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Adverse Health Outcomes among Rural Prostate Cancer Survivors: A Population-based Study

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Abstract

Introduction: Rural cancer survivors experience considerable health disparities compared to urban cancer survivors for cancer treatment and survival. The objective of our study was to investigate the risk of developing diseases for rural compared to urban prostate cancer survivors in Utah.

Methods: We identified a cohort of 3,575 rural prostate cancer survivors and 17,778 urban prostate cancer survivors from the Utah Cancer Registry. The Fine-Gray subdistribution hazards model was used to estimate hazard ratios and 95% confidence intervals for diseases in major body systems among rural compared to urban prostate cancer survivors at >1 to 5 years and >5 years after prostate cancer diagnosis.

Results: Rural residence was associated with an increased risk of diseases of the respiratory system at >5 years (HR: 1.16, 95% CI: 1.01-1.32) after cancer diagnosis compared to urban residence among prostate cancer survivors in Utah. Decreased risks were observed in infectious and parasitic diseases, diseases of the blood and blood-forming organs, diseases of the nervous

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system and sense organs, and diseases of the skin and subcutaneous tissue for rural prostate cancer survivors between 1 to 5 years after cancer diagnosis.

Conclusions: Rural prostate cancer survivors in Utah were somewhat healthier compared to urban prostate cancer survivors. Further studies are needed to confirm whether these associations are also supported for rural prostate cancer survivors in other regions of the U.S.

Keywords

Prostate cancer survivors; rural health; health disparity; comorbid disease; respiratory system

Introduction

Prostate cancer is the most prevalent cancer in the United States with as many as 3.5 million individuals with a history of prostate cancer [1]. An estimated 288,300 new prostate cancer cases and 34,700 prostate cancer deaths are predicted to occur in the U.S. in 2023 [2]. The 5-year survival rate was 97% for prostate cancer diagnosed from 2012-2018 [2].

A systematic review including 25 studies showed that men living in rural areas were less likely to be screened for prostate cancer compared to men living in urban areas [3]. In addition, rural residents had higher death rates after prostate cancer diagnosis [3]. A population-based study including 367 rural prostate cancer patients reported that the distance to travel for diagnostic scans, including CT, MRI, and bone scans, was greater among rural prostate cancer patients compared to urban prostate cancer patients [4]. A cross-sectional study including 170 rural breast, prostate, and colorectal cancer survivors reported the need for support in health promotion, access to screening, cancer treatment, mental health professionals, and financial assistance among rural cancer survivors [5]. Rural residents with cancer were more likely to have advanced stage at cancer diagnosis [6], and less likely to see medical oncologists given only 3% of clinicians practice in rural communities [7]. Rural cancer patients have barriers to access necessary cancer treatments due to the transportation barriers [8]. They were less likely to have a car and more likely to have limited public transportation to cancer care facilities [8, 9].

To our knowledge, no studies have comprehensively investigated diseases in the body systems among rural prostate cancer survivors compared to urban prostate cancer survivors. The objective of our study was to evaluate the risk of developing diseases in the major body systems for rural prostate cancer survivors compared to urban prostate cancer survivors in >1 to 5 years and >5 years after prostate cancer diagnosis in Utah.

Methods

Data sources

The Utah Population Database (UPDB) links the Utah cancer registry (UCR) data with Utah driver's license records, Utah voter registration data, death certificates, statewide healthcare facility data, and electronic medical records from the University of Utah and Intermountain Healthcare. The UCR has data on demographic characteristics, cancer diagnosis, cancer stage, histology, and the first course of cancer treatment. The statewide healthcare facility

data and electronic medical records consist of *International Classification of Diseases 9th/ 10th Edition* (ICD-9/10) codes.

Study Population

Men diagnosed with a first primary invasive prostate cancer at ≥18 years of age in Utah between 1997 and 2017 were identified from the UCR. The prostate cancer diagnosis was classified according to the *International Classification of Diseases for Oncology 3rd Edition* (ICD-O-3: C61.9). Exclusion criteria were missing cancer diagnosis date (N=44), non-adenocarcinoma histology (histology code, not 8140; N=517), missing residence information (N=24), and ≤1 year of follow-up (N=931). The census tract of patients at cancer diagnosis was linked to Rural-Urban Commuting Area (RUCA) codes to identify rural and urban residences. Rural RUCA codes included 4.0, 4.2, 5, 5.2, 6.0, 6.1, 7, 7.2, 7.3, 7.4, 8.0, 8.2, 8.3, 8.4, 9.0, 9.1, 9.2, 10.0, 10.2, 10.3, 10.4, 10.5, 10.6 and urban RUCA codes included 1.0, 1.1, 2.0, 2.1, 3.0, 4.1, 5.1, 7.1, 8.1, 10.1 [10]. We then matched one rural prostate cancer patient to up to five urban prostate cancer patients on cancer diagnosis age (±1) and year (±1) to increase statistical efficiency, especially after excluding prostate cancer survivors with the prevalent event for each disease in the analysis. A total of 3,575 rural prostate cancer survivors and 17,778 urban prostate cancer survivors were included in our final analysis.

