Research Article

Impact of Postdiagnosis Smoking on Long-term Survival of Cancer Patients: The Shanghai Cohort Study

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Abstract

Background: Cancer is the number one cause of death among men in China. Cigarette smoking is the most preventable cause of cancer. Data on the impact of continued smoking after cancer diagnosis on survival of patients with cancer are sparse.

Methods: We studied the association between postdiagnosis smoking and risk of all-cause death among 1,632 incident cancer patients in the Shanghai Cohort Study, a population-based prospective cohort of 18,244 men in Shanghai. The change of smoking status after baseline interview was ascertained through annual in-person interviews. Cox proportional hazards regression models were used to estimate HR and 95% confidence interval (CI) for all-cause mortality associated with change in smoking status.

Results: Patients who continued smoking after cancer diagnosis experienced a statistically significant 59% (95% CI, 36–86) increase in risk of death compared with patients with cancer who did not smoke after cancer diagnosis. Among current smokers at cancer diagnosis, HRs (95% CIs) were 1.79 (1.49–2.16) in all patients with cancer, 2.36 (1.63–3.42) in patients with lung cancer, 1.63 (0.98–2.73) in patients with stomach cancer, 2.31 (1.40–3.81) in patients with colorectal cancer, and 2.95 (1.09–7.95) in patients with bladder cancer who continued smoking compared with their counterparts who stopped smoking after cancer diagnosis.

Conclusion: Postdiagnosis cigarettes smoking significantly increased the risk of death for male patients with cancer.

Impact: These data provide new information about smoking and cancer survival, which should inform future research into the contextual and individual-level barriers that may result in inadequate attention of smoking among patients with cancer in the postdiagnosis setting. *Cancer Epidemiol Biomarkers Prev; 22(12); 2404–11. ©2013 AACR.*

Introduction

Cancer is the first and second leading cause of death for men in China and the United States, respectively (1, 2). Tobacco use is the most important recognized cause of cancer-related death (3). Among patients diagnosed with smoking-related cancers, smoking is attributable to 50% of the total mortality for men in China and 70% in the United States (4, 5). Strong evidence demonstrates the association between cigarette-smoking and increased cancer risk, as well as substantial health benefits as a result of smoking cessation (6–9). However, the impact of smoking after cancer diagnosed is not well studied. Existing evidence

about the impact of postdiagnosis smoking understandably focuses on treatment-related outcomes in patients with lung or head and neck cancer, for whom smoking is an established strong cause. A few hospital-based studies found improved short-term survival in early staged lung cancer patients who quit smoking after diagnosis compared with persistent smokers (10, 11), whereas others did not detect such difference (12–19). The impact of postdiagnosis smoking on long-term survival in patients with cancer is even less clear.

The advancement of modern technology for early detection and the innovations of therapies for patients with cancer resulted in increasing numbers of survivors and prolonged life expectancy after cancer occurrence. However, only a fraction of patients with cancer received formal smoking cessation counseling (20). As a consequence, there is considerable room for improvement with regard to tobacco control in the postdiagnosis setting for the growing population of cancer survivors. In the present study, taking advantage of the population-based prospective cohort of Chinese men with 25 years of follow-up, we examined the association between postcancer diagnosis smoking and overall survival in all patients with cancer as well as patients with specific types of cancers including lung, stomach, colorectal, urinary bladder, and prostate.

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The aim of the study is to provide evidence for healthcare providers, patients and family, and policy makers of the impact of postdiagnosis smoking on survival after cancer, and to assist in addressing the critical issue of tobacco control in cancer survivorship.

Materials and Methods

The Shanghai Cohort Study

The Shanghai Cohort Study is a prospective cohort study investigating the association between lifestyle characteristics and risk of cancer development among middle-age or older men in Shanghai, China. The cohort has been followed for 25 years by the end of 2010. Detailed methods for subject recruitment and data collection have been previously published (21, 22). Briefly, all male residents between the ages of 45 and 64 years and those who resided in one of the four geographically defined communities in Shanghai with no prior history of cancer were invited to participate in the study. Between January 1, 1986 and September 30, 1989, 18,244 men enrolled in the study. At enrollment, each participant completed an in-person interview using a structured questionnaire to obtain demographic information, history of tobacco and alcohol use, information of usual adult diet, and medical history.

