

Original Article

Post-diagnosis smoking and risk of cardiovascular, cancer, and all-cause mortality in survivors of 10 adult cancers: a prospective cohort study

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Abstract: Several studies have examined the relationship between smoking and mortality in cancer survivors. However, few have reported the relationships in several cancer sites (i.e., bladder, non-melanoma skin, uterine, melanoma, and lymphoma), and limited data exist on the dose-response relationship between number of cigarettes smoked per day or duration of smoking cessation and mortality. Cancer survivors (N = 35,093, 61% female, mean age = 47 years old) from the National Health Interview Survey with linked data retrieved from the National Death Index served as our study participants. Cox proportional-hazards models were used to assess associations between smoking status, all-cause, and disease-specific mortality. After a median follow-up of 13 years, 11,066 deaths occurred. Survivors who reported smoking at study entry had a 73%, 75%, 85% higher risk for cardiovascular disease, cancer, and all-cause mortality, respectively when compared to nonsmokers. Former smokers had a 31% and 37% higher risk of all-cause and cancer mortality, respectively when compared to nonsmokers. The observed relationships appeared to differ by the number of cigarettes smoked (i.e., ≥ 10 per day), especially for breast, cervix, lung, prostate, uterine and non-melanoma skin cancer survivors. Those who continued smoking post diagnosis were at greatest risk of all-cause and cancer mortality, but the associations varied substantially by cancer site. These data provide sufficient evidence of the health hazards associated with smoking for cancer survivors and provide further support for public health strategies designed to curb smoking in this vulnerable population.

Keywords: Post-diagnosis smoking, all-cause, cardiovascular, cancer survivors, mortality, cohort

Introduction

The number of cancer survivors is expected to reach 19 million by 2024 in the United States [1]. Cancer survivors represent a vulnerable population because they have a higher risk for cardiovascular disease (CVD), diabetes, osteoporosis, second cancers, and premature mortality when compared to age-matched controls [2-4]. Given their increased vulnerability to chronic health conditions, the American Cancer Society and the Institute of Medicine has advocated for engaging in healthy lifestyle behaviors throughout the survivorship continuum [5,

6]. Smoking, in particular, may increase one's risk for cancer because it stimulates cancer-promoting signaling cascades [7-9]. However, for those with a prior cancer diagnosis, it may escalate the risk for poor cancer-specific and all-cause mortality [10]. Thus, it is of considerable importance to clarify the association between smoking and risk of disease-specific and all-cause mortality among cancer survivors who smoke.

Previous studies have examined the association between smoking and disease-specific mortality among cancer survivors [11-18]. The

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studies in their entirety have confirmed associations between smoking and all-cause mortality among colon, prostate, and lung cancer survivors [13, 14, 19, 20], and for cancer-specific mortality among colon, prostate, and breast cancer survivors [13, 14, 19, 21, 22]. However, several gaps in the literature remain unknown. For example, to our knowledge, few if any studies have examined the relationship between smoking and mortality in bladder, lymphoma, and uterine cancer survivors. In addition, limited data exist on the dose-response relationship between number of cigarettes smoked per day or duration of smoking cessation and mortality [14].

Therefore, the purpose of this study was to examine the relationship between both post-diagnosis smoking status and smoking intensity and both all-cause and disease-specific mortality among cancer survivors in the United States.

Materials and methods

Study population

The National Health Interview Survey (NHIS) is a stratified, multistage probability survey designed to examine the prevalence and incidence of disease and disability as well as the use of health care services in the United States. Black and Hispanic were oversampled to ensure equal representation in the study, but sample weights were used to ensure that estimates conform to national ethnic proportions. A detailed description of the probability sampling strategy and consenting methods were described elsewhere [23].

A total of 35,093 cancer adults from the 13 cross-sectional waves identified from 1997 to 2013 and their linked mortality data ending on December 31, 2015 were included in this analysis. For site-specific cancer, we focused on the ten most common cancer sites (i.e., bladder, breast, cervix, colon, lung, prostate, non-melanoma skin, uterine, melanoma, and lymphoma).

Mortality

Ascertainment of mortality was established using the International Classification of Diseases-10 Revision codes [24]. Study outcomes

were defined as follows: 1) all-cause mortality; 2) cancer mortality (C00 to C97); and 3) CVD-mortality (I00 to I09, I11, I13, and I20 to I51, I60 to I69).

Exposure assessment

Smoking status (never, former, or current) was ascertained at the initial interview via two binary coded (i.e., yes/no) items: 1) have you smoked at least 100 cigarettes in your entire life? and 2) do you now still smoke cigarettes? Those participants responding “No” to both questions were classified as nonsmokers. Those participants responding “Yes” to the first item and “No” to the second item were classified as former smokers. Those who responded “Yes” to both questions were classified as current smokers. To distinguish between current and former smokers, time since last cigarette (i.e., quit \geq 20 years ago; quit 10 to 19 years ago; quit < 10 years ago) were used to classify former smokers, and cigarettes smoked per day (i.e. > 10 cigarettes per day; \leq 10 cigarettes per day) were used to classify current smoker.

Covariates

Several covariates were included in the study. In particular, we included demographic variables (i.e., race, gender, education, and marital status), lifestyle variables (i.e., body mass index, physical activity, and alcohol consumption), comorbid conditions (i.e., hypertension, stroke and coronary heart disease), and self-rated health. Body mass index was calculated as weight in kilograms divided by height in meters squared.

Detailed information on the highest level of school completed was collected and the variable was categorized as “less than high school degree” (high school not completed), “high school degree” (high school diploma or general equivalency diploma), and “more than high school degree” (some college, vocational, or technical school; associate’s degree; Bachelor’s, Master’s, or professional degree) [25].

NHIS study participants answered questionnaires about their alcohol consumption and patterns of use [26]. These questions obtained information about the following: 1) consumption of \geq 12 drinks in one’s lifetime, in any previous year, or the past year; 2) drinking frequency (da-

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ys per week, month, or year) and drinking quantity (drinks per day) in the past year; and 3) binge drinking in the past year. Using these variables, we categorized survivors into four alcohol consumption groups: 1) lifetime abstainers: < 12 drinks in one's lifetime; 2) former drinkers: ≥ 12 drinks in a previous year; 3) current drinker: current use of drinks/week.

Socioeconomic status was assessed based on the family income to poverty ratio (PIR) [27]. We separated participants into 3 groups: low-income (i.e., at or below the poverty ratio), middle-income (i.e., above the PIR to < 4), and high-income (i.e., PIR, ≥ 4) adults.

Statistical analysis

Weighted descriptive characteristics were used to describe the sample. Chi-square test of independence was used to examine categorical differences in the weighted percentages by smoking status. We also used Cox proportional hazard models with proportionality assumptions to examine all associations between smoking status and disease-specific and all-cause mortality. We adjusted for potential covariates and conducted two sensitivity analyses: (1) exclusion of individuals who died within the first 2-years and (2) participants with a history of CHD or stroke. In addition, we made comparisons between current smokers (> 10 cigarettes per day; ≤ 10 cigarettes per day) and former smokers (quit ≥ 20 years ago; quit 10 to 19 years ago; quit < 10 years ago). All analyses took into account the complex survey design (strata, clusters, and weights). All analyses were performed using STATA version 13.0 (Stata Corp, College Station, TX, USA). All *P*-values were two-sided and statistical significance was determined at $P \leq 0.05$.

Results

The mean age of participants was 47 years at study entry. Compared with nonsmokers, former or current smokers were more likely to be men and non-Hispanic whites (*p*-value < 0.001). Never smokers appeared to be more educated. Current smokers were less physically active, leaner (i.e., BMI < 25 kg/m²) and consumed more alcohol. Former smokers were more likely to have a history of hypertension, diabetes, CHD and stroke. Descriptive statistics were reported in **Table 1**.

Among 35,093 cancer survivors, 11,066 died of all-causes (including 3,979 cancer and 2,156 CVD deaths) after a median follow-up of 13 years. The most common deaths occurred among survivors of breast (752 deaths), prostate (559 deaths), lung (467 deaths), colon (435 deaths), and non-melanoma skin (384 deaths) cancer survivors. Similarly, CVD deaths occurred mostly in breast (389 deaths), prostate (348 deaths), and non-melanoma skin (334 deaths) cancer survivors (**Figure 1** Analytic sample selection).

Smoking status

All-cause mortality: Among all survivors, current smokers had an 85%, 75% and 73% higher risk for all-cause, cancer, and CVD-related mortality when compared to never smokers. However, former smokers had a higher risk for all-cause (31%) and cancer mortality (37%), but not CVD mortality (see **Figures 2, 3** and **Table 2**). For specific cancer sites, there was a 60% increase in all-cause mortality among current smokers who were survivors of bladder, breast, lung, colon, lymphoma and prostate cancer, and 130% increase in all-cause mortality among survivors of cervical, uterine, melanoma and non-melanoma cancer when compared to never smokers. Similarly, former smokers had a 27% higher risk for all-cause mortality when compared to select cancer survivors (i.e., breast, colon, lung, melanoma, prostate, uterine and non-melanoma skin cancer survivors) who never smoked. These relationships were stronger for cervical cancer survivors (Hazard Ratio [HR] = 1.58, 95% CI = 1.16 to 2.15) who never smoked, but no associations were observed in bladder and lymphoma cancer survivors (**Figure 2**-Current smoking and risk of all-cause mortality).

Cancer mortality: The HRs for cancer mortality ranged from 1.47 to 3.01 among current smokers who were survivors of non-melanoma skin (HR = 3.01, 95% CI = 2.15 to 4.21) and uterine cancer (HR = 2.57, 95% CI = 1.51 to 4.37), followed by survivors of melanoma (HR = 2.31, 95% CI = 1.35 to 3.93), prostate (HR = 1.95, 95% CI = 1.45 to 2.64), lymphoma (HR = 1.69, 95% CI = 1.04 to 2.74), and breast (HR = 1.47, 95% CI = 1.16 to 1.85) cancer. In contrast, former smokers who were survivors of on-melanoma skin cancer (HR = 1.47, 95% CI = 1.12 to

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Table 1. Baseline characteristics of cancer patients by smoking status