Study variables

We used the clinical classifications software (CCS) to categorize ICD-9 and ICD-10 diagnosis codes for diseases with multi-level diagnoses hierarchy [11]. For example, chronic obstructive pulmonary disease and bronchiectasis (CCS Code 8.2), a level 2 disease, is a subcategory of diseases of the respiratory system (CCS Code 8), a level 1 disease [11]. We analyzed 11 level 1 diseases of the major body systems. A modified baseline Charlson comorbidity index (CCI) was calculated with the exclusion of cancer since all the patients in our study have had cancer [12]. The census tract at cancer diagnosis was linked to Yost state-based quintile for Yost socioeconomic (SES) status [13]. The tobacco use status at baseline was determined as “yes” if we identified any ICD and Current Procedural Terminology (CPT) codes regarding tobacco use, such as tobacco use disorder, smoking/tobacco abuse cessation counseling visit, nicotine dependence, and personal history of nicotine [14, 15], before the prostate cancer diagnosis (N=3,022). We obtained height and weight from the Utah driver’s license records to calculate baseline body mass index (BMI). Baseline BMIs were imputed using age at cancer diagnosis, race/ethnicity, and baseline CCI to account for missing data (21.4%).

Statistical Analysis

The distributions of demographic characteristics, clinical characteristics, and the prevalence of comorbid diseases at baseline between rural and urban prostate cancer survivors were compared using the chi-square test. The Fine-Gray subdistribution hazards model stratified by matched pairs was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for level 1 and 2 diseases among rural prostate cancer survivors compared to urban prostate cancer survivors [16-18]. Death was considered a competing risk in the model. We analyzed the risk of diseases between >1 to 5 years and >5 years after prostate cancer

diagnosis. Prostate cancer survivors diagnosed with the specific outcome of interest before the study period were considered prevalent cases and were excluded from the analysis. Prostate cancer survivors were followed from cancer diagnosis to disease diagnosis, end of follow-up, or death, whichever occurred first.

Matched pairs were adjusted using the STRATA statement in SAS statistical software. Potential confounders were selected based on the 3 properties of confounders and causal directed acyclic graphs (DAGs). The potential confounders we adjusted for included race/ethnicity, baseline body mass index (BMI), baseline CCI, and baseline Yost index (Supplemental Figure 1). The proportional hazards assumption was tested for each model by adding an interaction term between the predictor and time at risk. A flexible parametric survival model with restricted cubic splines was performed if the assumption was violated [19, 20]. The flexible model HR was used if the inference changed from the subdistribution hazards model. We compared the HRs with and without imputed BMI as a covariate. If the inference changed, HRs without imputed BMI as a covariate were presented. We analyzed the data using SAS version 9.4 (Cary, NC) and STATA version 17 (College Station, TX).

Results

We observed a higher proportion of non-Hispanic Whites, low income (<$60,000), low socioeconomic status (Quintiles 1 and 2), and tobacco smoking among rural prostate cancer survivors compared to urban prostate cancer survivors (P<0.0001, Table 1). There was no difference in the distribution of baseline BMI, first-degree family history of prostate cancer, and baseline CCI between rural and urban prostate cancer survivors. The mean age at cancer diagnosis for prostate cancer survivors was 66.9±8.8 years. The mean follow-up time for prostate cancer survivors was 9.4±5.3 (range: 1 to 23) years.

Rural prostate cancer survivors had a slightly higher proportion of distant cancer stage (3.1% vs. 2.3%, P=0.022) and a lower proportion of receiving surgery (40.9% vs. 45.0%) than the urban prostate cancer survivors (P<0.0001, Table 2). A higher proportion of rural prostate cancer survivors were treated with radiation alone (20% vs. 18.1%) and hormone therapy alone (5.8% vs. 5.2%) than urban prostate cancer survivors (P=0.001). Rural prostate cancer survivors had a lower prevalence of most diseases in the major body systems compared to urban prostate cancer survivors at cancer diagnosis (Table 3).