Identification of incident cancer cases and deaths among cohort participants has been accomplished via linkage analysis of the cohort database with the population-based Shanghai Cancer Registry and Shanghai Municipal Vital Statistics Office databases. Surviving cohort members have been contacted in-person annually. A study staff member visited the last known address of each surviving cohort member to administer the follow-up questionnaire. Medical histories including treatment received for patients with cancer were also updated. As of July 2010, the cutoff date for case ascertainment for the present study, 550 (3.0%) original cohort participants were lost to annual follow-up interview. In addition, 492 (2.7%) subjects refused the request for annual follow-up interviews. The cancer and vital status of these subjects were ascertained through record linkage analysis only.

Assessment of smoking status

At the baseline interview, nurse interviewers asked each participant about whether he had ever smoked one or more cigarettes per day for 6 months or longer. Among smokers, information of age at smoking initiation, current smoking status, number of cigarettes smoked per day, and number of years of smoking was obtained. For those who had quit smoking at the baseline, additional information on age at quitting was recorded. After the baseline interview, information of smoking status and number of cigarettes per day during the preceding years was collected in all surviving cohort members during annual follow-up interviews. Total number of pack-years of cigarettes smoked before cancer diagnosis was defined as the cumulative year of smoking until cancer diagnosis multiplied by the average number of packs (20 cigarettes/ pack) smoked per day for a given smoker.

We define lifetime never smokers as patients who never smoked cigarettes over their lifetime from the baseline interview until the last annual follow-up interview immediately preceding cancer diagnosis, whereas current smokers were those who reported currently smoking cigarettes during the past 6 months at the last follow-up before diagnosis. The remaining patients, who ever smoked at or before enrollment but no longer smoked cigarettes at the last follow-up before cancer diagnosis, were defined as former smokers.

Recognizing that the change in smoking status for a given patient occurred frequently from cancer diagnosis to death or latest follow-up interviews that were ascertained at multiple annual follow-up interviews, we calculated a ratio (r) of the number of years of smoking divided by the total number of years survived after cancer diagnosis to reflect the true smoking status for each patient over the years. This ratio had a value ranged from 0 to 1 whereby 0 meant a patient never smoked cigarettes after diagnosis and 1 meant a patient continued to smoke until death or the latest follow-up interview. A value of r between 0 and 1 indicated that a patient stopped smoking for some years during follow-up period after cancer diagnosis.

Statistical analysis

As of July 31, 2010, 3,310 participants of the Shanghai Cohort Study who were free of cancer at enrollment were diagnosed with cancer. Given our study's primary interest of postdiagnosis smoking, patients who did not provide an updated smoking status after cancer diagnosis during annual follow-ups were ineligible. In addition, change on smoking status right after cancer diagnosis, especially during treatment course, may have limited impact on the overall survival for patients who were dying within months. Therefore, 1,591 (48.1%) patients died before their first annual follow-up interview after cancer diagnosis (on average 4.2 months of survival after cancer diagnosis), and an additional 87 (2.6%) patients who survived beyond the first follow-up but were not able to provide postdiagnosis smoking information were excluded from the study (Fig. 1). The present study included 1,632 patients, 931 (57.1%) of whom died from any cause as of July 31, 2010. For each cancer patient, person-years at risk were calculated from the date of 1 year after cancer diagnosis to the date of death or the cutoff date (July 31, 2010), whichever occurred first.