Characteristic	Subgroups	Never smoking		Former smoking		Current smoking		P value
		No.	%	No	%	No	%	
Age								< 0.001
	< 45 years	2364	15.99%	861	7.20%	1777	30.21%	
	45-65 years	5382	37.62%	4159	35.31%	2893	47.57%	
	> 65 years	8116	46.39%	7974	57.49%	1567	22.22%	
Sex								< 0.001
	Male	4791	34.25%	6831	56.13%	2157	36.84%	
	Female	11071	65.75%	6163	43.87%	4080	63.16%	
Race/ethnicity								< 0.001
	Hispanic	1321	5.78%	582	3.08%	315	3.23%	
	Non-Hispanic White	12752	85.73%	11221	90.67%	5153	87.62%	
	Non-Hispanic Black	1354	5.92%	987	4.92%	634	7.00%	
	Non-Hispanic Other	435	2.57%	204	1.34%	135	2.14%	
Education								< 0.001
	Less than high school degree	2679	13.73%	2537	17.50%	1427	21.33%	
	High school degree	4338	27.33%	3691	28.62%	2114	35.86%	
	More than high school degree	8845	58.94%	6766	53.88%	2696	42.80%	
Marital status								< 0.001
	Married/Living with partner	7991	64.97%	7080	69.19%	2648	56.85%	
	Widowed/Divorced/Separated/Never married	7871	35.03%	5914	30.81%	3589	43.15%	
Income level								< 0.001
	Low	1848	8.11%	1137	6.26%	1414	18.60%	
	Middle	8215	48.49%	7167	52.49%	3381	55.03%	
	High	5799	43.40%	4690	41.25%	1442	26.37%	
Body mass index								< 0.001
	< 25 kg/m ²	6087	38.62%	4521	33.79%	2885	45.61%	
	25-30 kg/m ²	5549	35.01%	4992	39.15%	1960	32.12%	
	> 30 kg/m ²	4226	26.37%	3481	27.06%	1392	22.28%	
Physical activity								< 0.001
	Low	9927	59.51%	8083	59.74%	4378	69.52%	
	high	5935	40.49%	4911	40.26%	1859	30.48%	
Alcohol intake								< 0.001
	Lifetime abstainer	5171	29.74%	1366	9.93%	681	10.28%	
	Former drinker	2972	17.97%	4001	28.92%	1589	25.34%	
	Current drinker	7648	51.83%	7539	60.53%	3915	63.71%	
Self-rated health								< 0.001
	Excellent	2702	18.84%	1735	14.16%	595	9.65%	
	Very good	4306	28.46%	3282	25.89%	1337	22.37%	
	Good	5015	31.04%	4167	32.22%	1955	31.53%	
	Fair	2774	15.67%	2581	18.84%	1512	23.26%	
	Poor	1065	5.99%	1229	8.88%	838	13.19%	
History of hypertension								< 0.001
	Yes	7835	46.52%	7081	52.97%	2632	40.77%	
	No	8027	53.48%	5913	47.03%	3605	59.23%	
History of diabetes								< 0.001
	Yes	2317	13.83%	2286	16.96%	680	10.69%	
	No	13545	86.17%	10708	83.04%	5557	89.31%	
History of CHD								< 0.001
	Yes	1466	9.04%	2065	16.24%	607	9.15%	
	No	14396	90.96%	10929	83.76%	5630	90.85%	
History of stroke								< 0.001
	Yes	939	5.45%	992	7.45%	477	6.79%	
	No	14923	94.55%	12002	92.55%	5760	93.21%	

Abbreviations: CHD = coronary heart disease.

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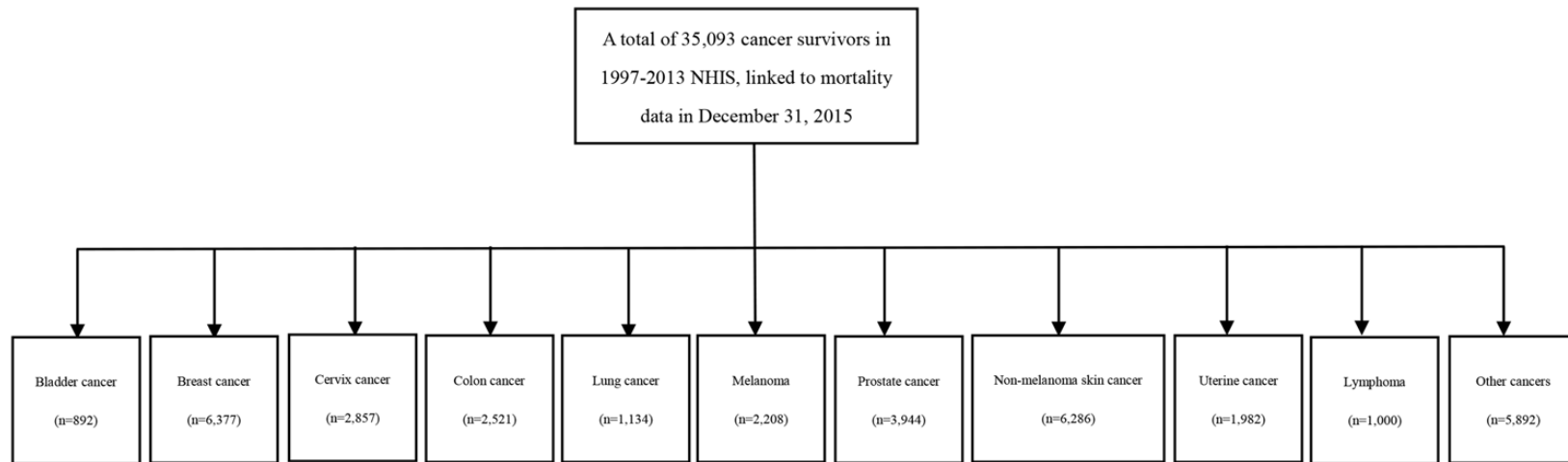


Figure 1. Analytic sample.

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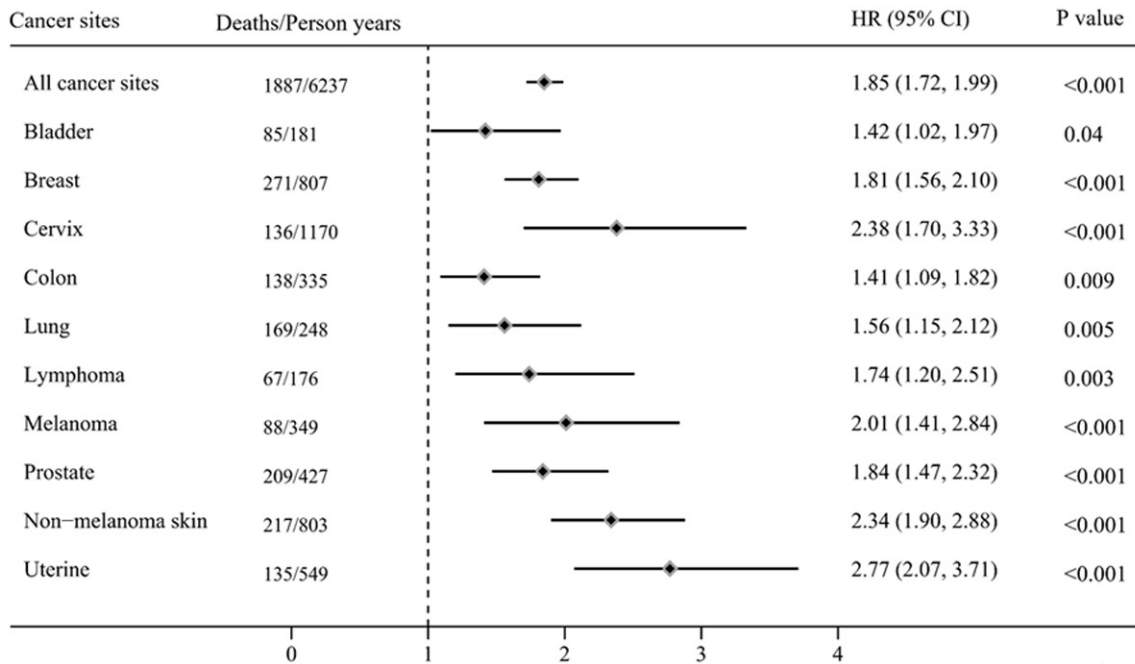


Figure 2. Current smoking and risk of all-cause mortality.

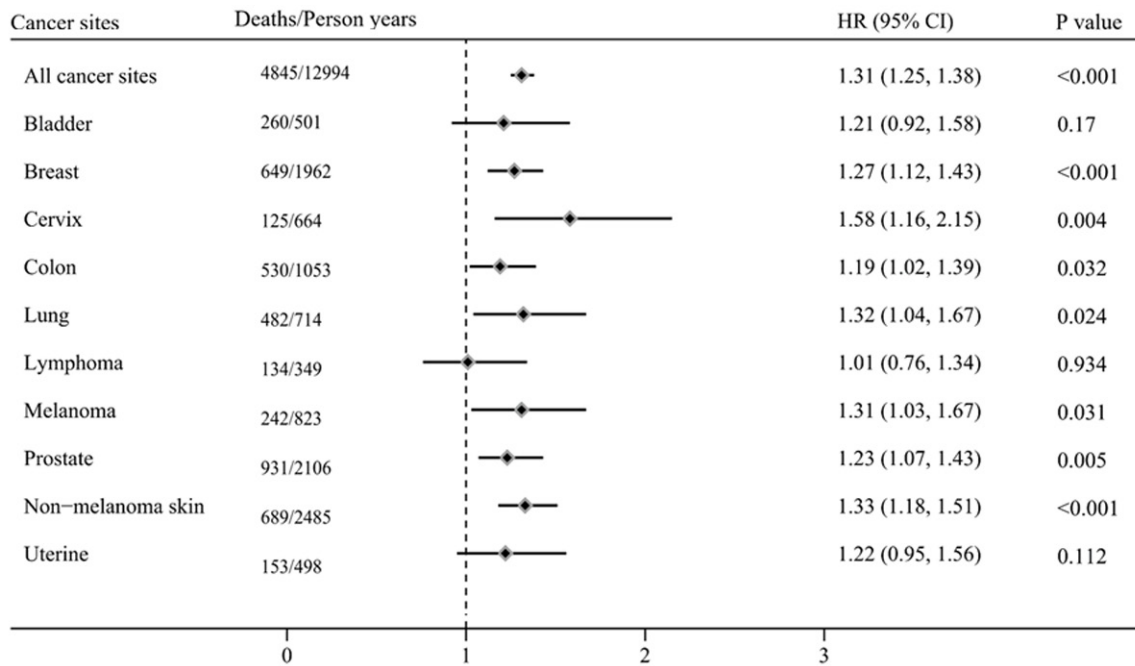


Figure 3. Former smoking and risk of all-cause mortality.

1.94) had a higher risk for cancer mortality than survivors who never smoked.