In terms of incident events, rural prostate cancer survivors had a lower risk for diseases of the blood and blood-forming organs in both >1 to 5 years and >5 years after cancer diagnosis period (Table 4). In the subcategory (level 2 CCS diseases) of diseases of the blood and blood-forming organs, rural prostate cancer survivors had a decreased risk of anemia compared to urban prostate cancer survivors during >1 to 5 years (HR: 0.83, 95% CI: 0.74-0.93) and >5 years (HR: 0.84, 95% CI: 0.76-0.94) after cancer diagnosis (Supplemental Table 1). Rural prostate cancer survivors were also less likely to be diagnosed with the following level 1 CCS diseases compared to urban prostate cancer survivors: 1) infectious and parasitic diseases, 2) diseases of the nervous system and sense organs, and 3) diseases of the skin and subcutaneous tissue from >1 to 5 years after cancer diagnosis (Table 4).

A higher risk of diseases of the respiratory system among rural prostate cancer survivors compared to urban prostate cancer survivors was observed >5 years after cancer diagnosis (Table 4). In the subcategory of diseases of the respiratory system, rural prostate cancer survivors had an increased risk of chronic obstructive pulmonary diseases (COPD) and bronchiectasis during both >1 to 5 years (HR: 1.26, 95% CI: 1.10-1.46), and >5 years (HR: 1.15, 95% CI: 1.01-1.30) after cancer diagnosis compared to urban prostate cancer survivors (Supplemental Table 1).

Discussions

In this population-based cohort study, we examined the risks of diseases in the major body systems among rural prostate cancer survivors compared to urban prostate cancer survivors in Utah. We observed that rural prostate cancer survivors had a lower prevalence of most diseases in the major body systems. The underdiagnosis of various diseases due to lack of access or use of healthcare services in rural communities could be a potential reason. Lower risk was observed for infectious and parasitic diseases, diseases of the nervous system and sense organs, and diseases of the skin and subcutaneous tissue among rural prostate cancer survivors during >1 to 5 years after cancer diagnosis. However, there was no difference in the risks of these diseases during >5 years after cancer diagnosis.

Rural prostate cancer survivors had a 1.16-fold risk of diseases of the respiratory system (95% CI: 1.01-1.32) compared to urban prostate cancer survivors >5 years after cancer diagnosis in our study. A previous study reported that residents in rural counties experienced higher mortality rates due to chronic lower respiratory disease than residents in urban counties [21]. Other studies reported rural population had higher COPD prevalence than the urban population due to “smoking and asthma history, environmental air quality, occupational exposures, low socioeconomic status, or genetics” [22, 23]. Similarly, we observed an increased risk of COPD and bronchiectasis in rural prostate cancer survivors compared to urban prostate cancer survivors in both time periods. Since rural residents had a higher prevalence of COPD and deaths due to COPD than urban residents in the U.S. [24], it is possible that rural men had an increased risk of diseases of the respiratory system, such as COPD, compared to urban men regardless of cancer status. Further research is needed to explore risk factors of poverty, air pollution, occupational exposures to mining, industrial farming, power production on the potential increased risks of respiratory diseases in rural prostate cancer survivors. According to the National Comprehensive Cancer Network (NCCN), after initial treatment prostate cancer survivors should be followed up for a prostate-specific antigen (PSA) test every 6-12 months for 5 years, followed by once a year after that, in addition to a digital rectal exam every 12 months [25]. If lymph node metastases (N1) were to be found, a physical exam with a PSA every 3-6 months with imaging for symptoms or increasing PSA is recommended [25]. Additional follow up is recommended if the cancer returns [25]. Although cancer recurrence is the main concern for patients and clinicians during the follow-up, our findings suggest that monitoring diseases of the respiratory systems could be useful among rural prostate cancer survivors to enable timely interventions and alleviate potential complications.

