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Exploring Factors Related to Cancer Recurrence in Nebraska

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Abstract

Currently, the studies of cancer burden are focused on the incidence, mortality, and survival of cancer. Due to the early detection and advancement of therapies, more patients can live much longer after a cancer diagnosis. Health care providers and patients want to know more about cancer recurrence, which can significantly impact cancer survivors' quality of life. At this moment, the cancer recurrence studies are clinically based on specific treatments of particular cancers and are usually limited to small and selected populations. This study utilized the population-based cancer registry data between 1996-2015 to examine the cancer recurrence status in Nebraska. The overall all-cancer recurrence rate is 7.32%, and the age-adjusted incidence rate for cancer recurrence was 38.09 per 100,000. This study focuses on female breast cancer and colorectal cancer, two of the most common cancers in Nebraska. The female breast cancer recurrence rate was 6.64%, and the age-adjusted incidence rate for cancer recurrence was 5.61 per 100,000 population. The colorectal cancer recurrence rate was 7.8%, and the age-adjusted incidence for cancer recurrence was 4.40 per 100,000 population. Logistic regression analysis demonstrated that age at diagnosis, year diagnosed, stage and grade of the initial tumor, and urban/rural status were significantly associated with cancer recurrence for both types of cancer. There was also an association between the type of insurance and cancer recurrence among female breast cancer patients. No significant associations were found between marital status, census tract poverty, and education level with cancer recurrence in both types of cancer.

Background

Although cancer death rates have decreased almost 30% during the past 10 years, cancer is still the second leading cause of death in the United States, accounting for one of every four deaths. In 2018, there were 1,708,921 new diagnosed cancer cases and 599,265 cancer deaths, equivalent to 436 new cancer cases and 149 cancer deaths for every 100,000 people (Centers for Disease Control and Prevention, 2021). The most common cancers are lung, colorectal, breast, and prostate. We saw a similar trend in Nebraska where cancer is also the second leading cause of death. In 2018, there were 10,825 newly diagnosed cancer cases among residents in Nebraska, with an incident rate of 478.8 cases per 100,000 population (Nebraska Cancer Registry, 2021). In 2018, 3,498 Nebraska residents died from cancer, with a mortality rate of 150.0 cancer deaths per 100,000 population (Nebraska Cancer Registry, 2021).

Breast cancer is the most common type of cancer among women and the second leading cause of female cancer. In 2018, there were 845,972 new diagnosed breast cancer cases reported among women, and 283,718 women died in the United States, equivalent to 413 new cases and 129 deaths for every 100,000 women (Centers for Disease Control and Prevention, 2021). The 5-year relative survival rate for women diagnosed with breast cancer is around 89%. In 2018, there were 1,542 new female breast cancer (invasive) cases in Nebraska (136.8 cases per 100,000 women) (Nebraska Cancer Registry, 2021). Also in 2018, 222 women died due to breast cancer (invasive cases) (18.0 deaths per 100,000 women) in Nebraska (Nebraska Cancer Registry, 2021).

Colorectal cancer, also known as bowel cancer, colon cancer, or rectal cancer, is the fourth most frequently diagnosed cancer in the U.S. In 2018, there were 141,074 new colorectal cancer cases and 52,163 deaths from this cancer in the U.S., equivalent to 37 new cases and 13

deaths in every 100,000 population (Centers for Disease Control and Prevention, 2021). Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death among Nebraska residents. It accounted for 946 new cases (42.3 cases per 100,000 population) and 355 deaths (15.5 death per 100,000 population) in the state (Nebraska Cancer Registry, 2021).

Currently, public health authorities and researchers evaluate cancer burden based on metrics such as cancer incidence, mortality rate, and 5-year survival rates. However, due to the improvement of cancer diagnosis techniques and cancer treatments, cancer survivorship in the U.S. has increased. The current metrics for cancer burden are inadequate to evaluate the actual burden of the disease, and there is an increasing demand to understand the intermediate outcomes reflecting the postdiagnosis of the disease. One metric that can be studied is cancer recurrence, which is defined as a tumor that comes back after the patient is disease-free (National Cancer Institute, 2020). There are four different types of cancer recurrence: local recurrence (cancer recurs in the initial primary organ), trocar recurrence (organ removed and cancer recurs in scar tissue from removal), regional recurrence (cancer recurs in adjacent tissue or lymph nodes draining the organ), and distant recurrence (cancer recurs in another part of the body, also called metastatic recurrence or stage 4). The fear of cancer recurring is a prominent issue that brings enduring psychological burdens to cancer patients and families and has negatively impacted their quality of life. About 49% of cancer survivors experience moderate to severe levels of cancer recurrence fear, and 7% of patients experience severe and highly disabling fear (Butow et al., 2018). Cancer recurrence is the foremost concern of patients and their health care providers because it negatively impacts the patients' quality of life after treatment. Cancer recurrence causes a substantial financial burden to the patient and family due to the cost of cancer treatment.

The fear of cancer recurrence is a chronic psychological burden. The risk of cancer recurrence can be a crucial measure of the cancer burden and evaluation for the outcome of cancer therapies and care. It can also offer vital information to patients and health care providers when making decisions on the increasingly costly treatment of cancer.