CVD mortality: For CVD mortality, current smokers had a higher risk of CVD mortality in uterine (HR = 2.78, 95% CI = 1.54 to 5.04), breast (HR

= 1.79, 95% CI = 1.17 to 2.72), and non-melanoma skin cancer survivors (HR = 1.73, 95% CI = 1.07 to 2.81) when compared to those who never smoked. Former smokers, regardless of cancer diagnosis did not have a higher risk for CVD mortality when compared to never smok-

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Table 2. Cancer, CVD and other cause mortality among cancer survivors according to smoking status

Cancer sites	Smoking status	Subgroups	Cancer mortality				CVD mortality				Other mortality			
			Deaths	Person years	HR (95% CI)	P value ^a	Deaths	Person years	HR (95% CI)	P value ^a	Deaths	Person years	HR (95% CI)	P value ^a
All sites	Never smoking		1386	15862	1 (Reference)		941	15862	1 (Reference)		2007	15862	1 (Reference)	
	Current smoking		825	6237	1.75 (1.57 to 1.95)	< 0.001	292	6237	1.73 (1.47 to 2.05)	< 0.001	770	6237	2.06 (1.83 to 2.33)	< 0.001
		< 10 cigarette per day			1.74 (1.50 to 2.03)	< 0.001			1.83 (1.42 to 2.37)	< 0.001			1.80 (1.50 to 2.16)	< 0.001
		≥ 10 cigarette per day			1.89 (1.67 to 2.14)	< 0.001			1.79 (1.47 to 2.18)	< 0.001			2.39 (2.09 to 2.75)	< 0.001
	Former smoking		1768	12994	1.37 (1.25 to 1.49)	< 0.001	923	12994	1.08 (0.96 to 1.22)	0.194	2154	12994	1.38 (1.27 to 1.49)	< 0.001
		Quit smoking < 10 years			1.87 (1.66 to 2.10)	< 0.001			1.50 (1.23 to 1.83)	< 0.001			1.88 (1.65 to 2.14)	< 0.001
		Quit smoking 10-19 years			1.49 (1.31 to 1.68)	< 0.001			1.26 (1.07 to 1.48)	0.006			1.42 (1.27 to 1.60)	< 0.001
		Quit smoking ≥ 20 years			1.09 (0.98 to 1.21)	0.122			0.91 (0.79 to 1.05)	0.204			1.21 (1.11 to 1.33)	< 0.001
		P for trend				< 0.001				< 0.001				< 0.001
	Bladder	Never smoking		23	210	1 (Reference)		17	210	1 (Reference)		47	210	1 (Reference)
Current smoking			34	181	1.62 (0.92 to 2.86)	0.092	13	181	1.11 (0.45 to 2.70)	0.824	38	181	1.37 (0.81 to 2.32)	0.242
		< 10 cigarette per day			2.40 (1.07 to 5.38)	0.033			0.33 (0.07 to 1.57)	0.163			0.93 (0.39 to 2.25)	0.877
		≥ 10 cigarette per day			1.73 (0.91 to 3.26)	0.092			1.41 (0.54 to 3.64)	0.48			0.68 (0.96 to 2.97)	0.071
Former smoking			86	501	1.11 (0.66 to 1.87)	0.682	50	501	1.29 (0.70 to 2.38)	0.419	124	501	1.18 (0.82 to 1.71)	0.366
		Quit smoking < 10 years			2.11 (1.06 to 4.19)	0.033			0.98 (0.31 to 3.10)	0.978			1.59 (0.86 to 2.93)	0.135
		Quit smoking 10-19 years			1.16 (0.60 to 2.22)	0.657			1.72 (0.83 to 3.59)	0.147			1.19 (0.73 to 1.96)	0.487
		Quit smoking ≥ 20 years			0.86 (0.47 to 1.57)	0.612			1.20 (0.60 to 2.40)	0.615			1.15 (0.76 to 1.73)	0.507
		P for trend				0.075				0.504				0.293
Breast		Never smoking		392	3608	1 (Reference)		240	3608	1 (Reference)		473	3608	1 (Reference)
	Current smoking		120	807	1.47 (1.16 to 1.85)	0.001	39	807	1.79 (1.17 to 2.72)	0.007	112	807	2.46 (1.90 to 3.18)	< 0.001
		< 10 cigarette per day			1.53 (1.12 to 2.11)	0.008			2.16 (1.29 to 3.63)	0.004			1.83 (1.26 to 2.65)	0.002
		≥ 10 cigarette per day			1.55 (1.15 to 2.10)	0.005			1.97 (1.08 to 3.58)	0.028			3.32 (2.43 to 4.54)	< 0.001
	Former smoking		240	1962	1.20 (1.00 to 1.45)	0.053	110	1962	0.95 (0.71 to 1.26)	0.702	299	1962	1.50 (1.25 to 1.81)	< 0.001
		Quit smoking < 10 years			1.31 (0.96 to 1.78)	0.086			1.89 (1.17 to 3.06)	0.01			1.90 (1.39 to 2.61)	< 0.001
		Quit smoking 10-19 years			1.51 (1.12 to 2.04)	0.007			0.87 (0.58 to 1.31)	0.516			1.20 (0.88 to 1.63)	0.241
		Quit smoking ≥ 20 years			0.95 (0.72 to 1.24)	0.682			0.67 (0.44 to 1.02)	0.062			1.54 (1.23 to 1.94)	< 0.001

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	P for trend				0.011				0.253				< 0.001	
Cervix														
	Never smoking	41	1023	1 (Reference)		34	1023	1 (Reference)		56	1023	1 (Reference)		
	Current smoking	40	1170	1.67 (0.91 to 3.06)	0.098	16	1170	1.50 (0.68 to 3.34)	0.315	80	1170	3.66 (2.28 to 5.89)	< 0.001	
				< 10 cigarette per day	1.43 (0.61 to 3.36)	0.407			2.36 (0.80 to 6.95)	0.119			2.54 (1.40 to 4.60)	0.002
				≥ 10 cigarette per day	1.94 (1.03 to 3.63)	0.039			1.16 (0.49 to 2.80)	0.732			4.46 (2.67 to 7.43)	< 0.001
	Former smoking	32	664	1.44 (0.85 to 2.45)	0.172	22	664	0.96 (0.50 to 1.83)	0.895	71	664	2.08 (1.33 to 3.25)	0.001	
				Quit smoking < 10 years	1.73 (0.93 to 3.21)	0.085			1.39 (0.58 to 3.32)	0.463			2.39 (1.42 to 4.02)	0.001
				Quit smoking 10-19 years	1.52 (0.62 to 3.68)	0.356			1.24 (0.40 to 3.85)	0.706			2.60 (1.50 to 4.51)	0.001
				Quit smoking ≥ 20 years	1.15 (0.46 to 2.84)	0.765			0.54 (0.22 to 1.33)	0.179			1.65 (0.83 to 3.29)	0.156
	P for trend					0.09				0.321			< 0.001	
Colon														
	Never smoking	165	1133	1 (Reference)		107	1133	1 (Reference)		234	1133	1 (Reference)		
	Current smoking	63	335	1.33 (0.95 to 1.88)	0.098	22	335	1.81 (0.98 to 3.34)	0.06	53	335	1.46 (0.98 to 2.17)	0.062	
				< 10 cigarette per day	1.24 (0.74 to 2.08)	0.416			2.22 (0.93 to 5.29)	0.072			1.11 (0.50 to 2.46)	0.8
				≥ 10 cigarette per day	1.38 (0.92 to 2.07)	0.114			1.62 (0.75 to 3.53)	0.22			1.79 (1.15 to 2.81)	0.011
	Former smoking	207	1053	1.26 (0.99 to 1.61)	0.061	109	1053	1.17 (0.84 to 1.62)	0.342	214	1053	1.18 (0.89 to 1.55)	0.242	
				Quit smoking < 10 years	1.32 (0.88 to 2.00)	0.181			1.84 (1.02 to 3.32)	0.043			1.93 (1.16 to 3.21)	0.011
				Quit smoking 10-19 years	1.18 (0.83 to 1.69)	0.349			1.15 (0.69 to 1.92)	0.578			1.40 (1.01 to 1.93)	0.042
				Quit smoking ≥ 20 years	1.27 (0.98 to 1.66)	0.076			1.00 (0.68 to 1.47)	0.985			0.90 (0.68 to 1.20)	0.477
	P for trend					0.13				0.059			0.004	
Lung														
	Never smoking	58	172	1 (Reference)		8	172	1 (Reference)		23	172	1 (Reference)		
	Current smoking	115	248	1.24 (0.87 to 1.76)	0.242	15	248	1.13 (0.34 to 3.79)	0.837	39	248	3.78 (1.99 to 7.18)	< 0.001	
				< 10 cigarette per day	1.09 (0.73 to 1.63)	0.683			1.87 (0.54 to 6.47)	0.32			3.62 (1.76 to 7.44)	0.001
				≥ 10 cigarette per day	1.43 (0.95 to 2.15)	0.085			0.51 (0.10 to 2.62)	0.419			4.10 (1.94 to 8.67)	< 0.001
	Former smoking	294	714	1.09 (0.82 to 1.45)	0.538	47	714	1.15 (0.44 to 3.00)	0.771	141	714	2.27 (1.36 to 3.79)	0.002	
				Quit smoking < 10 years	1.11 (0.81 to 0.92)	0.522			1.15 (0.41 to 3.23)	0.79			2.50 (1.42 to 4.40)	0.002
				Quit smoking 10-19 years	1.12 (0.78 to 1.59)	0.541			1.31 (0.46 to 3.75)	0.612			2.12 (1.20 to 3.75)	0.01
				Quit smoking ≥ 20 years	1.05 (0.76 to 1.46)	0.751			0.91 (0.27 to 3.08)	0.877			2.15 (1.20 to 3.86)	0.01
	P for trend					0.433				0.545			0.004	
Lymphoma														
	Never smoking	72	475	1 (Reference)		23	475	1 (Reference)		54	475	1 (Reference)		

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Melanoma	Current smoking	39	176	1.69 (1.04 to 2.74)	0.035	4	176	0.81 (0.22 to 3.02)	0.751	24	176	1.92 (0.96 to 3.82)	0.065
	< 10 cigarette per day			0.91 (0.43 to 1.93)	0.813			0.26 (0.02 to 2.94)	0.273			0.96 (0.27 to 3.34)	0.945
	≥ 10 cigarette per day			2.21 (1.33 to 3.65)	0.002			0.91 (0.18 to 4.56)	0.904			2.35 (1.09 to 5.09)	0.03
	Former smoking	70	349	1.01 (0.68 to 1.49)	0.976	20	349	1.09 (0.49 to 2.42)	0.838	44	349	0.97 (0.59 to 1.57)	0.886
	Quit smoking < 10 years			1.15 (0.63 to 2.09)	0.651			0.73 (0.16 to 3.24)	0.677			0.89 (0.36 to 2.21)	0.799
	Quit smoking 10-19 years			0.94 (0.51 to 1.73)	0.853			1.46 (0.53 to 4.06)	0.464			1.44 (0.74 to 2.80)	0.287
	Quit smoking ≥ 20 years			0.93 (0.57 to 1.52)	0.782			0.98 (0.35 to 2.79)	0.973			0.79 (0.44 to 1.43)	0.432
	P for trend				0.77				0.95				0.525
	Never smoking	64	1036	1 (Reference)		53	1036	1 (Reference)		99	1036	1 (Reference)	
	Current smoking	40	349	2.31 (1.35 to 3.93)	0.002	9	349	1.34 (0.48 to 3.75)	0.572	39	349	2.15 (1.26 to 3.66)	0.005
< 10 cigarette per day			2.12 (1.02 to 4.44)	0.046			3.32 (0.84 to 13.17)	0.087			3.12 (1.39 to 7.02)	0.006	
≥ 10 cigarette per day			2.34 (1.30 to 4.22)	0.005			0.86 (0.28 to 2.63)	0.789			2.29 (1.26 to 4.15)	0.006	
Former smoking	80	823	1.18 (0.75 to 1.88)	0.473	50	823	1.05 (0.63 to 1.74)	0.85	112	823	1.50 (1.04 to 2.17)	0.031	
Quit smoking < 10 years			1.04 (0.56 to 1.94)	0.897			1.39 (0.65 to 2.96)	0.396			2.94 (1.82 to 4.77)	< 0.001	
Quit smoking 10-19 years			1.71 (0.89 to 3.27)	0.107			0.83 (0.38 to 1.82)	0.647			1.20 (0.69 to 2.11)	0.515	
Quit smoking ≥ 20 years			1.09 (0.64 to 1.86)	0.755			0.99 (0.55 to 1.79)	0.967			1.19 (0.81 to 1.75)	0.378	
P for trend				0.389				0.74				0.003	
Prostate	Never smoking	161	1411	1 (Reference)		112	1411	1 (Reference)		225	1411	1 (Reference)	
Current smoking	86	427	1.95 (1.45 to 2.64)	< 0.001	43	427	1.39 (0.89 to 2.16)	0.15	80	427	2.00 (1.39 to 2.88)	< 0.001	
< 10 cigarette per day			2.19 (1.52 to 3.16)	< 0.001			0.91 (0.39 to 2.14)	0.832			1.50 (0.75 to 2.98)	0.251	
≥ 10 cigarette per day			1.97 (1.32 to 2.95)	0.001			1.97 (1.24 to 3.13)	0.004			2.40 (1.63 to 3.54)	< 0.001	
Former smoking	312	2106	1.26 (1.00 to 1.59)	0.052	193	2106	0.96 (0.73 to 1.27)	0.77	426	2106	1.37 (1.11 to 1.70)	0.004	
Quit smoking < 10 years			1.56 (1.07 to 2.27)	0.02			1.85 (1.12 to 3.05)	0.016			1.82 (1.29 to 2.56)	0.001	
Quit smoking 10-19 years			1.65 (1.20 to 2.25)	0.002			0.89 (0.58 to 1.37)	0.587			1.72 (1.32 to 2.26)	< 0.001	
Quit smoking ≥ 20 years			1.07 (0.82 to 1.39)	0.619			0.85 (0.65 to 1.12)	0.257			1.22 (0.96 to 1.55)	0.101	
P for trend				0.001				0.144				0.042	
Non-melanoma skin	Never smoking	123	2998	1 (Reference)		145	2998	1 (Reference)		324	2998	1 (Reference)	
Current smoking	81	803	3.01 (2.15 to 4.21)	< 0.001	33	803	1.73 (1.07 to 2.81)	0.026	103	803	2.27 (1.69 to 3.05)	< 0.001	
< 10 cigarette per day			2.58 (1.49 to 4.46)	0.001			1.77 (0.89 to 3.53)	0.104			1.86 (1.21 to 2.86)	0.005	
≥ 10 cigarette per day			3.44 (2.36 to 5.00)	< 0.001			1.66 (0.93 to 2.98)	0.089			2.62 (1.84 to 3.72)	< 0.001	