We observed that rural prostate cancer survivors were less likely to be diagnosed with infectious and parasitic diseases compared to urban prostate cancer survivors. We cannot rule out the possibility of underdiagnosis due to barriers of travel distance to care for infectious and parasitic diseases among rural prostate cancer survivors. It is also possible the rural population in Utah may be healthier than the rural population in the U.S.. According to the Behavioral Risk Factor Surveillance System (BRFSS) in 2021, Utahns had lower prevalence of smoking, with 22.8% reporting ever smoking, compared to the U.S. population where 39.8% of individuals reported ever smoking [26]. Moreover, a higher percentage of Utahns engage in physical activity (82.7%), compared to the US population (76.3%), which can positively impact overall health [26]. Additionally, the prevalence of obesity among Utahns was lower (30.9%) compared to the U.S. population (33.9%), which is a risk factor for several chronic diseases [26].

There was no association between mental illness and rural residence among prostate cancer survivors in our study. A previous study using data from the National Health Interview Survey reported the odds of having mild, moderate, or severe psychological distress among rural cancer survivors were 1.62-fold that of urban cancer survivors (95% CI: 1.33-1.98) [27]. Only 14.8% of rural cancer survivors in the previous study had prostate cancer [27]. The prior study utilized patient-reported data, whereas we relied on diagnosis codes in this study which could be a reason why we saw two different conclusions. More studies are needed to investigate the risk of incident mental health among rural prostate cancer survivors and the available resources following a cancer diagnosis. External beam radiation therapy and brachytherapy are associated with sexual, bowel, and urinary symptoms such as frequent urination, bowel urgency, and erectile dysfunction [28, 29]. Long-term side effects of prostatectomy included sexual dysfunction and urinary leakage and incontinence. [29] We did not observe an association between receiving radiation therapy and rural residence among prostate cancer survivors. The risks of diseases of the genitourinary system and diseases of the digestive system were similar between rural and urban prostate cancer survivors.

Our study had several limitations. One limitation is that the results from our study population may not be generalizable due to less diversity of race and ethnicity than in other states [2]. The Utah population has become more diverse amidst a growing proportion of Hispanics over the last few decades, followed by Native Hawaiian or Pacific Islander, Asians, American Indian or Alaska Native, and Black or African American [30]. Secondly, if prostate cancer survivors did not seek medical care for their conditions, we cannot capture their diagnoses through the electronic health record (EMR) or statewide healthcare facility data. Rural prostate cancer survivors may be less likely to seek medical care due to barriers of travel distance to care. Thus, the associations between rural residence and comorbid diseases may be underestimated [31], especially for comorbid diseases that involve mild symptoms not requiring hospital visits.

One strength of this study is that the data linked by UPDB, including statewide healthcare facility data, EMR, and UCR, allowed us to comprehensively estimate the risks of diseases in the major body systems. In addition, no recall bias was present since we do not rely on self-reported diseases. Lastly, this study contains a large sample size of >3,500 rural

prostate cancer survivors and >17,500 urban prostate cancer survivors with up to 23 years of follow-up.

In conclusion, this study provides important descriptive information on the diagnosis of comorbid diseases among rural prostate cancer survivors. Further efforts are needed to confirm whether these associations are also present for rural prostate cancer survivors in other regions of the U.S.. Understanding the potential risk of late effects of cancer therapy and other comorbidities for rural prostate cancer survivors would be prudent for clinical care implications and cancer survivorship programs in rural communities [1, 32].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographic characteristics of prostate cancer survivors, stratified by rural and urban residence in Utah

Characteristics	Rural (n=3,575)		Urban (n=17,778)		Chi-square *p* value
	n	%*	n	%*	
Race/ethnicity [b]					**<.0001**
Non-Hispanic White	3,293	92.1%	15,586	87.7%	
Hispanic (all races)	167	4.7%	1,443	8.1%	
Black or African American	.-[a]	.-[a]	114	0.6%	
Asian	.-[a]	.-[a]	87	0.5%	
Native Hawaiian and other Pacific Islanders	.-[a]	.-[a]	.-[a]	.-[a]	
Native American	14	0.4%	.-[a]	.-[a]	
Multiple races	74	2.1%	426	2.4%	
Age at cancer diagnosis					0.998
39 to 44	11	0.3%	50	0.3%	
45 to 54	289	8.1%	1,420	8.0%	
55 to 64	1,083	30.3%	5,401	30.4%	
65 to 74	1,484	41.5%	7,405	41.7%	
75 to 94	708	19.8%	3,502	19.7%	
Baseline body mass index [c]					0.790
<18.5 kg/m^2	.-[a]	.-[a]	39	0.2%	
18.5 to 24.9 kg/m^2	936	26.2%	4,547	25.6%	
25 to 29.9 kg/m^2	1,869	52.3%	9,283	52.2%	
30+ kg/m^2	.-[a]	.-[a]	3,909	22.0%	
Census-tract level income					**<.0001**
<$50,000	1,484	41.5%	4,646	26.1%	
$50,000 to <$60,000	1,478	41.3%	4,387	24.7%	
$60,000 to <$70,000	291	8.1%	3,013	17.0%	
$70,000+	322	9.0%	5,732	32.2%	
Yost index[b,d]					**<.0001**
Quintile 1 (lowest SES)	1,081	30.2%	2,814	15.8%	
Quintile 2 (lower-middle SES)	1,403	39.2%	2,737	15.4%	
Quintile 3 (middle SES)	536	15.0%	3,868	21.8%	
Quintile 4 (higher-middle SES)	.-[a]	.-[a]	3,614	20.3%	
Quintile 5 (highest SES)	.-[a]	.-[a]	4,586	25.8%	
Tobacco smoking at baseline					**<.0001**
No	3,000	83.9%	15,331	86.2%	
Yes	575	16.1%	2,447	13.8%	
First degree family history of prostate cancer					0.068
No	2,748	76.9%	13,912	78.3%	