To evaluate the impact of postdiagnosis smoking on mortality, we used Cox proportional hazards regression to estimate HRs and associated 95% confidence intervals (CI). In addition, we developed a time-dependent variable that measured the current smoking status (yes or no) on a yearly basis after cancer diagnosis. Similar to the ratio (r), the time-dependent variable integrated the dynamic changes in smoking status over all annual follow-up interviews for a given patient after diagnosis (23). All Cox models included the following covariates: age at cancer diagnosis (continuous), level of education (less than primary school, middle school, and college or above),
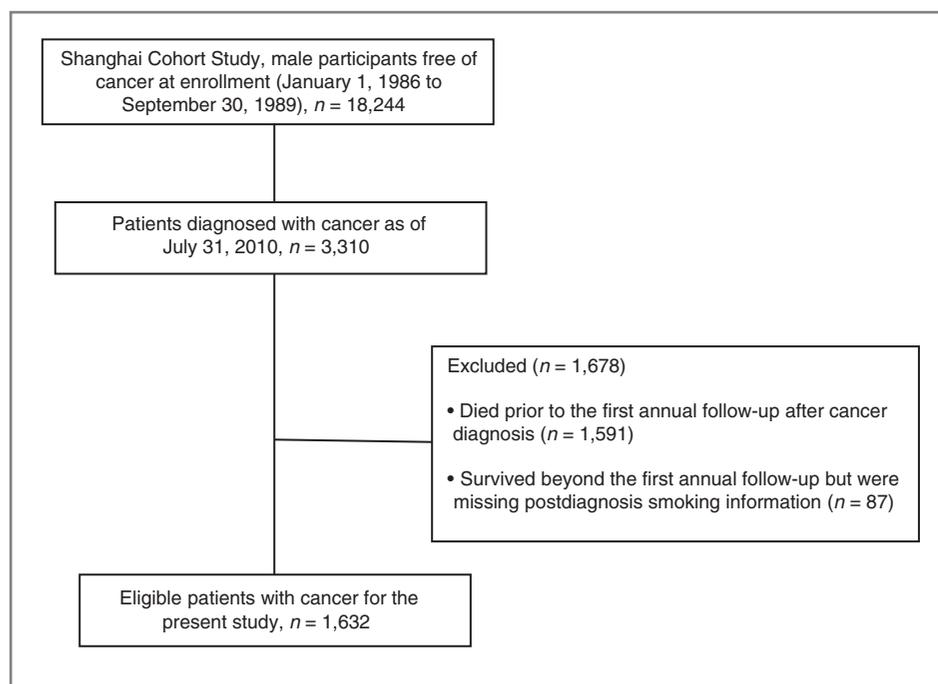
Figure 1. Consort diagram for eligible patients with cancer of the present study.

cumulative pack-years before cancer diagnosis (continuous), and the type of therapies (surgery, radiation, and chemotherapy) that a patient received for cancer (yes or no for each therapy). The association between smoking status after diagnosis and risk of all-cause mortality was examined in all patients as well as in patients with specific types of cancers including lung, stomach, colorectal, urinary bladder, and prostate. The Kaplan–Meier method and log-rank test were used to compare overall survival in smokers by smoking status after cancer diagnosis.

All statistical analyses were carried out using SAS software version 9.3 (SAS Institute). All P values reported are two-sided, and those that were <0.05 were considered to be statistically significant.

Results

With a mean follow-up of 5.3 ($\pm$ 4.8) years after cancer diagnosis and a median survival time of 5.4 years, the mean age at diagnosis ($\pm$ SD) for all 1,632 eligible patients with cancer in this cohort of Chinese men was 68.8 ($\pm$7.2) years. Table 1 shows that after adjustment for potential prognostic factors, the 545 patients who quit smoking before diagnosis (i.e., former smokers) and the 747 patients who were smoking at diagnosis (current smokers) had a comparable HR of death relative to the 340 lifelong nonsmokers. Among the total 747 current smokers at diagnosis, 214 (28.6%) patients completely quit smoking after diagnosis ($r = 0$), whereas 197 (26.4%) patients continued smoking persistently ($r = 1$). The remaining 336 (45.0%) patients smoked intermittently ($0 < r < 1$ or the median value of $r = 0.47$). The Spearman correlation coefficient between r and number of years of survival after cancer diagnosis was 0.09 ($P = 0.17$).