The recurrence rate differs widely between cancer type, the stage of cancer, histology and genetic factors, and treatment. Most data come from clinical studies. Some types of cancer have relatively high rates of recurrence, such as glioblastoma (nearly 100%) and ovarian cancer (85%) (Nabors et al., 2017; Corrado et al., 2017). Half of the bladder cancer and soft tissue sarcoma cases will return after treatment (Casaali, 2015; Spiess et al., 2017). Other types of cancer like breast, pancreas, prostate, and thyroid cancers have recurrence rates between 10-40% depending on the kind of treatments (Goss et al., 2016; Nishio et al., 2017; Kurbegovic et al., 2017; Haddad, et al., 2018). Cancers such as colorectal cancer, head/neck cancer, and Hodgkin's lymphoma have a recurrence rate of around 20% (Pugh et al., 2016; Brockstein et al., 2004; Townsend & Linch, 2012).

Most cancer recurrence studies are centered on clinical-based research that reviewed the data in the electronic health records from several hospitals. The studies on population-based data were mostly completed in Europe, such as Denmark and Germany. One study used data from five state registries to assess the cancer recurrence and progression in breast and colorectal cancer to provide a generalizable picture of cancer outcomes in the U.S. (Thompson et al., 2019). The registries trained abstractors to review the medical records to determine documented disease-free status, recurrence, progression, and residual disease. The authors analyzed the demographics of the cancer recurrence and progression based on the data.

The goal of this capstone project was to study the characteristics of overall cancer, breast, and colorectal cancer recurrence burden in Nebraska. The first aim was to investigate the demographics of cancer recurrence overall as well as for breast cancer and colon cancer. The second aim was to examine the relationship between patients' demographic, clinical, and socioeconomic characteristics with whether individuals have cancer recurrence or not. The study was the first to evaluate the current cancer recurrence data in Nebraska and set the foundation for further studies.

Methods

Data Sources

The dataset for cancer cases in Nebraska was obtained from the Nebraska Cancer Registry (NCR), Nebraska Department of Health and Human Services (DHHS). NCR is a population-based cancer registry that has collected and maintained data since 1987. Registry data is collected from hospitals, medical clinics, pathology laboratories, and other settings in the state. The information included patient demographic characteristics, cancer diagnosis, insurance coverage, pathology-related information, treatment-related information, etc.

Study Population

Our study sample included Nebraska residents that were diagnosed with in-situ and invasive tumors in the NCR database between 1996-2015. The information related to cancer, such as the primary site of cancer, stage of disease at diagnosis, and histological type, were coded by the International Classification of Disease for Oncology, 3rd edition (ICD-O-3). The data included the patients' cancer recurrence information that was followed up until the end of 2018.

Two subgroups were further examined: females with breast cancer and individuals with colorectal cancer. Breast cancer and colorectal cancer were identified as ICD-O-3 codes C50.0-C50.9 and C18.0-20.9, respectively.

Outcomes and Explanatory Variables

The primary outcome of this study was whether our study patient had cancer recurrence. The cancer recurrence cases in this study were identified as patient cases with recurrence dates in the database. The recurrence data is required by Commission on Cancer (CoC) hospitals.

- Yes = patient diagnosed with female breast/colorectal cancer experienced cancer recurrence
- No = patient diagnosed with female breast/colorectal cancer did not experience cancer recurrence

The explanatory variables included the following demographic, clinical, and socioeconomic information of the patients.

- Age was registered when cancer was first diagnosed. In the female breast cancer study, the age was grouped into five groups: <45 years, 45-54 years, 55-64 years, 65-74 years, and 75+ years. In the colorectal cancer study, the age was grouped into <55 years, 55-64 years, 65-74 years, 75-84 years, and 85+ years.
- Gender was extracted from the registry data. For colorectal cancer, gender was grouped into male and female. For breast cancer, only female patients were selected.
- Race/ethnicity was registered separately. A consolidated variable was created to classify race and ethnicity into three groups: Non-Hispanic White, other, and unknown.
- Residence was categorized based on the ~~population of~~ county that patients resided in when diagnosed. There are four groups of residence: urban large, urban small, rural, and unknown. The groups are consistent with the Nebraska health assessment report (DHHS Nebraska, 2016). The urban large group consists of seven counties, including those counties that comprise the Lincoln and Omaha areas and their surrounding metropolitan

outlying counties; the urban small group consists of 15 counties, including the Grand Island and Sioux areas and their metropolitan outlying countries as well as all micropolitan core counties; the rural group consists of the remaining 71 counties in Nebraska.

- Year was registered when the first cancer was diagnosed and was divided into four groups: 1996-2000, 2001-2005, 2006-2010, and 2011-2015.
- Stage was registered when cancer was first diagnosed. The stage was categorized into five groups: in situ, localized, regional, distant, and unknown.
- Tumor Grade was registered when cancer was first diagnosed. Tumor grade was categorized into five groups: Grade I, Grade II, Grade III, Grade IV, and unknown.
- Insurance was registered when cancer was first diagnosed. Seven groups were presented: private, Medicare, Medicaid, other government, insured (not specified), uninsured and unknown.