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	Former smoking	180	2485	1.47 (1.12 to 1.94)	0.005	156	2485	1.12 (0.84 to 1.50)	0.429	353	2485	1.38 (1.15 to 1.66)	0.001
	Quit smoking < 10 years			2.71 (1.84 to 3.99)	< 0.001			1.14 (0.61 to 2.15)	0.677			1.93 (1.38 to 2.70)	< 0.001
	Quit smoking 10-19 years			1.65 (1.05 to 2.59)	0.031			1.75 (1.17 to 2.61)	0.006			1.63 (1.23 to 2.17)	0.001
	Quit smoking ≥ 20 years			1.17 (0.85 to 1.59)	0.337			0.98 (0.71 to 1.36)	0.926			1.24 (1.01 to 1.53)	0.039
	P for trend				< 0.001				0.097				0.001
Uterine	Never smoking	65	935	1 (Reference)		64	935	1 (Reference)		145	935	1 (Reference)	
	Current smoking	41	549	2.57 (1.51 to 4.37)	0.001	48	549	2.78 (1.54 to 5.04)	0.001	66	549	2.96 (2.00 to 4.38)	< 0.001
	< 10 cigarette per day			2.26 (1.05 to 4.89)	0.038			1.65 (0.72 to 3.79)	0.237			3.55 (1.98 to 6.39)	< 0.001
	≥ 10 cigarette per day			3.14 (1.71 to 5.77)	< 0.001			3.62 (1.85 to 7.09)	< 0.001			2.58 (1.65 to 4.05)	< 0.001
	Former smoking	35	498	1.18 (0.76 to 1.85)	0.461	32	498	0.92 (0.54 to 1.56)	0.761	86	498	1.40 (1.01 to 1.96)	0.046
	Quit smoking < 10 years			1.61 (0.76 to 3.43)	0.213			0.42 (0.15 to 1.14)	0.089			1.42 (0.79 to 2.57)	0.239
	Quit smoking 10-19 years			2.15 (1.18 to 3.92)	0.012			0.97 (0.39 to 2.45)	0.952			1.39 (0.80 to 2.40)	0.245
	Quit smoking ≥ 20 years			0.56 (0.27 to 1.17)	0.125			1.12 (0.59 to 2.15)	0.726			1.35 (0.88 to 2.07)	0.173
	P for trend				0.073				0.366				0.342

Abbreviations: CVD = cardiovascular disease; CI = confidence interval; HR = hazard ratio, CHD = coronary heart disease. *Adjusted for age, sex, race, education level, marital status, body mass index, physical activity, alcohol intake, income level, self-rated health, history of hypertension, diabetes, CHD, stroke and duration of cancer.

ers (**Figure 3** Former smoking and risk of all-cause mortality).

Smoking intensity

All-cause mortality: As summarized in **Figure 4A, 4B** and **Table 2**, when compared to those who never smoked, current smokers who smoked ≥ 10 cigarettes per day had a higher risk of all-cause (HR = 2.04, 95% CI = 1.87 to 2.22) and cancer (HR = 1.89, 95% CI = 1.67 to 2.14) mortality when compared to those who smoked < 10 cigarettes per day. For site-specific cancers, current smokers who smoked ≥ 10 cigarettes per day had a higher risk for all-cause mortality than those who smoked < 10 cigarettes per day for breast, cervix, lung, prostate, uterine and non-melanoma skin cancer survivors.

Cancer mortality: When compared to those who never smoked, the risk for cancer mortality was higher for current smokers who smoked ≥ 10 cigarettes per day than those who smoked < 10 cigarettes per day for breast, melanoma, uterine and non-melanoma skin cancer survivors.

CVD mortality: There were no statistically significant differences between CVD mortality and cigarettes per day for current smokers in other select cancer sites survivors excepted in breast cancer survivors [**Figure 4A, 4B** Cigarettes per day and risk of all-cause mortality among current smokers. (A) Current smokers smoked < 10 cigarettes per day and risk of all-cause mortality; (B) Current smokers smoked ≥ 10 cigarettes per day and risk of all-cause mortality].

Time since smoking cessations

Figure 4C-E and **Table 2** showed that the risk for all-cause mortality was higher for former smokers who had quit more recently than for those who had quit earlier (Ptrend < 0.001). For all-cause mortality, there were obvious dose-response relationships among former smokers as the quit time increased in those diagnosed with non-melanoma skin cancer (Ptrend < 0.001). For cancer mortality, there were no apparent dose-response relationships among former smokers as the quit time increased in any survivor groups. In addition, there was no apparent significant dose-response relationship between former smoking and the risk of

CVD mortality [**Figure 4C-E** Time since smoking cessation and risk of all-cause mortality among former smokers. (C) Former smokers quit smoking < 10 years and risk of all-cause mortality; (D) Former smokers quit smoking 10-19 years and risk of all-cause mortality; (E) Former smokers quit smoking ≥ 20 years and risk of all-cause mortality].

Sensitivity analysis

When deaths within the first 2-years of follow-up were excluded for models examining associations between risk factors and all-cause mortality, the dose-response relationship was apparent for former smokers as the smoking quit time increased in lung cancer survivors (Ptrend < 0.001). Former smoking was associated with a higher risk for cancer mortality among breast (HR = 1.26, 95% CI = 1.04 to 1.54) cancer survivors when compared to those who never smoked. Current smoking was associated with a higher risk for cancer mortality among lung (HR = 1.58, 95% CI = 1.05 to 2.37) and colon (HR = 1.50, 95% CI = 1.06 to 2.13) cancer survivors when compared to those who never smoked. There were no statistically significant differences between former smoking and never smokers for the risk of all-cause mortality in lung cancer survivors. (Detailed in **Table 3**).

Excluding patients with a CVD history, there was a 57% increase in all-cause mortality among former smokers who were diagnosed with bladder cancer and a 91% increase in CVD mortality among all cancer survivors when compared to never smokers. Current smoking was associated with a higher risk for cancer mortality in bladder (HR = 2.12, 95% CI = 1.05 to 4.30) and colon (HR = 1.49, 95% CI = 1.03 to 2.15) cancer survivors when compared to those who never smoked. (Detailed in **Table 4**).

Discussion

This large prospective study showed that cancer survivors who reported being current or former smokers had a higher risk for all-cause and cancer mortality when compared with those who never smoked, but effects varied substantially by cancer site, especially for breast, prostate, and non-melanoma skin cancer survivors. Compared to nonsmokers, risk of CVD mortality increased among current smokers diagnosed

Post-diagnosis smoking and risk of mortality in survivors of cancers

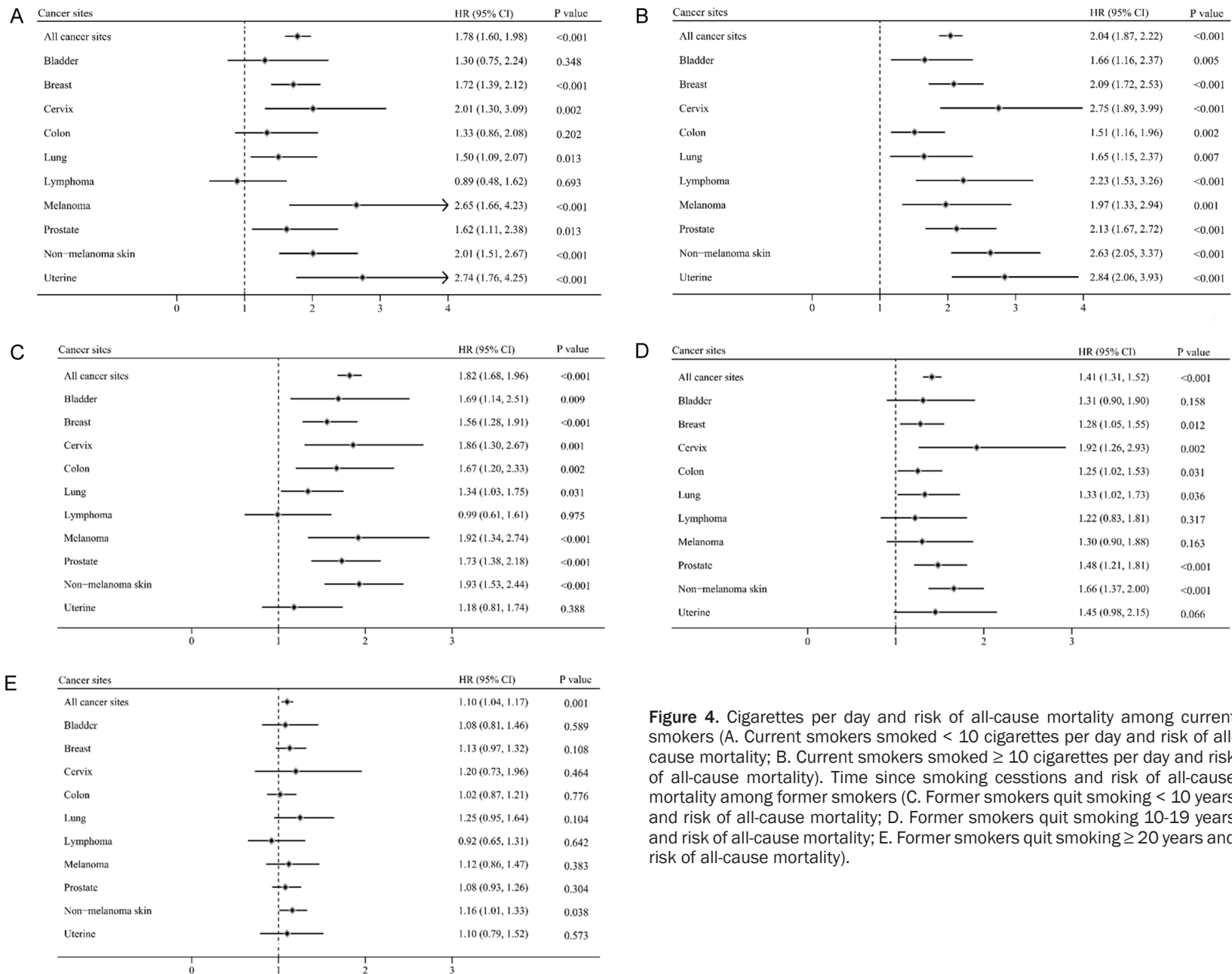


Figure 4. Cigarettes per day and risk of all-cause mortality among current smokers (A. Current smokers smoked < 10 cigarettes per day and risk of all-cause mortality; B. Current smokers smoked ≥ 10 cigarettes per day and risk of all-cause mortality). Time since smoking cessation and risk of all-cause mortality among former smokers (C. Former smokers quit smoking < 10 years and risk of all-cause mortality; D. Former smokers quit smoking 10-19 years and risk of all-cause mortality; E. Former smokers quit smoking ≥ 20 years and risk of all-cause mortality).