The median survival of patients who continued to smoke after diagnosis was 2.1 years, which was more than 50% shorter than quitters with a median survival of 4.4 years (Table 1). Among all current smokers at cancer diagnosis, the Kaplan–Meier curves showed that persistent smokers had inferior overall survival compared with quitters ($P_{\text{log-rank}} = 0.009$) and intermittent smokers ($P_{\text{log-rank}} <0.001$; Fig. 2). After adjusting for age at diagnosis, education, cumulative number of pack-years of prediagnosis smoking, cancer site, as well as treatment modalities, patients who continued smoking after cancer diagnosis persistently experienced a substantial 76% (95% CI, 37–127) increased risk of death compared with patients who quit smoking and remained nonsmoking after cancer diagnosis. Although intermittent smokers were observed with higher median survival time (7.1 years) and better overall survival shown on the Kaplan–Meier curve, the lower hazard of death of these patients, compared with quitters, was not statistically significant after adjusting for age at diagnosis, cumulative exposure of smoking, and other prognostic factors (Table 1). This artificial effect could be explained by the fact that these patients were diagnosed at a younger age and smoked less before diagnosis (Supplementary Table S1).

Table 2 shows HRs of death for all patients with cancer and selected cancer-specific patients associated with the changing of smoking status after diagnosis using the time-dependent approach. For all patients, a statistically significant 59% (95% CI, 36–86) increased mortality risk was associated with smoking relative to nonsmoking after cancer diagnosis. When analyzed separately for cancer-specific patients, the multivariate-adjusted HRs (95% CIs) of death for smoking relative to nonsmoking after cancer

Table 1. Selected characteristics and risk of death for patients with cancer who had eligible postdiagnosis information on smoking status, by smoking status before and after cancer diagnosis, The Shanghai Cohort Study 1986–2010

	No. of cases	No. of deaths (%)	Person-years at risk[a]	Average person-years[a]	Median survival (y)	Average age at diagnosis	Received surgery (%)	Received chemotherapy (%)	Received radiation therapy (%)	HR[b] (95% CI)
All patients with cancer	1632	931 (57.0%)	6,971	4.3	5.4	68.8	73.9	45.7	18.0	
Lifetime never nonsmokers	340	170 (50.0%)	1,696	5.0	7.5	68.6	76.5	43.2	17.1	1.00 (reference)
Former smokers at cancer diagnosis	545	270 (49.5%)	1,944	3.6	5.9	71.4	76.9	44.2	14.3	0.97 (0.79–1.19)
Current smokers at cancer diagnosis	747	491 (65.7%)	3,331	4.5	4.2	67.0	70.5	47.9	21.2	1.13 (0.91–1.41)
Patients with cancer who were current smokers at cancer diagnosis and survived until the next annual follow-up interview										
Quitters after cancer diagnosis (r = 0)	214	120 (56.1%)	696	3.3	4.4	68.9	74.3	51.9	12.6	1.00 (reference)
Intermittent smokers after cancer diagnosis (r >0 and r <1)	336	223 (66.4%)	2,152	6.4	7.1	65.8	74.7	48.5	25.9	0.89 (0.70–1.12)
Continued smokers after cancer diagnosis (r = 1)	197	148 (75.1%)	482	2.4	2.1	67.0	59.4	42.6	22.3	1.76 (1.37–2.27)

[a]Person-years at risk began at one year after cancer diagnosis (see details in the Materials and Methods).
[b]All Cox models were adjusted for age at diagnosis (continuous), level of education (primary school, middle school, or college or above), cumulative number of pack-year of smoking before diagnosis (continuous), treatment modalities: surgery (yes/no), chemotherapy (yes/no), and radiation therapy (yes/no), and cancer site.

diagnosis were 1.92 (1.41–2.60) for patients with lung cancer, 1.76 (1.11–2.79) for patients with stomach cancer, 1.65 (1.14–2.38) for patients with colorectal cancer, and 3.66 (1.56–8.60) for patients with bladder cancer. Similar analyses for current smokers at cancer diagnosis revealed that smoking after cancer diagnosis was associated with a statistically significant 79% increased risk of death (95% CI, 49–116) relative to nonsmoking after cancer diagnosis for all patients. Among cancer-specific patients, the HRs (95% CIs) of death for smoking versus nonsmoking after cancer diagnosis were 2.36 (1.63–3.42) in patients with lung cancer, 1.63 (0.98–2.73) in patients with stomach cancer, 2.31 (1.40–3.81) in patients with colorectal cancer, 2.95 (1.09–7.95) in patients with bladder cancer, 2.27 (0.40–12.80) in patients with prostate cancer, and 1.34 (0.96–1.80) in all other patients with cancer. HRs for intermittent smokers relative to quitters varied by cancer site and were not statistically significant after adjusting for all potential prognostic factors (Table 2).