The census tract poverty, income, and education level were obtained from the 2008-2012 American Community Survey (ACS) database of the U.S. Census Bureau, based on the census tract of patients when their cancer was first diagnosed.

- Census tract poverty was divided into five groups: < 10% below poverty level, 10-19% below poverty level, 20-29 % below poverty level, ≥30% below poverty level, and unknown.
- Census tract education level was divided into three groups based on the percent of the population with at least a 4-year college degree: 0-33%, 34+%, and unknown.

Statistical Software

All statistical analysis was performed using SAS on Demand for Academics (SAS Institute Inc. Cary, NC)

Statistical Analysis

- Descriptive statistics were presented as the categorical variables and mean with standard deviation for the continuous variables, to summarize the demographic, clinical, and socioeconomic characteristics of the study sample in cancer and cancer recurrence cases.
- The bivariate relationships between recurrence and patients' demographic, clinical, and socioeconomic characteristics were examined using Chi-square tests. For all analyses, a two-sided p-value < 0.05 was considered statistically significant.
- Multivariable logistic regression models were conducted to investigate the simultaneous effects of patients' characteristics on cancer recurrence.

Results

Overall and Trend of Cancer Recurrence in Nebraska

A total of 195,252 persons were reported to NCR as cancer patients between 1996-2015 in Nebraska. Among those, 14,284 were reported as having cancer recurrence, and the overall cancer recurrence rate was 7.32%. The top three cancers that had the highest recurrence rate were cancers in the urinary bladder, soft tissue, and ovarian with the recurrence rate of 23.74%, 15.50%, and 13.19% respectively (Table 1). The types of cancer having the highest recurrence case numbers were breast (2,045), urinary bladder (1,927), colorectal (1,668), lung & bronchus (1,342), and prostate (1,116).

The rate of cancer incidence and cancer recurrence were age-adjusted to the 2000 U.S. population. The age-adjusted incident rate for cancer was 514.49 per 100,000 and the rate for cancer recurrence was 38.09 per 100,000. The types of cancer having the highest cancer recurrence rates were breast cancer (5.61 per 100,000 population), urinary bladder (5.05 per 100,000 population), colorectal (4.40 per 100,000 population), lung & bronchus (3.53 per 100,000 population), and prostate (2.90 per 100,000 population).

The overall cancer recurrence case number was steady at around 800 cases per year between 1996-2007, and dramatically decreased starting in 2008 with 500-600 cases per year in 2009-2013 and around 450 in 2014-2015 (Figure 1a). Female breast cancer cases decreased from about 140 cases a year between 1996-2000 to about 60 cases a year between 2009-2015. The same trend could be found in colorectal cancer which changed from approximately 100 cases a year between 1996-2006 to approximately 50 cases between 2009-2015.

A similar trend was found in the recurrence rate (Figure 1b). For all cancer types, the recurrence rate dropped from 8-10% between 1996-2006 to about 4-5% in recent years. The

recurrence rate for female breast cancer was 10.75% in 1996 and has decreased to 3.15% in 2015. Colorectal cancer kept a high recurrence rate between 1996-2006, but decreased dramatically by about half in 2009, and was in an even lower range between 2009-2015.

Table 1

Cancer and Cancer Recurrence Status in Nebraska (1996 – 2015)