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Table 3. All-cause, cancer, CVD and other cause mortality among cancer survivors by cigarettes per day and time since quitting smoking after excluding individuals who died within the 2 years

Cancer sites	Smoking status	Subgroups	All cause mortality		Cancer mortality		CVD mortality		Other mortality	
			HR (95% CI)	P value ^a	HR (95% CI)	P value ^a	HR (95% CI)	P value ^a	HR (95% CI)	P value ^a
All sites										
	Never smoking		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking		1.96 (1.82 to 2.11)	< 0.001	1.92 (1.72 to 2.15)	< 0.001	1.83 (1.54 to 2.18)	< 0.001	2.11 (1.87 to 2.38)	< 0.001
		< 10 cigarette per day	1.87 (1.68 to 2.07)	< 0.001	1.89 (1.61 to 2.21)	< 0.001	1.94 (1.49 to 2.52)	< 0.001	1.82 (1.51 to 2.19)	< 0.001
		≥ 10 cigarette per day	2.18 (2.01 to 2.38)	< 0.001	2.09 (1.85 to 2.37)	< 0.001	1.92 (1.56 to 2.36)	< 0.001	2.47 (2.15 to 2.84)	< 0.001
	Former smoking		1.31 (1.25 to 1.38)	< 0.001	1.36 (1.25 to 1.49)	< 0.001	1.09 (0.97 to 8.18)	0.162	1.38 (1.27 to 1.49)	< 0.001
		Quit smoking < 10 years	1.84 (1.70 to 1.99)	< 0.001	1.89 (1.67 to 2.14)	< 0.001	1.57 (1.28 to 1.92)	< 0.001	1.91 (1.67 to 2.18)	< 0.001
		Quit smoking 10-19 years	1.42 (1.32 to 1.53)	< 0.001	1.47 (1.29 to 1.68)	< 0.001	1.30 (1.10 to 1.54)	0.002	1.44 (1.28 to 1.62)	< 0.001
		Quit smoking ≥ 20 years	1.10 (1.04 to 1.16)	0.001	1.09 (0.98 to 1.21)	0.133	0.89 (0.77 to 1.04)	0.139	1.21 (1.10 to 1.32)	< 0.001
		P for trend		< 0.001		< 0.001		< 0.001		< 0.001
Bladder										
	Never smoking		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking		1.52 (1.09 to 2.11)	0.013	1.72 (0.97 to 3.05)	0.062	1.41 (0.54 to 1.18)	0.479	1.39 (0.82 to 2.36)	0.216
		< 10 cigarette per day	1.47 (0.85 to 2.55)	0.167	2.87 (1.28 to 6.41)	0.01	0.42 (0.09 to 2.05)	0.282	1.05 (0.43 to 2.56)	0.919
		≥ 10 cigarette per day	1.74 (1.22 to 2.49)	0.003	1.78 (0.93 to 3.40)	0.079	1.76 (0.63 to 2.91)	0.281	1.66 (0.94 to 2.95)	0.082
	Former smoking		1.18 (0.89 to 1.55)	0.246	0.95 (0.57 to 1.57)	0.828	1.59 (0.82 to 4.18)	0.168	1.16 (0.79 to 1.71)	0.442
		Quit smoking < 10 years	1.58 (1.07 to 2.36)	0.023	1.73 (0.90 to 3.34)	0.102	1.26 (0.37 to 2.27)	0.71	1.46 (0.77 to 2.80)	0.247
		Quit smoking 10-19 years	1.30 (0.89 to 1.90)	0.181	0.99 (0.50 to 1.94)	0.971	2.18 (1.01 to 1.71)	0.048	1.19 (0.71 to 1.98)	0.507
		Quit smoking ≥ 20 years	1.06 (0.79 to 1.43)	0.69	0.73 (0.39 to 1.34)	0.309	1.39 (0.66 to 2.93)	0.388	1.16 (0.76 to 1.77)	0.479
		P for trend		0.058		0.192		0.215		0.402
Breast										
	Never smoking		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking		1.90 (1.64 to 2.22)	< 0.001	1.56 (1.22 to 1.98)	< 0.001	1.84 (1.19 to 3.18)	0.007	2.57 (1.99 to 3.32)	< 0.001
		< 10 cigarette per day	1.78 (1.43 to 2.21)	< 0.001	1.61 (1.15 to 2.26)	0.005	2.01 (1.14 to 2.53)	0.015	1.92 (1.33 to 2.78)	0.001
		≥ 10 cigarette per day	2.22 (1.83 to 2.69)	< 0.001	1.65 (1.22 to 2.24)	0.001	1.91 (1.02 to 2.56)	0.043	3.47 (2.54 to 4.74)	< 0.001
	Former smoking		1.30 (1.15 to 1.47)	< 0.001	1.26 (1.04 to 1.54)	0.018	0.90 (0.66 to 1.18)	0.498	1.54 (1.27 to 1.85)	< 0.001
		Quit smoking < 10 years	1.58 (1.29 to 1.94)	< 0.001	1.39 (1.02 to 1.91)	0.04	1.59 (0.98 to 1.60)	0.062	1.92 (1.39 to 2.65)	< 0.001
		Quit smoking 10-19 years	1.31 (1.08 to 1.59)	0.006	1.60 (1.18 to 2.18)	0.003	0.88 (0.57 to 1.34)	0.539	1.23 (0.91 to 1.67)	0.185
		Quit smoking ≥ 20 years	1.16 (1.00 to 1.36)	0.057	0.97 (0.74 to 1.29)	0.847	0.69 (0.44 to 1.09)	0.115	1.58 (1.26 to 1.98)	< 0.001
		P for trend		< 0.001		0.003		0.554		0.129
Cervix										
	Never smoking		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking		2.50 (1.80 to 3.48)	< 0.001	1.84 (0.99 to 3.42)	0.055	1.53 (0.67 to 1.18)	0.309	3.87 (2.44 to 6.14)	< 0.001
		< 10 cigarette per day	2.12 (1.35 to 3.32)	0.001	1.58 (0.67 to 3.72)	0.299	2.38 (0.79 to 3.17)	0.124	2.62 (1.39 to 4.92)	0.003
		≥ 10 cigarette per day	2.86 (1.98 to 4.13)	< 0.001	2.10 (1.10 to 4.00)	0.024	1.19 (0.49 to 4.88)	0.699	4.73 (2.88 to 7.76)	< 0.001
	Former smoking		1.61 (1.18 to 2.18)	0.003	1.29 (0.74 to 2.24)	0.363	0.98 (0.50 to 2.18)	0.95	2.30 (1.49 to 3.54)	< 0.001

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	Quit smoking < 10 years	1.86 (1.29 to 2.66)	0.001	1.43 (0.73 to 2.82)	0.296	1.41 (0.59 to 2.37)	0.442	2.70 (1.62 to 4.49)	< 0.001
	Quit smoking 10-19 years	1.94 (1.26 to 3.00)	0.003	1.40 (0.55 to 3.56)	0.482	1.31 (0.40 to 3.22)	0.655	2.72 (1.54 to 4.80)	0.001
	Quit smoking ≥ 20 years	1.27 (0.79 to 2.04)	0.316	1.12 (0.46 to 2.74)	0.803	0.54 (0.21 to 1.35)	0.187	1.88 (0.97 to 3.65)	0.063
	P for trend		< 0.001		0.264		0.295		0.006
Colon	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	1.51 (1.16 to 1.97)	0.002	1.50 (1.06 to 2.13)	0.023	1.99 (1.04 to 2.18)	0.038	1.44 (0.94 to 2.21)	0.09
	< 10 cigarette per day	1.48 (0.93 to 2.34)	0.098	1.41 (0.83 to 2.40)	0.203	2.51 (1.07 to 2.90)	0.034	1.14 (0.49 to 2.66)	0.764
	≥ 10 cigarette per day	1.63 (1.23 to 2.15)	0.001	1.56 (1.03 to 2.36)	0.036	1.76 (0.71 to 2.32)	0.219	1.80 (1.12 to 2.91)	0.016
	Former smoking	1.18 (1.01 to 1.39)	0.039	1.26 (0.97 to 1.63)	0.087	1.14 (0.83 to 9.18)	0.423	1.18 (0.89 to 1.56)	0.249
	Quit smoking < 10 years	1.80 (1.29 to 2.52)	0.001	1.43 (0.92 to 2.21)	0.111	1.98 (1.11 to 2.54)	0.022	2.02 (1.22 to 3.36)	0.007
	Quit smoking 10-19 years	1.22 (1.00 to 1.49)	0.05	1.10 (0.75 to 1.61)	0.627	1.22 (0.72 to 1.05)	0.458	1.39 (0.99 to 1.94)	0.057
	Quit smoking ≥ 20 years	1.00 (0.84 to 1.18)	0.966	1.26 (0.95 to 1.66)	0.108	0.91 (0.61 to 1.35)	0.637	0.90 (0.67 to 1.20)	0.475
	P for trend		< 0.001		0.123		0.03		0.092
Lung	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	1.94 (1.38 to 2.73)	< 0.001	1.58 (1.05 to 2.37)	0.028	1.36 (0.34 to 1.18)	0.667	3.91 (2.02 to 7.60)	< 0.001
	< 10 cigarette per day	1.79 (1.24 to 2.58)	0.002	1.28 (0.79 to 2.05)	0.314	2.25 (0.56 to 2.96)	0.249	3.80 (1.75 to 8.27)	0.001
	≥ 10 cigarette per day	2.14 (1.44 to 3.18)	< 0.001	1.94 (1.24 to 3.03)	0.004	0.57 (0.08 to 3.02)	0.573	4.22 (1.94 to 9.19)	< 0.001
	Former smoking	1.46 (1.11 to 1.92)	0.006	1.17 (0.83 to 1.63)	0.371	1.43 (0.47 to 4.18)	0.529	2.50 (1.45 to 4.32)	0.001
	Quit smoking < 10 years	1.53 (1.13 to 2.06)	0.006	1.20 (0.83 to 1.73)	0.335	1.57 (0.48 to 2.09)	0.452	2.78 (1.50 to 5.14)	0.001
	Quit smoking 10-19 years	1.47 (1.09 to 1.98)	0.011	1.18 (0.78 to 1.78)	0.439	1.62 (0.49 to 1.36)	0.427	2.28 (1.25 to 4.17)	0.008
	Quit smoking ≥ 20 years	1.35 (1.00 to 1.81)	0.049	1.11 (0.76 to 1.61)	0.6	0.80 (0.21 to 3.02)	0.74	2.41 (1.31 to 4.46)	0.005
	P for trend		0.002		0.198		0.241		0.193
Lymphoma	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	2.01 (1.39 to 2.91)	< 0.001	1.83 (1.08 to 3.10)	0.026	1.00 (0.27 to 4.18)	0.995	2.55 (1.35 to 4.80)	0.004
	< 10 cigarette per day	1.08 (0.59 to 1.98)	0.8	1.04 (0.47 to 2.28)	0.924	0.31 (0.02 to 1.15)	0.372	1.36 (0.41 to 4.52)	0.619
	≥ 10 cigarette per day	2.59 (1.77 to 3.79)	< 0.001	2.38 (1.37 to 4.13)	0.002	1.18 (0.24 to 3.75)	0.833	3.25 (1.60 to 6.62)	0.001
	Former smoking	1.10 (0.82 to 1.47)	0.537	1.06 (0.70 to 1.60)	0.789	1.06 (0.45 to 1.18)	0.891	1.12 (0.69 to 1.82)	0.632
	Quit smoking < 10 years	1.14 (0.70 to 1.83)	0.603	1.19 (0.64 to 2.23)	0.576	0.96 (0.22 to 1.09)	0.953	1.15 (0.47 to 2.81)	0.766
	Quit smoking 10-19 years	1.31 (0.86 to 1.99)	0.207	0.90 (0.45 to 1.79)	0.755	1.56 (0.51 to 1.71)	0.433	1.71 (0.86 to 3.37)	0.123
	Quit smoking ≥ 20 years	1.00 (0.69 to 1.45)	0.998	1.02 (0.62 to 1.69)	0.934	0.82 (0.25 to 2.74)	0.748	0.96 (0.53 to 1.73)	0.889
	P for trend		0.425		0.678		0.806		0.855
Melanoma	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	2.08 (1.44 to 3.01)	< 0.001	2.39 (1.38 to 4.12)	0.002	1.46 (0.52 to 9.18)	0.468	2.20 (1.25 to 3.86)	0.006
	< 10 cigarette per day	2.87 (1.77 to 4.66)	< 0.001	2.25 (1.07 to 4.73)	0.032	3.60 (0.92 to 4.15)	0.067	3.41 (1.47 to 7.88)	0.004
	≥ 10 cigarette per day	2.02 (1.33 to 3.09)	0.001	2.40 (1.30 to 4.43)	0.005	0.93 (0.30 to 3.87)	0.904	2.36 (1.27 to 4.40)	0.007
	Former smoking	1.29 (1.01 to 1.65)	0.04	1.10 (0.71 to 1.71)	0.677	1.14 (0.69 to 4.18)	0.603	1.48 (1.01 to 2.16)	0.045
	Quit smoking < 10 years	1.98 (1.39 to 2.83)	< 0.001	1.07 (0.57 to 2.02)	0.825	1.39 (0.64 to 2.01)	0.403	3.07 (1.88 to 5.01)	< 0.001