Discussion

The present prospective study of 1,632 eligible male patients with cancer in Shanghai, China demonstrated a substantial poorer prognosis for patients who continued smoking than those who quit after cancer diagnosis. Among the 747 current smokers at diagnosis, compared with patients who stopped smoking after diagnosis, those who continued smoking experienced a statistically significant 79% increased risk of mortality. In these smokers at diagnosis, patients diagnosed with lung, colorectal, or bladder cancers may have a more than 2-fold increased risk of death from all cause if they continued smoking after diagnosis.

Epidemiologic studies evaluating the impact of smoking after cancer diagnosis on survival of patients with cancer are sparse. A few hospital-based studies found no significant difference in survival rates between persistent smokers and quitters in surgically treated patients with lung cancer among smokers (12, 15, 18, 19), whereas others found poor survival rates in smokers at 2 years after diagnosis (11, 12). Overall, these studies involved small number of patients and suffered from cross-sectional or retrospective study designs with single assessment of smoking status after diagnosis or limited time period of follow-up. To our knowledge, the present study is the first population-based study with long-term follow-up for cancer survivors and multiple annual assessment of smoking status after diagnosis, and the first to report evidence on increase mortality associated with postdiagnosis smoking in many cancer sites. Findings of the present study underscore the importance of smoking cessation intervention on patients with cancer that could improve their survival.

Several factors may contribute to the poor survival in patients with cancer who continued to smoke after diagnosis. Studies showed that in patients with lung or head and neck cancer, smoking after cancer diagnosis was
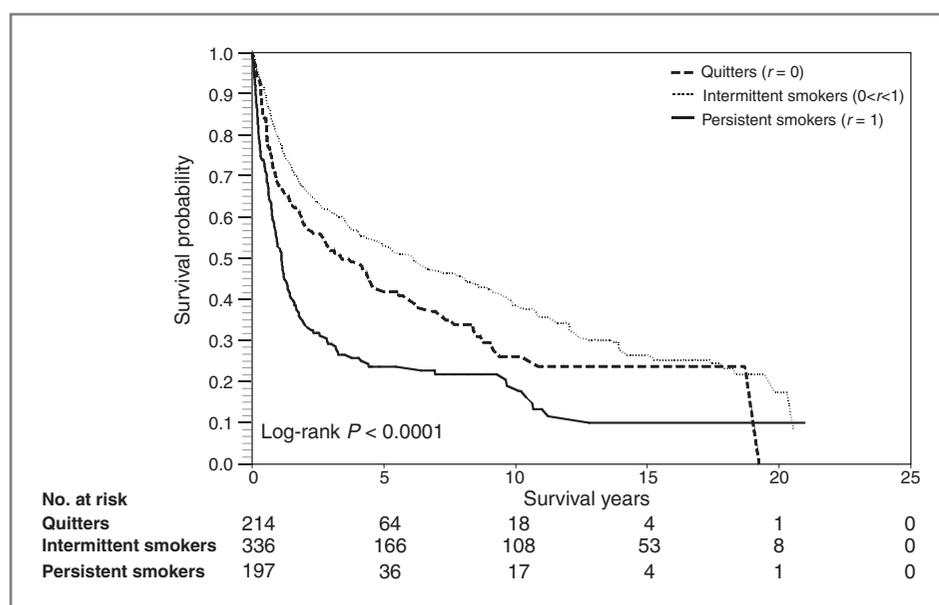
Figure 2. Kaplan–Meier survival curves by smoking status after cancer diagnosis for eligible patients with cancer who were current smokers at diagnosis, the Shanghai Cohort Study 1986–2010.