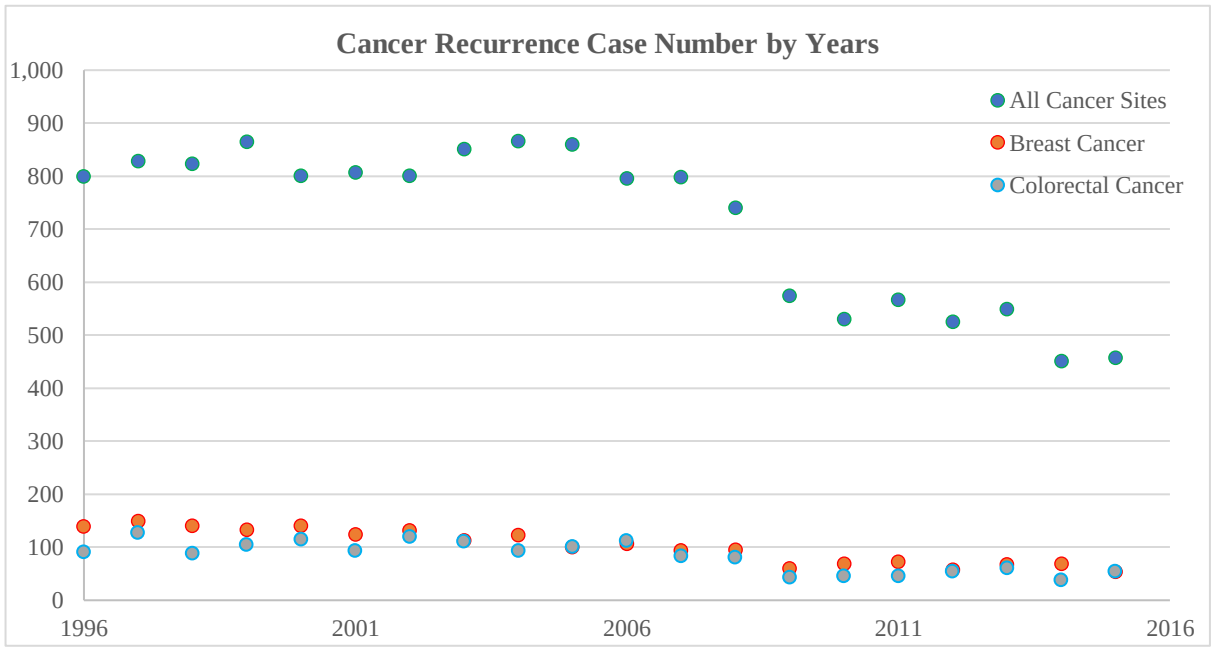
	Cancer Cases		Cancer Recurrence Cases		
	Case Number	Age-adjusted Rate*	Case Number	Age-adjusted Rate*	Recurrence Rate
All Sites	195,252	514.49	14,284	38.09	7.32%
Brain & Central Nervous System	5,191	14.07	298	0.84	5.74%
Breast	30,778	82.60	2,045	5.61	6.64%
Colon & Rectum (Colorectal)	21,389	55.29	1,668	4.40	7.80%
Esophagus	1,872	4.86	169	0.44	9.03%
Hodgkin Lymphoma	1,147	3.20	73	0.20	6.36%
Kidney & Renal Pelvis	6,031	15.90	519	1.37	8.61%
Larynx	1,432	3.75	170	0.45	11.87%
Leukemia	5,408	14.15	256	0.71	4.73%
Liver & Intrahepatic Bile Ducts	1,744	4.55	75	0.20	4.30%
Lung & Bronchus	23,831	62.23	1,342	3.53	5.63%
Melanoma of the Skin	10,404	28.12	674	1.81	6.48%
Myeloma	2,347	6.09	131	0.34	5.58%
Non-Hodgkin Lymphoma	7,836	20.60	711	1.91	9.07%
Oral Cavity & Pharynx	4,399	11.54	499	1.32	11.34%
Ovary	2,706	7.20	357	0.96	13.19%
Pancreas	4,341	11.21	162	0.43	3.73%
Prostate	25,600	66.35	1,116	2.90	4.36%
Small Intestine	838	2.21	75	0.20	8.95%
Soft Tissue	1,181	3.17	183	0.50	15.50%
Stomach	2,106	5.48	141	0.37	6.70%
Testis	1,140	3.34	69	0.20	6.05%
Thyroid Gland	3,910	11.02	182	0.51	4.65%
Urinary Bladder	8,159	21.05	1,937	5.05	23.74%
Uterine Cervix	1,377	3.97	144	0.42	10.46%
Uterine Corpus & Unspecified	5,527	14.50	416	1.09	7.53%
Other Cancers	14,558	38.05	872	2.34	5.99%

Note. Total case rate and recurrence case rate are per 100,000 population and are age-adjusted to the 2000 US population.

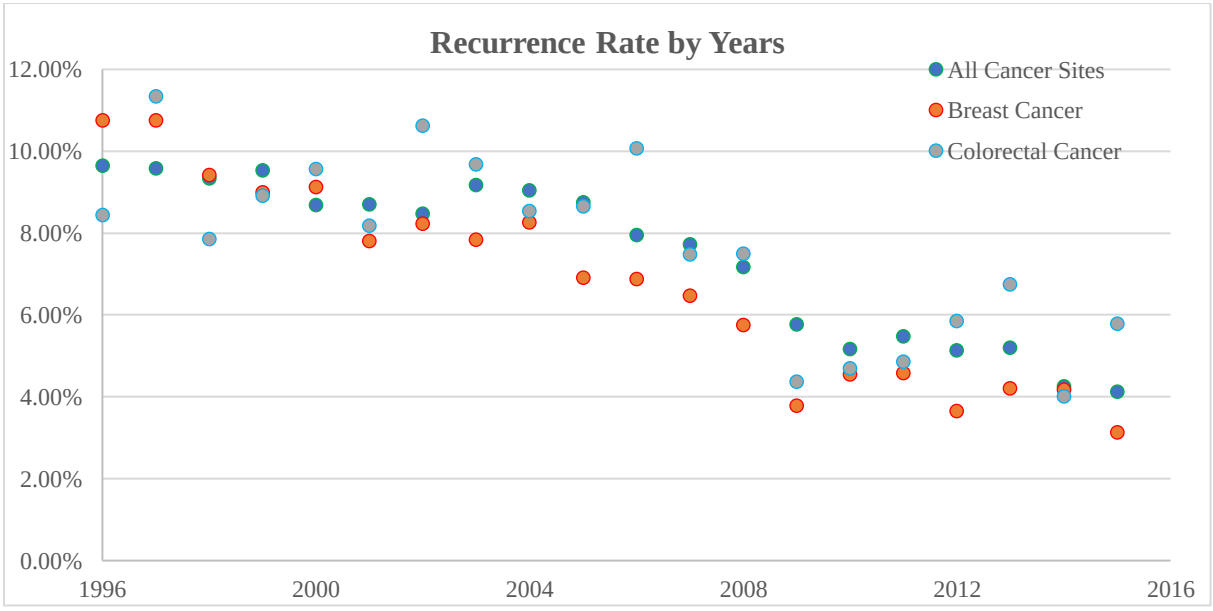
Figure 1

Trend of Cancer Recurrence for All Cancer Sites, Breast Cancer, and Colorectal Cancer in Nebraska