Characteristics	Rural (n=3,575)		Urban (n=17,778)		Chi-square *p* value
	n	%*	n	%*	
Yes	827	23.1%	3,866	21.8%	
Baseline Charlson comorbidity index					0.407
0	2,070	57.9%	10,112	56.9%	
1	779	21.8%	3,889	21.9%	
2+	726	20.3%	3,777	21.3%	

a. Counts and % were not shown per Utah Department of Health data suppression guidelines (e.g. N<11).

b. Unknowns for Race/ethnicity, 14 (0.4%) rural, 65 (0.4%) urban; SES status <11(<0.3%) rural, 159(0.9%) urban.

c. Imputed BMI.

d. The Yost index was constructed using a factor analysis of seven variables of socioeconomic, linked by census tract.

* Sum of percentages may not add up to 100 due to rounding.

Table 2.

Clinical characteristics of prostate cancer survivors, stratified by rural and urban residence in Utah

Characteristics	Rural (n=3,575)		Urban (n=17,778)		Chi-square *p* value
	n	%*	n	%*	
Cancer primary					0.436
One primary cancer only	3,146	88.0%	15,561	87.5%	
First of two or more cancer primaries	429	12.0%	2,217	12.5%	
Cancer diagnosis year					0.887
1997 to 2001	782	21.9%	3,847	21.6%	
2002 to 2006	973	27.2%	4,759	26.8%	
2007 to 2011	925	25.9%	4,694	26.4%	
2012 to 2017	895	25.0%	4,478	25.2%	
Cancer stage					**0.022**
Localized	2,931	82.0%	14,723	82.8%	
Regional	491	13.7%	2,469	13.9%	
Distant	111	3.1%	402	2.3%	
Unknown	42	1.2%	184	1.0%	
Received surgery					**<.0001**
No	2,036	57.0%	9,420	53.0%	
Yes	1,463	40.9%	7,997	45.0%	
Unknown	76	2.1%	361	2.0%	
Received radiation therapy					0.068
No	2,251	63.0%	11,555	65.0%	
Yes	1,216	34.0%	5,716	32.2%	
Unknown	108	3.0%	507	2.9%	
Received hormone therapy					0.189
No	2,716	76.0%	13,756	77.4%	
Yes	750	21.0%	3,513	19.8%	
Unknown	109	3.1%	509	2.9%	
Received chemotherapy					0.365
No	3,448	96.5%	17,206	96.8%	
Yes	19	0.5%	68	0.4%	
Unknown	108	3.0%	504	2.8%	
First course treatment [b]					**0.001**
Surgery ± hormone therapy	1,375	38.5%	7,550	42.5%	
Radiation alone	715	20.0%	3,225	18.1%	
Radiation with hormone therapy	404	11.3%	2,031	11.4%	
Hormone therapy alone	207	5.8%	921	5.2%	
Chemotherapy ± hormone therapy	84	2.4%	425	2.4%	
Surgery and radiation ± hormone therapy	.-[a]	.-[a]	25	0.1%	
Other treatment[c]	.-[a]	.-[a]	63	0.4%	

Characteristics	Rural (n=3,575)		Urban (n=17,778)		Chi-square *p* value
	n	%*	n	%*	
No treatment documented	768	21.5%	3,538	19.9%	

a. Counts and % were not shown per Utah Department of Health data suppression guidelines (e.g. N<11).

b. Included all treatment combination.

c. Combination of surgery, radiation, chemotherapy, immunotherapy, and hormone therapy.