Post-diagnosis smoking and risk of mortality in survivors of cancers

	Quit smoking 10-19 years	1.24 (0.85 to 1.80)	0.259	1.60 (0.82 to 3.09)	0.164	0.92 (0.42 to 1.03)	0.841	1.10 (0.61 to 1.99)	0.74
	Quit smoking ≥ 20 years	1.09 (0.84 to 1.42)	0.509	0.97 (0.57 to 1.64)	0.904	1.10 (0.61 to 1.99)	0.761	1.15 (0.77 to 1.71)	0.504
	P for trend		0.002		0.379		0.617		0.002
Prostate	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	1.91 (1.51 to 2.41)	< 0.001	2.14 (1.58 to 2.89)	< 0.001	1.43 (0.91 to 4.18)	0.125	1.97 (1.35 to 2.86)	< 0.001
	< 10 cigarette per day	1.65 (1.13 to 2.42)	0.01	2.31 (1.60 to 3.33)	< 0.001	0.99 (0.42 to 2.34)	0.979	1.41 (0.68 to 2.90)	0.356
	≥ 10 cigarette per day	2.23 (1.74 to 2.86)	< 0.001	2.19 (1.46 to 3.28)	< 0.001	2.02 (1.26 to 2.24)	0.004	2.41 (1.63 to 3.56)	< 0.001
	Former smoking	1.24 (1.07 to 1.43)	0.005	1.27 (1.00 to 1.61)	0.05	0.98 (0.73 to 1.18)	0.885	1.35 (1.09 to 1.68)	0.006
	Quit smoking < 10 years	1.76 (1.40 to 2.23)	< 0.001	1.51 (1.03 to 2.21)	0.036	2.03 (1.22 to 2.38)	0.007	1.85 (1.30 to 2.62)	0.001
	Quit smoking 10-19 years	1.50 (1.22 to 1.83)	< 0.001	1.62 (1.18 to 2.24)	0.003	0.96 (0.62 to 1.47)	0.838	1.73 (1.32 to 2.28)	< 0.001
	Quit smoking ≥ 20 years	1.08 (0.93 to 1.26)	0.302	1.10 (0.84 to 1.44)	0.478	0.84 (0.63 to 1.12)	0.224	1.20 (0.95 to 1.53)	0.129
	P for trend		< 0.001		0.002		0.068		0.036
Non-melanoma skin	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	2.39 (1.94 to 2.95)	< 0.001	3.09 (2.20 to 4.33)	< 0.001	1.89 (1.17 to 3.18)	0.01	2.25 (1.67 to 3.02)	< 0.001
	< 10 cigarette per day	2.04 (1.52 to 2.74)	< 0.001	2.64 (1.52 to 4.57)	0.001	1.94 (0.98 to 2.87)	0.059	1.81 (1.17 to 2.82)	0.009
	≥ 10 cigarette per day	2.69 (2.10 to 3.45)	< 0.001	3.52 (2.41 to 5.13)	< 0.001	1.82 (1.02 to 3.24)	0.043	2.60 (1.83 to 3.70)	< 0.001
	Former smoking	1.32 (1.17 to 1.50)	< 0.001	1.47 (1.12 to 1.94)	0.006	1.13 (0.84 to 1.18)	0.417	1.35 (1.12 to 1.63)	0.002
	Quit smoking < 10 years	1.92 (1.52 to 2.44)	< 0.001	2.63 (1.78 to 3.89)	< 0.001	1.22 (0.64 to 2.30)	0.543	1.91 (1.36 to 2.68)	< 0.001
	Quit smoking 10-19 years	1.68 (1.39 to 2.04)	< 0.001	1.66 (1.05 to 2.63)	0.029	1.84 (1.23 to 2.76)	0.003	1.63 (1.23 to 2.17)	0.001
	Quit smoking ≥ 20 years	1.14 (0.99 to 1.31)	0.072	1.17 (0.85 to 1.61)	0.322	0.96 (0.69 to 1.35)	0.826	1.21 (0.98 to 1.49)	0.08
	P for trend		< 0.001		< 0.001		0.061		0.001
Uterine	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	2.93 (2.19 to 3.92)	< 0.001	2.91 (1.69 to 5.00)	< 0.001	2.84 (1.56 to 2.18)	0.001	3.08 (2.08 to 4.57)	< 0.001
	< 10 cigarette per day	2.93 (1.89 to 4.54)	< 0.001	2.78 (1.29 to 5.96)	0.009	1.71 (0.76 to 4.88)	0.195	3.64 (2.00 to 6.62)	< 0.001
	≥ 10 cigarette per day	3.00 (2.15 to 4.16)	< 0.001	3.36 (1.79 to 6.31)	< 0.001	3.66 (1.82 to 4.35)	< 0.001	2.75 (1.75 to 4.31)	< 0.001
	Former smoking	1.26 (0.98 to 1.61)	0.068	1.28 (0.80 to 2.06)	0.308	0.92 (0.53 to 3.18)	0.747	1.44 (1.03 to 2.02)	0.032
	Quit smoking < 10 years	1.26 (0.85 to 1.87)	0.246	1.86 (0.88 to 3.93)	0.105	0.43 (0.16 to 1.17)	0.098	1.50 (0.83 to 2.71)	0.18
	Quit smoking 10-19 years	1.44 (0.96 to 2.15)	0.079	2.19 (1.16 to 4.13)	0.015	0.90 (0.34 to 2.39)	0.83	1.41 (0.81 to 2.45)	0.221
	Quit smoking ≥ 20 years	1.14 (0.83 to 1.58)	0.422	0.61 (0.29 to 1.32)	0.209	1.14 (0.60 to 2.18)	0.695	1.38 (0.90 to 2.14)	0.143
	P for trend		0.042		0.032		0.352		0.293

Abbreviations: CVD = cardiovascular disease; CI = confidence interval; HR = hazard ratio, CHD = coronary heart disease. ^aAdjusted for age, sex, race, education level, marital status, body mass index, physical activity, alcohol intake, income level, self-rated health, history of hypertension, diabetes, CHD, stroke and duration of cancer.

Post-diagnosis smoking and risk of mortality in survivors of cancers

Table 4. All-cause, cancer, CVD and other cause mortality among cancer survivors by cigarettes per day and time since quitting smoking after excluding participants with CVD history