a. Cancer Recurrence Case Number by Years



b. Recurrence Rate by Years



Descriptive Statistics

There was a total of 30,778 patients diagnosed with female breast cancer between 1996-2015. Table 2 shows the demographic, clinical, and socioeconomic characteristics of the female breast cancer study samples. Of the study sample, 2,045 (6.65%) individuals had a diagnosis of cancer recurrence and 28,733 (93.3%) did not have a recurrence diagnosis. The average age of primary diagnosis for those who experienced recurrence was 59.7 ± 14.7 years, compared with a higher average age of 63.4 ± 14.2 years for those who did not experience recurrence. The average time between cancer diagnosis and recurrence was 4.5 ± 4.6 years. Overall, most cancer recurrence patients were non-Hispanic white (94.1%), the initial tumor was localized (36.2%) or regional (47.8%) stage, Grade II (34.2%) and Grade III (42.1%), married (61.0%), living in an urban large area (47.6%), census tract poverty percent less than 10% (51.4%), and less 33% census tract with a four-year college degree (70.6%).

A similar analysis was conducted on the data of colorectal cancer patients and the characteristics were presented in Table 3. There was a total of 21,389 patients diagnosed with colorectal cancer between 1996-2015, including 1,668 (7.78%) individuals who had a diagnosis of cancer recurrence and 19,721 (92.2%) were not diagnosed with cancer recurrence. The average age of primary diagnosis for the patients who experienced colorectal cancer recurrence was 66.5 ± 13.2 years and the average years between cancer diagnosis and recurrence was 2.7 ± 3.6 years. Most colorectal cancer recurrence patients were non-Hispanic white (94.7%), married (63.9%), living in an urban large area (41.3%), census tract poverty percent less than 10% (48.6%), and less 33% census tract with a four-year college degree (77.8%). There were slightly more male recurrence patients (53.3%) than female patients (46.7%). Most tumors were regional stage (63.2%) and Grade II (65.6%).

Bivariate Analysis

The female breast patients with or without recurrence were significantly different in age and year of diagnosis. The group of patients younger than 45 years had a much higher recurrent rate (11.1%) compared with the patients that were in older age groups (5.1% - 7.7%). The data shows that the recurrent rate decreases the more recent the cancer diagnosis occurs. Both the stage and grade of the initial tumor were significantly different between the two groups. Patients diagnosed at a regional stage had a much higher recurrence rate (13.3%) than those diagnosed at the in-situ stage (2.8%) and at the localized stage (4.6%). Similarly, there were 10.2% of Grade III patients suffered from cancer recurrence, compared with 2.8% in Grade I patients and 6.5% in Grade II patients. The recurrences of female breast cancer were also associated with residence (urban/rural), marital status, insurance types, and the percentage of a census tract with a four-year college degree, but not in the census tract poverty percentage.

Patient age and year of diagnosis were also significantly correlated with colorectal cancer recurrence with the same trend in breast cancer. The stage and grade of the initial tumor are significantly related to cancer recurrence, with a higher recurrence rate in the regional stage compared with in situ/localized group (12.8% vs. 4.3%), and Grade II compared with Grade I (8.9% vs. 4.3%). Residence (urban/rural), marital status, insurance types, and census tract poverty percentage significantly differed between the two groups, which was slightly different from the female breast cancer.

Table 2

Characteristics of Female Breast Cancer Patients: Recurrence vs. Non-Recurrence 1996-2015, Nebraska

	Recurrence Cases	Non-Recurrence Case	Recurrence Rate	p-value
Total	2,045	28,733	6.6%	
Age (years) at Diagnosis	59.7 ± 14.7	63.4 ± 14.2		
Age Group				<.01
<45 years	329	2,636	11.1%	
45 - 54 years	496	5,914	7.7%	
55 - 64 years	442	6,587	6.3%	
65 - 74 years	400	6,589	5.7%	
75+ years	378	7,007	5.1%	
Race and Ethnicity				0.63
Non-Hispanic White	1,924	26,960	6.7%	
Other	114	1,519	7.0%	
Unknown	7	254		
Diagnosed Year				<.01
1996 - 2000	704	6,507	9.8%	
2001 - 2005	594	7,014	7.8%	
2006 - 2010	425	7,351	5.5%	
2011 - 2015	322	7,861	3.9%	
Stage				<.01
In situ	144	5,092	2.8%	
Localized	740	15,210	4.6%	
Regional	977	6,379	13.3%	
Distant	93	1,047	8.2%	
Unknown	91	1,005		
Grade				<.01
I	185	6,383	2.8%	
II	699	10,063	6.5%	
III	861	7,564	10.2%	
IV	38	334	10.2%	
Unknown	262	4,389		
Residence				<.01