* Sum of percentages may not add up to 100 due to rounding.

Table 3.

Prevalence of diseases in the major body systems among prostate cancer survivors at cancer diagnosis, stratified by rural and urban residence in Utah (N=21,353)

Diagnosis	Rural		Urban		Chi-square *p* value
	n	%	n	%	
Infectious and parasitic diseases	1,005	28.1%	6,178	34.8%	**<.0001**
Endocrine; nutritional; and metabolic diseases and immunity disorders	1,819	50.9%	10,048	56.5%	**<.0001**
Diseases of the blood and blood-forming organs	457	12.8%	2,819	15.9%	**<.0001**
Mental illness	1,026	28.7%	5,105	28.7%	0.985
Diseases of the nervous system and sense organs	1,585	44.3%	9,287	52.2%	**<.0001**
Diseases of the respiratory system	1,660	46.4%	9,162	51.5%	**<.0001**
Diseases of the digestive system	2,051	57.4%	10,526	59.2%	**0.042**
Diseases of the genitourinary system	2,226	62.3%	10,926	61.5%	0.365
Diseases of the skin and subcutaneous tissue	1,007	28.2%	5,840	32.9%	**<.0001**
Diseases of the musculoskeletal system and connective tissue	1,935	54.1%	10,238	57.6%	**0.0001**
Injury and poisoning	1,812	50.7%	9,140	51.4%	0.428

Table 4.

The risks of incident diseases in the major body systems among rural prostate cancer survivors compared to urban prostate cancer survivors in Utah, stratified by follow-up period

Diagnosis	>1 to 5 years after cancer diagnosis					>5 years after cancer diagnosis				
	Rural		Urban		HR (95% CI)[a]	Rural		Urban		HR (95% CI)[a]
	n	%	n	%		n	%	n	%	
Infectious and parasitic diseases	440	18.7%	1,706	22.7%	**0.87 (0.78, 0.96)**	549	39.0%	1,406	41.4%	0.99 (0.90, 1.10)
Endocrine; nutritional; and metabolic diseases and immunity disorders	430	35.9%	998	37.8%	1.01 (0.89, 1.13)	331	65.7%	535	65.5%	1.07 (0.91, 1.25)
Diseases of the blood and blood-forming organs	416	15.0%	1,642	15.7%	**0.89 (0.80, 0.99)**	553	31.0%	1,867	34.3%	**0.83 (0.75, 0.91)**
Mental illness	430	19.6%	1,329	18.7%	1.03 (0.93, 1.16)	569	41.8%	1,525	43.4%	1.06 (0.95, 1.17)
Diseases of the nervous system and sense organs	525	32.9%	1,532	37.7%	**0.89 (0.80, 0.98)**	431	61.8%	871	65.6%	0.92 (0.81, 1.04)
Diseases of the respiratory system	461	30.6%	1,181	31.6%	1.00 (0.90, 1.11)[b]	429	57.7%	724	53.3%	**1.16 (1.01, 1.32)** [b]
Diseases of the digestive system	397	41.3%	1,000	46.2%	0.88 (0.77, 1.00)[*]	205	64.1%	311	64.9%	1.05 (0.86, 1.28)
Diseases of the genitourinary system	229	30.7%	492	34.8%	1.02 (0.86, 1.20)	166	51.7%	260	53.5%	1.00 (0.79, 1.27)
Diseases of the skin and subcutaneous tissue	380	15.9%	1,580	20.1%	**0.81 (0.73, 0.91)**	496	33.9%	1,402	38.3%	0.96 (0.86, 1.07)
Diseases of the musculoskeletal system and connective tissue	378	32.7%	966	36.7%	0.99 (0.80, 1.02)	292	57.7%	499	60.1%	0.95 (0.81, 1.12)
Injury and poisoning	420	31.8%	1,207	37.0%	0.90 (0.79, 1.01)[*]	329	56.5%	624	62.2%	0.87 (0.75, 1.01)

Abbreviation: HR, hazard ratio; CI, confidence interval.

[a.] Models adjusted for matched pair (diagnosis year and diagnosis age), race/ethnicity, baseline BMI, baseline Charlson Comorbidity Index, and socioeconomic status. Urban residence was the reference group.

[b.] Model additionally adjusted for tobacco smoking.

[*] Flexible model was used due to assumption violation and inference change.