contributing to their likelihood of receiving NCCN guideline-adherent care is warranted. Several areas of future research focused on physician factors, patient experiences, and quality improvement within healthcare systems are needed (Figure 6).

We propose the receipt of NCCN guideline adherence as a potential metric for the accountability of quality cancer care across healthcare systems. While guideline-adherent care may be a proxy for other factors such as SES, insurance type, stage, geographic, and hospital characteristics that are all well-established factors in influencing disease-specific survival; we have controlled for these factors in our model and demonstrate a consistent pattern in the relationship between improved cancer specific survival with guideline-adherence. While several organizations including the NCCN and American Society of Clinical Oncology (ASCO) have developed practice guidelines and quality measures to assess quality, more research is needed to identify other measurement tools that can account for the quality

that are most influential to survival. Our study supports the use of NCCN guideline adherence as a tool towards equity in cancer care and addressing disparities. In addition, further research is needed to demonstrate the usability and efficacy of the NCCN guidelines. While published online and in print, the NCCN guidelines are not available through a user-friendly application and we suspect significant barriers in the use and application of these guidelines in clinical practice. Further investigation is needed to understand the impact of these guidelines across different oncologic practice types.

Our study is strengthened by the use of a racially/ethnically diverse cancer registry within California. In our study, we analyzed Asian American/Pacific Islander sub-ethnic groups and found statistically significant differences between sub-ethnic groups that would have been masked by the aggregated data. This type of disaggregated data is critical to identifying the most marginalized groups who are most at risk of non-adherent care and worse survival. We also acknowledge the heterogeneity within Black and Hispanic patients and the differences that may be potentially observed within these groups. Additional research is needed to study the sub-groups within racial/ethnic categories with further disaggregation of data to help understand the potential impact of culture and language in the receipt of quality cancer care.

Figure 6: Future areas of research regarding physician, patient, and health systems.



Despite the robustness of our findings across different cancer types, our study has several limitations. First, treatment variables were based on registry data, and thus we cannot assess the quality of surgery or radiation therapy received. Additionally, there remains limited information regarding the dose of radiation therapy or specific types of chemotherapeutic, biologic, or immunotherapeutic regimens. Data from the cancer registry is collected from licensed hospitals and so patients who are treated in other centers may not be captured through the registry data. Our categorization of insurance types does not distinguish between private insurance type and overlooks the variation that may exist among different policies. Despite these limitations, insurance type with coverage from Medicare or Medicaid programs was found to be a significant predictor of not receiving guideline adherent care. In addition, Asian/Pacific Islanders represent a heterogeneous group, and may mask important sub-group differences regarding receipt of care and survival.

There are also several limitations in regard to our assessment of "NCCN guideline-adherent" care. Disease based algorithms were adopted from each respective NCCN practice guideline with the assistance of a sub-specialist. Given the increasing complexity of

treatment practice and incorporation of genetic and molecular testing in treatment decisions, the algorithms were restricted by the availability of registry treatment variables. Moreover, the added complexity of co-morbidities, performance status, and patient centered decision-making factors are not captured through a registry-based assessment. Despite these limitations, we found significant differences in cancer survival in association with NCCN guideline-adherent care.

CONCLUSIONS

In this large cohort study, we found that increased adherence with NCCN guideline-based care was associated with improved survival across several cancer types. We identified disparities among patients of lower socioeconomic groups, Medicaid and Medicare insurance types, and specific racial/ethnic groups who are most at risk of not receiving guideline-adherent care. In a multivariate model, controlling for disease stage, socioeconomic status, and insurance type, significant differences in the likelihood of receiving NCCN guideline adherent care persisted by race/ethnicity. Black patients were consistently less likely to receive guideline-adherent care across several cancer types. The measurement of cancer outcomes is primarily focused on stage of diagnosis and overall survival. We propose consideration of guideline adherence as the basis for addressing biases/preferences within different healthcare systems and with specific populations to help address disparities in quality care. As the rates of insurance coverage continue to increase, particularly following the implementation of (and subsequent modifications to) the Affordable Care Act in

California, further studies are needed to evaluate access and quality of cancer treatment received to decrease disparities in cancer survival.

SUMMARY

In summary, the receipt of NCCN guideline-adherent care is consistently associated with improved disease-specific survival across 8 different cancer types. We investigated the likelihood of receiving NCCN guideline-adherent care by race/ethnicity, SES, payer type, and tumor grade and stage. Even after controlling for these factors in our multivariate model, there were persistent disparities in the likelihood of Black and Hispanic patients to receive NCCN guideline adherent care. We also demonstrate a pattern across all cancer types in the relationship between NCCN guideline adherent care improved survival; therefore, suggesting quality care as an important predictor for disparities in disease-specific survival. Additional studies are needed to better understand the specific aspects of treatment that contributing to the deviation from guideline-based care. We propose guideline-adherence as a potential objective metric to assess quality cancer care to mitigate the disparities experienced by specific racial/ethnic and SES groups. Given the consistent pattern of treatment deviation across all disease types, structural factors such as racial/ethnic discrimination and implicit bias should be areas of future investigation.

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