Urban Large	973	15,369	6.0%	
Urban Small	528	6,582	7.4%	
Rural	543	6,782	7.4%	
Unknown	1			
Marital Status				0.03
Married/Partner	1,247	17,003	6.8%	
Single	163	2,359	6.5%	
Separated/Divorced	218	2,656	7.6%	
Widowed	362	5,668	6.0%	
Unknown	55	1,047	5.0%	
Insurance				<.01
Private	514	7,942	6.1%	
Medicaid	111	1,132	8.9%	
Other Government	16	411	3.7%	
Medicare	606	10,835	5.3%	
Insured, No Specifics	389	4,419	8.1%	
Uninsured	104	719	12.6%	
Unknown	305	3,275	8.5%	
Census Tract Poverty				0.34
<10%	1,045	14,743	6.6%	
10-19%	708	9,907	6.7%	
20-29%	144	2,380	5.7%	
≥30%	91	1,324	6.4%	
Unknown	57	379		
% of census tract with 4 year college degree				0.01
0-33%	1,444	19,806	6.8%	
34+%	551	8,649	6.0%	
Unknown	50	278		

Table 3

Characteristics of Colorectal Cancer Patients: Recurrence vs. Non-Recurrence 1996-2015, Nebraska

	Recurrence Cases	Non-Recurrence Cases	Recurrence Rate	p-value
Total	1,668	19,721	7.8%	
Age (years) at Diagnosis	66.5 ± 13.2	70.5 ± 13.8		
Age Group				<.01
<55 years	318	2,703	10.5%	
55 - 64 years	364	3,366	9.8%	
65 - 74 years	464	5,048	8.4%	
75 - 84 years	408	5,553	6.8%	
85+ years	114	3,051	3.6%	
Gender				0.13
Male	889	10,134	8.1%	
Female	779	9,587	7.5%	
Race and Ethnicity				0.22
Non-Hispanic White	1,580	18,383	7.9%	
Other	81	1,090	6.9%	
Unknown	7	248		
Diagnosed Year				<.01
1996 - 2000	527	5,187	9.2%	
2001 - 2005	519	5,168	9.1%	
2006 - 2010	367	4,928	6.9%	
2011 - 2015	255	4,438	5.4%	
Stage				<.01
In situ/Localized	342	7,669	4.3%	
Regional	1,054	7,151	12.8%	
Distant	208	3,345	5.9%	
Unknown	64	1,556		
Grade				<.01
I	63	1,410	4.3%	
II	1,095	11,170	8.9%	
III	338	3,193	9.6%	
IV	51	566	8.3%	

Unknown	121	3,382		
Residence				0.01
Urban Large	689	8,962	7.1%	
Urban Small	452	5,025	8.3%	
Rural	527	5,734	8.4%	
Marital Status				<.01
Single	116	1,788	6.1%	
Married/Partner	1,066	10,884	8.9%	
Separated/Divorced	141	1,446	8.9%	
Widowed	317	4,705	6.3%	
Unknown	28	898		
Insurance				<.01
Private	302	2,820	9.7%	
Medicaid	51	739	6.5%	
Other Government	41	451	8.3%	
Medicare	755	10,246	6.9%	
Insured, No Specifics	184	1,836	9.1%	
Uninsured	80	594	11.9%	
Unknown	255	3,035		
Census Tract Poverty				0.01
<10%	806	9,141	8.1%	
10-19%	650	7,445	8.0%	
20-29%	141	1,952	6.7%	
≥30%	50	953	5.0%	
Unknown	21	230		
% of census tract with 4 year college degree				0.30
0-33%	1,297	15,114	7.9%	
34+%	355	4,414	7.4%	
Unknown	16	193		

Multivariable Analysis Results

Table 4 shows the multivariable logistic regression examining factors associated with female breast cancer recurrence. Compared to patients aged less than 45 years, the patients with ages 65-74 years (OR = 0.61, 95% CI: 0.47 – 0.80) and 75+ years (OR = 0.57, 95% CI: 0.43 – 0.76) have a significantly lower rate in experiencing cancer recurrence after adjustment for other variables in the model. Compared to the patients who were diagnosed with cancer between1996 to 2000, the odds ratios of cancer recurrence were lower in patients who were diagnosed with cancer in 2001-2005 (OR = 0.81, 95% CI: 0.70 – 0.94), in 2006-2010 (OR = 0.55, 95% CI: 0.46 – 0.64), and in 2011-2015 (OR = 0.39, 95% CI: 0.33 – 0.46). The stage of initial tumor was also associated with cancer recurrence, with those who were localized stage (OR = 2.04, 95% CI: 1.59 – 2.63), regional stage (OR = 5.42, 95% CI: 4.22 – 6.96), and distant stage (OR = 3.82, 95% CI: 2.70 – 5.41) having greater odds of cancer recurrence compared with that in-situ stage. The cancer recurrence rate was higher for patients with Grade II (OR = 1.78, 95% CI: 1.31 – 2.41), Grade III (OR =2.98, 95% CI: 2.48 – 3.58), and Grade IV (OR = 2.98, 95% CI: 1.96 – 4.54) compared to those with Grade I tumor. Female patients residing in urban small counties (OR = 1.22, 95% CI: 1.05 – 1.43) and rural counties (OR = 1.32, 95% CI: 1.12 – 1.55) had 22.3% and 32.1% higher odds of being diagnosed with cancer recurrence, compared to patients living in urban large counties. Finally, some types of insurance were significantly associated with recurrence, with Medicaid having 1.466 (95% CI: 1.13 – 1.90) and uninsured having 1.60 (95% CI: 1.22 – 2.11) times the odds of recurrence compared to private insurance.