Cancer sites	Smoking status	Subgroups	All cause mortality		Cancer mortality		CVD mortality		Other mortality	
			HR (95% CI)	P value ^a	HR (95% CI)	P value ^a	HR (95% CI)	P value ^a	HR (95% CI)	P value ^a
All cancer sites										
	Never smoking		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking		1.87 (1.72 to 2.02)	< 0.001	1.72 (1.51 to 1.94)	< 0.001	1.91 (1.57 to 2.33)	< 0.001	2.09 (1.82 to 2.38)	< 0.001
		< 10 cigarette per day	1.77 (1.56 to 2.00)	< 0.001	1.69 (1.42 to 2.02)	< 0.001	1.97 (1.45 to 2.67)	< 0.001	1.77 (1.43 to 2.20)	< 0.001
		≥ 10 cigarette per day	2.06 (1.87 to 2.26)	< 0.001	1.85 (1.61 to 2.14)	< 0.001	1.99 (1.57 to 2.52)	< 0.001	2.40 (2.06 to 2.80)	< 0.001
	Former smoking		1.34 (1.26 to 1.42)	< 0.001	1.39 (1.26 to 1.53)	< 0.001	1.18 (1.57 to 1.37)	0.025	1.35 (1.23 to 1.48)	< 0.001
		Quit smoking < 10 years	1.86 (1.72 to 2.01)	< 0.001	1.88 (1.65 to 2.15)	< 0.001	1.74 (1.39 to 2.18)	< 0.001	1.80 (1.59 to 2.04)	< 0.001
		Quit smoking 10-19 years	1.42 (1.30 to 1.55)	< 0.001	1.46 (1.27 to 1.67)	< 0.001	1.32 (1.08 to 1.63)	0.008	1.44 (1.25 to 1.67)	< 0.001
		Quit smoking ≥ 20 years	1.11 (1.04 to 1.19)	0.003	1.10 (0.98 to 1.23)	0.106	0.98 (0.81 to 1.18)	0.814	1.18 (1.05 to 1.32)	0.004
		P for trend		< 0.001		< 0.001		< 0.001		< 0.001
Bladder										
	Never smoking		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking		1.58 (1.06 to 2.37)	0.026	2.12 (1.05 to 4.30)	0.036	1.64 (0.44 to 6.22)	0.462	1.23 (1.65 to 2.31)	0.52
		< 10 cigarette per day	1.37 (0.62 to 3.00)	0.433	2.32 (0.64 to 8.41)	0.2	0.88 (0.11 to 7.08)	0.903	0.90 (0.27 to 3.02)	0.864
		≥ 10 cigarette per day	1.89 (1.24 to 2.88)	0.003	2.32 (1.14 to 4.73)	0.021	2.09 (0.56 to 7.83)	0.273	1.51 (0.77 to 2.93)	0.226
	Former smoking		1.57 (1.13 to 2.18)	0.007	1.65 (0.90 to 3.03)	0.107	1.96 (0.72 to 5.37)	0.19	1.39 (0.89 to 2.17)	0.151
		Quit smoking < 10 years	2.21 (1.37 to 3.56)	0.001	2.87 (1.32 to 6.20)	0.008	1.64 (0.39 to 6.88)	0.499	1.71 (0.78 to 3.73)	0.176
		Quit smoking 10-19 years	1.47 (0.92 to 2.34)	0.104	1.40 (0.66 to 2.97)	0.372	1.52 (0.43 to 5.33)	0.51	1.33 (0.73 to 2.41)	0.347
		Quit smoking ≥ 20 years	1.62 (1.13 to 2.32)	0.009	1.23 (0.60 to 2.50)	0.568	2.51 (0.91 to 6.91)	0.075	1.55 (0.92 to 2.62)	0.099
		P for trend		0.009		0.002		0.636		0.983
Breast										
	Never smoking		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking		1.78 (1.50 to 2.11)	< 0.001	1.36 (1.05 to 1.75)	0.02	1.69 (1.01 to 2.80)	0.044	2.87 (2.09 to 3.94)	< 0.001
		< 10 cigarette per day	1.62 (1.26 to 2.07)	< 0.001	1.36 (0.95 to 1.94)	0.095	2.06 (1.06 to 3.99)	0.034	1.98 (1.28 to 3.07)	0.002
		≥ 10 cigarette per day	2.11 (1.69 to 2.62)	< 0.001	1.45 (1.05 to 2.00)	0.025	1.71 (0.85 to 3.46)	0.131	4.06 (2.77 to 5.95)	< 0.001
	Former smoking		1.27 (1.11 to 1.45)	0.001	1.21 (0.99 to 1.47)	0.06	0.88 (0.62 to 1.27)	0.507	1.53 (1.23 to 1.92)	< 0.001
		Quit smoking < 10 years	1.46 (1.16 to 1.84)	0.002	1.21 (0.87 to 1.69)	0.249	2.04 (1.17 to 3.58)	0.012	1.69 (1.10 to 2.59)	0.016
		Quit smoking 10-19 years	1.23 (0.99 to 1.53)	0.059	1.50 (1.10 to 2.04)	0.011	0.83 (0.48 to 1.44)	0.509	1.13 (0.77 to 1.64)	0.534
		Quit smoking ≥ 20 years	1.19 (1.00 to 1.42)	0.049	1.01 (0.76 to 1.35)	0.93	0.58 (0.32 to 1.05)	0.074	1.70 (1.32 to 2.19)	< 0.001
		P for trend		0.001		0.04		0.303		0.449
Cervix										
	Never smoking		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking		2.72 (1.87 to 3.97)	< 0.001	1.89 (0.96 to 3.71)	0.067	3.01 (1.32 to 6.88)	0.009	3.73 (2.18 to 6.38)	< 0.001
		< 10 cigarette per day	2.17 (1.27 to 3.71)	0.005	1.65 (0.64 to 4.22)	0.296	4.26 (1.49 to 12.18)	0.007	2.18 (0.99 to 4.81)	0.054
		≥ 10 cigarette per day	3.17 (2.13 to 4.72)	< 0.001	2.15 (1.05 to 4.38)	0.035	2.63 (1.04 to 6.65)	0.041	4.55 (2.61 to 7.96)	< 0.001
	Former smoking		2.08 (1.48 to 2.92)	< 0.001	1.70 (0.99 to 2.94)	0.056	1.91 (0.91 to 4.02)	0.087	2.72 (1.65 to 4.49)	< 0.001
		Quit smoking < 10 years	2.17 (1.44 to 3.27)	< 0.001	1.82 (0.92 to 3.59)	0.085	1.89 (0.63 to 5.69)	0.256	2.83 (1.58 to 5.07)	< 0.001

Post-diagnosis smoking and risk of mortality in survivors of cancers

	Quit smoking 10-19 years	2.39 (1.46 to 3.92)	0.001	1.95 (0.79 to 4.80)	0.146	5.17 (1.64 to 16.29)	0.005	2.21 (1.06 to 4.63)	0.036
	Quit smoking ≥ 20 years	1.93 (1.15 to 3.24)	0.013	1.49 (0.59 to 3.74)	0.399	0.74 (0.23 to 2.41)	0.617	3.08 (1.49 to 6.35)	0.002
	P for trend		< 0.001		0.091		0.003		0.01
Colon	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	1.57 (1.19 to 2.06)	0.001	1.49 (1.03 to 2.15)	0.032	2.60 (1.32 to 5.10)	0.006	1.41 (0.88 to 2.24)	0.151
	< 10 cigarette per day	1.45 (0.88 to 2.40)	0.148	1.56 (0.91 to 2.69)	0.106	3.20 (1.20 to 8.55)	0.021	0.78 (0.23 to 2.59)	0.683
	≥ 10 cigarette per day	1.64 (1.25 to 2.16)	< 0.001	1.43 (0.92 to 2.22)	0.108	2.33 (1.05 to 5.19)	0.038	1.84 (1.13 to 3.02)	0.015
	Former smoking	1.13 (0.96 to 1.32)	0.137	1.22 (0.94 to 1.60)	0.139	1.48 (0.98 to 2.24)	0.066	0.95 (0.72 to 1.25)	0.709
	Quit smoking < 10 years	1.33 (1.03 to 1.73)	0.03	1.24 (0.78 to 1.97)	0.358	2.27 (1.12 to 4.56)	0.022	1.09 (0.69 to 1.72)	0.708
	Quit smoking 10-19 years	1.25 (1.01 to 1.54)	0.042	1.13 (0.76 to 1.66)	0.545	1.43 (0.77 to 2.64)	0.255	1.31 (0.92 to 1.87)	0.128
	Quit smoking ≥ 20 years	1.02 (0.84 to 1.24)	0.873	1.26 (0.94 to 1.68)	0.116	1.28 (0.78 to 2.10)	0.319	0.78 (0.55 to 1.10)	0.158
	P for trend		0.004		0.263		0.011		0.919
Lung	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	1.82 (1.31 to 2.52)	< 0.001	1.36 (0.92 to 2.01)	0.124	1.56 (0.32 to 7.71)	0.582	4.82 (2.38 to 9.77)	< 0.001
	< 10 cigarette per day	1.67 (1.16 to 2.40)	0.006	1.14 (0.73 to 1.78)	0.576	2.16 (0.35 to 13.39)	0.407	5.00 (2.22 to 11.25)	< 0.001
	≥ 10 cigarette per day	2.06 (1.40 to 3.01)	< 0.001	1.70 (1.09 to 2.67)	0.02	1.00 (0.14 to 6.94)	0.996	4.96 (2.12 to 11.60)	< 0.001
	Former smoking	1.42 (1.09 to 1.86)	0.01	1.15 (0.83 to 1.59)	0.405	1.87 (0.59 to 5.91)	0.287	2.50 (1.37 to 4.54)	0.003
	Quit smoking < 10 years	1.49 (1.11 to 2.01)	0.008	1.18 (0.82 to 1.68)	0.368	2.37 (0.74 to 7.54)	0.145	2.92 (1.50 to 5.68)	0.002
	Quit smoking 10-19 years	1.44 (1.06 to 1.95)	0.019	1.27 (0.86 to 1.89)	0.232	1.72 (0.44 to 6.65)	0.432	2.12 (1.05 to 4.27)	0.035
	Quit smoking ≥ 20 years	1.27 (0.92 to 1.77)	0.145	1.02 (0.68 to 1.52)	0.933	1.23 (0.29 to 5.24)	0.777	2.39 (1.18 to 4.82)	0.015
	P for trend		0.008		0.201		0.083		0.225
Lymphoma	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	1.66 (1.09 to 2.51)	0.017	1.40 (0.83 to 2.37)	0.211	1.99 (0.52 to 7.54)	0.313	2.61 (1.21 to 5.67)	0.015
	< 10 cigarette per day	0.61 (0.29 to 1.27)	0.185	0.61 (0.26 to 1.44)	0.258	0.79 (0.09 to 6.98)	0.829	0.60 (0.10 to 3.65)	0.577
	≥ 10 cigarette per day	2.23 (1.45 to 3.41)	< 0.001	1.91 (1.11 to 3.28)	0.02	1.81 (0.35 to 9.25)	0.477	3.41 (1.47 to 7.88)	0.004
	Former smoking	1.07 (0.77 to 1.49)	0.701	1.05 (0.67 to 1.64)	0.837	1.39 (0.49 to 3.93)	0.529	1.14 (0.65 to 2.02)	0.644
	Quit smoking < 10 years	1.02 (0.59 to 1.76)	0.949	1.12 (0.59 to 2.10)	0.73	0.96 (0.12 to 7.45)	0.971	0.95 (0.34 to 2.70)	0.929
	Quit smoking 10-19 years	1.29 (0.83 to 2.01)	0.257	1.02 (0.51 to 2.04)	0.955	1.96 (0.51 to 7.61)	0.327	1.79 (0.78 to 4.15)	0.171
	Quit smoking ≥ 20 years	0.99 (0.65 to 1.49)	0.945	0.98 (0.57 to 1.70)	0.955	1.33 (0.34 to 5.17)	0.675	0.89 (0.43 to 1.83)	0.742
	P for trend		0.744		0.868		0.636		0.86
Melanoma	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	2.23 (1.48 to 3.36)	< 0.001	2.08 (1.12 to 3.83)	0.02	1.90 (0.52 to 6.98)	0.33	2.49 (1.32 to 4.70)	0.005
	< 10 cigarette per day	3.09 (1.70 to 5.60)	< 0.001	1.78 (0.69 to 4.58)	0.229	6.93 (1.40 to 34.28)	0.018	3.90 (1.53 to 9.95)	0.005
	≥ 10 cigarette per day	2.20 (1.42 to 3.40)	< 0.001	2.13 (1.08 to 4.21)	0.029	0.89 (0.17 to 4.60)	0.894	2.65 (1.37 to 5.13)	0.004
	Former smoking	1.33 (1.01 to 1.76)	0.046	1.34 (0.81 to 2.21)	0.249	1.50 (0.84 to 2.67)	0.172	1.26 (0.80 to 2.01)	0.32
	Quit smoking < 10 years	1.52 (0.98 to 2.36)	0.061	1.30 (0.65 to 2.60)	0.453	1.21 (0.40 to 3.71)	0.736	1.76 (0.86 to 3.60)	0.118
	Quit smoking 10-19 years	1.41 (0.93 to 2.14)	0.108	1.80 (0.87 to 3.73)	0.111	0.88 (0.28 to 2.81)	0.83	1.30 (0.69 to 2.42)	0.417