Table 5 shows the multivariable results evaluating factors associated with colorectal cancer recurrence. Patients aged 75-84 years and 85+ years were less likely to be diagnosed with cancer recurrence compared with patients aged < 45 years. Compared to the patients who were

diagnosed with cancer in 1996-2005, patients who were diagnosed with cancer recurrence in 2006-2010 and 2011-2015 were less likely to be diagnosed with cancer recurrence. Patients with regional stage and distant stage had higher cancer recurrence rates compared to in situ/localized stage. Tumor Grade was also a significant factor that Grade II (OR = 1.78, 95% CI: 1.31 – 2.41), Grade III (OR = 1.84, 95% CI: 1.33 – 2.54), and Grade IV (OR = 1.65, 95% CI: 1.07 – 2.53) all had greater chance to develop recurrence compared with Grade I. Patients that live in rural counties were more likely (OR = 1.221, 95% CI: 1.03 – 1.45) to develop colorectal cancer recurrence compared with those in urban large counties. There was no significant difference between patients living in urban small counties and urban large counties. The study showed almost no significant association between gender, marital status, insurance, census tract poverty, and education level with colorectal cancer recurrence.

Table 4

Multivariable Logistic Regression of Female Breast Cancer Patient

	Odds Ratio	95% CI	
Age Group			
<45 years	REF		
45 - 54 years	0.83	0.69	0.99
55 - 64 years	0.75	0.63	0.91
65 - 74 years	0.61	0.47	0.80
75+ years	0.57	0.43	0.76
Race and Ethnicity			
Non-Hispanic White	REF		
Other	1.04	0.81	1.3
Diagnosed Year			
1996 - 2000	REF		
2001 - 2005	0.81	0.70	0.94
2006 - 2010	0.55	0.46	0.64
2011 - 2015	0.39	0.33	0.46
Stage			
In situ	REF		
Localized	2.04	1.59	2.63
Regional	5.42	4.22	6.96
Distant	3.82	2.70	5.41
Grade			
I	REF		
II	2.04	1.70	2.46
III	2.98	2.48	3.58
IV	2.98	1.96	4.54
Residence			
Urban Large	REF		
Urban Small	1.22	1.05	1.43
Rural	1.32	1.12	1.55
Marital Status			
Married/Partner	REF		

Single	0.86	0.70	1.07
Separated/Divorced	1.05	0.87	1.26
Widowed	1.07	0.90	1.27
Insurance			
Private	REF		
Medicaid	1.47	1.13	1.90
Other Government	0.74	0.44	1.24
Medicare	1.09	0.86	1.39
Insured, No Specifics	1.09	0.93	1.27
Uninsured	1.60	1.22	2.11
Census Tract Income			
<10%	REF		
10-19%	0.96	0.85	1.09
20-29%	0.79	0.63	0.98
≥30%	0.90	0.67	1.22
% of census tract with 4 year college degree			
0-33%	REF		
34+%	1.00	0.860	1.17

Table 5

Multivariable Logistic Regression of Colorectal Cancer Patients

	Odds Ratio	95% CI	
Age Group			
<55 years	REF		
55 - 64 years	0.85	0.70	1.03
65 - 74 years	0.71	0.55	0.91
75 - 84 years	0.54	0.42	0.71
85+ years	0.30	0.21	0.42
Gender			
Male	REF		
Female	0.98	0.86	1.11
Race and Ethnicity			
Non-Hispanic White	REF		
Other	0.95	0.70	1.27
Diagnosed Year			
1996 - 2000	REF		
2001 - 2005	1.03	0.88	1.21
2006 - 2010	0.74	0.62	0.88
2011 - 2015	0.61	0.50	0.74
Stage			
In situ/Localized	REF		
Regional	2.81	2.43	3.26
Distant	1.37	1.12	1.68
Grade			
I	REF		
II	1.78	1.31	2.41
III	1.84	1.33	2.54
IV	1.65	1.07	2.53
Residence			
Urban Large	REF		
Urban Small	1.15	0.97	1.36

Rural	1.22	1.03	1.45
Marital Status			
Married/Partner	REF		
Single	0.70	0.55	0.88
Separated/Divorced	0.98	0.78	1.22
Widowed	0.99	0.83	1.17
Insurance			
Private	REF		
Medicaid	0.91	0.64	1.29
Other Government	1.08	0.74	1.58
Medicare	0.95	0.75	1.20
Insured, No Specifics	0.81	0.655	1.005
Uninsured	1.17	0.865	1.587
Census Tract Poverty			
<10%	REF		
10-19%	1.01	0.89	1.15
20-29%	0.84	0.67	1.05
≥30%	0.77	0.54	1.10
% of census tract with 4 year college degree			
0-33%	REF		
34+%	0.98	0.82	1.17