Post-diagnosis smoking and risk of mortality in survivors of cancers

	Quit smoking ≥ 20 years	1.27 (0.93 to 1.73)	0.127	1.23 (0.69 to 2.18)	0.487	1.76 (0.93 to 3.34)	0.084	1.15 (0.68 to 1.93)	0.6
	P for trend		0.059		0.25		0.741		0.748
Prostate	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	1.86 (1.45 to 2.39)	< 0.001	1.82 (1.28 to 2.57)	0.001	1.51 (0.87 to 2.60)	0.14	2.02 (1.34 to 3.03)	0.001
	< 10 cigarette per day	1.84 (1.30 to 2.60)	0.001	2.11 (1.31 to 3.38)	0.002	0.95 (0.32 to 2.81)	0.927	1.81 (0.90 to 3.60)	0.094
	≥ 10 cigarette per day	2.02 (1.49 to 2.74)	< 0.001	1.81 (1.16 to 2.82)	0.009	2.05 (1.13 to 3.73)	0.019	2.14 (1.29 to 3.55)	0.003
	Former smoking	1.21 (1.04 to 1.41)	0.014	1.24 (0.96 to 1.61)	0.104	1.07 (0.76 to 1.51)	0.701	1.24 (0.98 to 1.57)	0.071
	Quit smoking < 10 years	1.75 (1.39 to 2.20)	< 0.001	1.58 (1.06 to 2.36)	0.024	2.37 (1.36 to 4.13)	0.002	1.61 (1.13 to 2.31)	0.009
	Quit smoking 10-19 years	1.58 (1.25 to 1.99)	< 0.001	1.54 (1.05 to 2.27)	0.029	0.92 (0.49 to 1.74)	0.805	1.93 (1.41 to 2.63)	< 0.001
	Quit smoking ≥ 20 years	1.03 (0.87 to 1.21)	0.748	1.06 (0.80 to 1.42)	0.673	0.90 (0.61 to 1.31)	0.574	1.04 (0.80 to 1.36)	0.766
	P for trend		< 0.001		0.004		0.026		0.168
Non-melanoma skin	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	2.34 (1.84 to 2.96)	< 0.001	3.68 (2.49 to 5.44)	< 0.001	1.89 (1.09 to 3.28)	0.024	1.92 (1.37 to 2.69)	< 0.001
	< 10 cigarette per day	1.85 (1.30 to 2.63)	0.001	3.09 (1.72 to 5.54)	< 0.001	1.60 (0.74 to 3.46)	0.235	1.39 (0.80 to 2.42)	0.242
	≥ 10 cigarette per day	2.75 (2.07 to 3.65)	< 0.001	4.30 (2.77 to 6.69)	< 0.001	2.02 (1.01 to 4.04)	0.047	2.35 (1.59 to 3.47)	< 0.001
	Former smoking	1.39 (1.19 to 1.63)	< 0.001	1.87 (1.35 to 2.57)	< 0.001	1.10 (0.77 to 1.58)	0.588	1.31 (1.04 to 1.65)	0.022
	Quit smoking < 10 years	2.27 (1.75 to 2.94)	< 0.001	3.47 (2.23 to 5.40)	< 0.001	1.66 (0.85 to 3.26)	0.138	1.99 (1.36 to 2.93)	< 0.001
	Quit smoking 10-19 years	1.77 (1.38 to 2.26)	< 0.001	2.18 (1.30 to 3.66)	0.003	1.69 (0.99 to 2.87)	0.054	1.60 (1.12 to 2.30)	0.01
	Quit smoking ≥ 20 years	1.13 (0.95 to 1.35)	0.171	1.40 (0.96 to 2.04)	0.077	0.88 (0.58 to 1.35)	0.564	1.12 (0.86 to 1.46)	0.394
	P for trend		< 0.001		< 0.001		0.05		0.003
Uterine	Never smoking	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
	Current smoking	3.44 (2.48 to 4.78)	< 0.001	3.17 (1.84 to 5.46)	< 0.001	3.49 (1.52 to 8.04)	0.003	3.62 (2.27 to 5.79)	< 0.001
	< 10 cigarette per day	3.39 (2.04 to 5.64)	< 0.001	2.36 (1.01 to 5.54)	0.048	2.58 (0.86 to 7.75)	0.09	4.36 (2.22 to 8.58)	< 0.001
	≥ 10 cigarette per day	3.55 (2.50 to 5.06)	< 0.001	4.17 (2.16 to 8.05)	< 0.001	4.17 (1.63 to 10.70)	0.003	3.16 (1.90 to 5.24)	< 0.001
	Former smoking	1.33 (1.00 to 1.78)	0.053	1.33 (0.81 to 2.19)	0.26	1.16 (0.64 to 2.11)	0.615	1.40 (0.93 to 2.11)	0.104
	Quit smoking < 10 years	1.17 (0.69 to 2.00)	0.556	1.67 (0.71 to 3.91)	0.235	0.30 (0.06 to 1.45)	0.134	1.36 (0.66 to 2.80)	0.41
	Quit smoking 10-19 years	1.65 (1.07 to 2.52)	0.022	2.25 (1.11 to 4.56)	0.025	1.92 (0.73 to 5.01)	0.184	1.34 (0.70 to 2.54)	0.379
	Quit smoking ≥ 20 years	1.22 (0.81 to 1.81)	0.338	0.72 (0.30 to 1.70)	0.455	1.31 (0.62 to 2.78)	0.479	1.40 (0.82 to 2.37)	0.215
	P for trend		0.097		0.058		0.868		0.301

Abbreviations: CVD = cardiovascular disease; CI = confidence interval; HR = hazard ratio, CHD = coronary heart disease. ^aAdjusted for age, sex, race, education level, marital status, body mass index, physical activity, alcohol intake, income level, self-rated health, history of hypertension, diabetes, CHD, stroke and duration of cancer.

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with breast, non-melanoma skin and uterine cancer. However, there were no differences between former and never smokers for CVD mortality. Also, smoking cessation appears to benefit those with longer quit times as observed by the decreasing risk of mortality, especially for non-melanoma skin cancer survivors.

In the present study, we observed that current or former smokers had a higher risk of all-cause mortality when compared to nonsmokers among cancer survivors, similar to what was observed in a recent study [28]. The associations observed here between smoking status and all-cause mortality among colon and prostate cancer survivors was lower than what was observed elsewhere [13, 19]. The difference might be explained by the statistical methods such as adjusting for lag time, family history of colon cancer, tumor stage and first course of cancer treatment in our models. Our study sheds new insight on the relationships between smoking status and all-cause mortality for bladder, lymphoma, melanoma, uterine and non-melanoma skin cancer survivors. In effort to advance our understanding of these relationships, future studies should consider examining the relationship smoking and mortality among various cancer survivor populations.

Previous studies have indicated that breast cancer survivors who report varying smoking histories have the same risk for cancer mortality [29]. However, here, we observed a different pattern of relationships. In particular, current smokers had higher risk for cancer mortality than never smokers. Similar associations were observed for prostate cancer survivors, with our study showing higher hazard ratios than what was observed in another prospective cohort study [14]. Conversely, we did not observe significant associations in cervical survivors, a finding which differs from what others have reported [21].

In our study, there was no dose-response relationships between duration of smoking cessation and risk of cancer mortality in prostate cancer survivors, consistent with a previous study [14], but a greater number of cigarettes per day was associated with a significantly increased risk of all-cause mortality. Significant dose-response association for breast cancer mortality was observed for number of cigarettes smoked per day (≤ 5 , 6-10, 11-15 and ≥ 16) [30]. In particular, our study found the risk of all-cause and cancer mortality increased as the cigarettes per day increased (< 10 and \geq

10). Besides, current smoking had the highest risk of all-cause mortality with daily cigarette consumption among cervical cancer survivors for cancer mortality, but another study found that both moderate and high daily cigarette consumption resulted in the highest risk for cervical cancer mortality [21]. We did not find any significant association between number of cigarettes per day and cancer mortality among colon cancer survivors, which differs from a previous study [13]. The dose-response relationship between duration of smoking cessation or cigarettes per day and risk of all-cause mortality was significant among non-melanoma skin cancer survivors, which was not reported previously.

Several potential mechanisms could contribute to the associations we observed between smoking and increased risk of all-cause mortality. In particular, smoking decreases the effectiveness of cancer treatments [31-33]. Studies have also shown that smoking increases the probability of recurrence and distant metastases [34, 35] and increases the risk for second primary tumors [36], and premature mortality in cancer survivors [37, 38].

Among survivors, we also observed a higher risk for CVD mortality. Several pathways might explain these associations. For example, smoking activates several CVD-relevant inflammatory markers, which lead to a significant shift toward a prothrombotic, procoagulative state, and release of pro-oxidant enzymes in the vascular wall by activating the nuclear factor-kB cascade [39]. The increase in reactive oxygen species and oxidant-generating systems induced by smoking leads to both systemic and local immune system activation [40, 41]. Systemic inflammation is supported by upregulating the expression of various matrix metalloproteinases and proinflammatory cytokines among smokers. Tumor necrosis factor- α and interleukin-1 β maintain sustained activation of nuclear factor-kB, perpetuating the inflammatory response in smokers [42]. Besides, nicotine also stimulates growth of advanced atherosclerotic lesions by increasing lesion vascularization [43] and smoking and/or nicotine might also accelerate atherosclerosis in other ways [44].

Limitations

Our study's strengths include a prospective design, a large number of cancer cases and examining the associations between active smoking

and risk of all-cause and disease-specific mortality. Information on smoking and other essential covariates was prospectively collected and updated periodically. However, there were several limitations. Firstly, smoking status was self-reported and assessed post-diagnosis, which may limit the risk difference comparison between pre-diagnosis and post-diagnosis smoking as well as be subject to recall and reporting biases. In addition, because of the nature of an observational study, causality cannot be established. Given that we have no information on passive smoking among non-smokers, the present risk estimate for the association between smoking and mortality may have been underestimated.

Implications for clinicians

The prevalence of smoking among cancer patients is still higher than expected since [45] smoking is detrimental to cancer therapy and survival [31, 32, 34-37]. Our data provides compelling evidence that smoking increases the risk of all-cause and cause-specific mortality among cancer survivors. Thus clinicians should provide survivors with care guidelines that promote smoking cessation as a crucial strategy for improving survival outcomes, especially since quit time was associated with mortality. The association between smoking and CVD mortality risk in select groups deserve further attention and has clinical implications for many as a reasonable proportion of survivors die of CVD. Thus, there is a need for strategies to manage CVD risk factors throughout the cancer continuum.

Conclusions

Post-diagnosis smoking was associated with increased all-cause, cancer and CVD mortality among cancer survivors, with varying associations depending on the survivor population. Dose-response associations of quit time for former smokers were obvious among all cancer survivors, especially in non-melanoma skin cancer survivors. Further research is needed to understand mechanisms whereby smoking may increase colorectal cancer-specific mortality and determine whether quit time after diagnosis lowers the risk of colorectal cancer-specific mortality.

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Disclosure of conflict of interest

None.

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