Discussion

To our knowledge, this study is the first to investigate cancer recurrence in Nebraska using population-based data from NCR. This study found that 7.32% of cancer patients, diagnosed between 1996-2015, had cancer recurrence with an overall age-adjusted incident rate of 38.09 per 100,000 persons in the general population. The recurrence rates for female breast cancer and colorectal cancer were 6.64% and 7.85%, which were similar to or lower than other previous studies: 6.1% and 13.0% in five states in the U.S. (Thompson, et al., 2020), and 8.6% - 13.9% and 15.1 – 30.7% in Denmark (Holmes, et al., 2014; Lash, et al. 2014; Rasmussen, et al. 2019a). For breast cancer recurrence patients, the average age when they were diagnosed was 59.7 ± 14.7 years and the time between first cancer diagnosis and cancer recurrence was 4.5 ± 4.6 years. For colorectal cancer recurrence patients, the average age when diagnosed was 66.5 ± 13.2 years and the time between first cancer diagnosis and cancer recurrence was 2.7 ± 3.6 years.

The association between demographic, clinical, and socioeconomic factors with the recurrence of female breast cancer and colorectal cancer was studied. Race/ethnicity and gender (for colorectal cancer only) made no significant difference between recurrence and non-recurrence patients. Recurrence for both types of cancer decreased when the diagnosed age of the patients increased, matching the trend found in other studies (Lash, et al., 2014; Rasmussen, et al., 2019b). This might be due to younger patients tending to have hereditary cancers or having more aggressive or advanced cancers at diagnosis than older ones (Aghili, et al., 2010; Kanwar, et al. 2012). Another possible reason is that younger patients tend to have a longer length of follow-up and more time to re-develop their cancer. The study also suggested that the recurrence was linked to the year of diagnosis, which might be the result of the improvement of cancer therapy and treatment outcomes. The stage and grade of the initial tumor were significantly

associated with the cancer recurrence. In female breast cancer, the recurrence odds for patients diagnosed as regional stage were 5.4- and 2.7-times higher than patients diagnosed as the in-situ and localized stage. Similarly in colorectal cancer, the odds of regional patients were 2.8 times higher than in situ/localized patients. The higher the initial tumor Grade, the higher odds of patients having a recurrence, although there was not much difference between Grade III and Grade IV. This was not surprising because the tumor stage and grade are used as morphological prognostic factors. The patients residing in urban small and rural counties had higher odds of suffering from cancer recurrence compared with urban large counties for both types of cancer. The study showed marital status, census tract income, and education level did not impact cancer recurrence significantly. For female breast cancer, the patients with private insurance had lower odds of cancer recurrence compared with patients with Medicaid or uninsured. These results are similar to the other female breast cancer studies that found that patients uninsured or covered by Medicaid presented with more advanced cancer and had lower survival rates as compared with patients with private insurance (Ayanian, et al., 1993). One of the explanations could be the reduced access to care for those with Medicaid or those uninsured. Individuals with private insurance are more likely to have a primary care physician and can screen for cancer on a regular basis. They can possibly have a better chance to undergo cancer treatment such as surgery, chemotherapy, or radiation therapy, and are less likely to have cancer come back later. To prevent cancer recurrence, one of the strategies can be to increase patients' access to care and treatment. Another would be to expand Medicaid coverage and to make more private insurance plans accessible and affordable.

One of the main limitations of this study is missing information and underreporting. First, the recurrence data is only required by Commission on Cancer (CoC) hospitals, but not other

hospitals, clinics, and other settings. There are 13 CoC hospitals in Nebraska, and half of them are in the Lincoln-Omaha area. Between 2015 and 2019, about 94% of new cancer cases are reported from CoC hospitals. Some recurrence cases may have been missed and the recurrence rate might be underestimated. Another limitation is that some sociodemographic information is optional and therefore sparse when the cancer registry collects information. For example, poverty level and education level were assigned based on patients' residence census tract data.

This study was an initial attempt to evaluate the cancer recurrence status in Nebraska. There are still some challenges in regard to the completeness and accuracy of the data, which require accurate abstraction and consistent interpretation. One challenge is to accurately classify the cancer recurrence status of the patients who died from cancer, especially those with rapid and lethal disease due to cancer recurrence. Another question is to precisely differentiate cancer recurrence from a second primary of the same cancer type. It would be beneficial to develop more detailed and standard coding rules for cancer follow-up to ensure consistency as well as provide guidance and training in abstracting cancer recurrence data. More registry resources should be assigned to cancer follow-up in order to obtain more accurate cancer recurrence data. Our future study plan includes survival analysis limiting the study population to those from CoC hospitals. We will use the 1st cancer diagnosis as starting time (Time 0), censor for death, and outcome as 1st cancer recurrence.

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