associated with increased risks of unfavorable posttreatment consequences, including anesthesia and surgery complications, delayed wound healing, toxicity and side effects of treatment, immune suppression, infection, cancer recurrence, or occurrence of a second primary cancer (12, 18, 24–28). Lower quality of life, worse performance status, higher level of usual pain, and poorer general health and social functioning were also reported in smokers compared with nonsmokers (13, 29–31). These adverse outcomes are likely to render high mortality risk in patients who smoke. In addition, tobacco substances may continue to cause genetic mutations that lead to the progression of cancer via carcinogenic pathways (32), which explains the increased mortality risk in patients with smoking-related cancer (e.g., lung, stomach, colorectal, and bladder) but not in nonsmoking-related cancers (e.g., prostate) in our study. In the present study, 85.8% of patient deaths occurred were due to the primary cancer. We found no association between postdiagnosis smoking and risk of death from cardiovascular (4.9% of deaths), respiratory (1.7% of deaths), and other diseases (data not shown). Therefore, it is highly likely that postdiagnosis smoking was associated with poor survival by exacerbating the tumor progression or response to cancer therapy.

Our findings provide important public health implications for cancer survivors, healthcare providers, and policy makers. After the diagnosis of cancer, smokers are expected to show great interest and motivation to quit smoking (33, 34). However, patients face tremendous physical, psychologic, and social stresses (35), which result in no reduction of the smoking prevalence in patients with cancer (36, 37), given smoking as a possible means for stress relief. Moreover, physicians are pessimistic to help the patients quit smoking (38), especially to patients with smoking-related cancers that are believed it

was too late to quit smoking given the smoking-induced damages had been occurred (6). In the United States, less than 50% smokers received formal smoking cessation counseling at diagnosis, during treatment, or on follow-up visits (20). Therefore, there is noticeable room for the improvement of self-managed or healthcare provider-assisted smoking cessation in the clinical setting for patients with cancer. Message of inferior survival associated with postdiagnosis smoking should be conveyed to patients and their families and included in guidelines and evidence-based clinical practices. In addition, smoking cessation is considered cost-effective in the general population (39) as well as for patients with lung cancer who have had surgery (40). It is worth promoting effective and sufficient cancer tolerable smoking cessation interventions and disease management strategies for patients with cancer.

The major strength of the present study was that smoking status was recorded in the Shanghai Cohort Study at baseline and updated on an annual basis for all surviving cohort members. The prospective nature of the study with large population-based samples plus long-term, almost complete follow-up for all patients with cancer for their vital status provided an unbiased estimate of mortality for patients with cancer. In addition, the time-dependent approach in the analysis captured the dynamic change of smoking on an annual basis over the years after cancer diagnosis.

Despite the considerable strengths, the present analysis may be subject to potential limitations. One concern is the lack of information on factors especially the clinical extent of disease at diagnosis. In our study, comparable proportion of lifelong nonsmokers, former, and current smokers at diagnosis received surgical treatment and chemotherapy ($Ps > 0.05$; more data available in Supplementary Table S2). In all analyses, the type of treatments

Table 2. Time-dependent HR (95% CI) of all-cause death for smoking after cancer diagnosis for all patients with cancer and for current smokers at cancer diagnosis, by cancer sites, The Shanghai Cohort Study 1986–2010

	All patients	Lung cancer	Stomach cancer	Colorectal cancer	Bladder cancer	Prostate cancer	Other cancers
All patients with cancer							
No. of cases	1,632	288	362	248	107	132	495
No. of deaths (%)	931 (57.0%)	229 (79.5%)	159 (43.9%)	152 (61.3%)	40 (37.4%)	47 (35.6%)	304 (61.4%)
Person-years at risk	6,971	838	1,805	1,077	669	445	2,137
Average person-years	4.3	2.9	5.0	4.3	6.3	3.4	4.3
Average age at diagnosis	68.8	68.1	69.6	67.9	69.2	73.3	67.9
Median survival time (y)	5.4	2.1	10.9	4.0	15.0	8.4	5.2
HR (95%CI) time-dependent smoking status[a]	1.59 (1.36–1.86)	1.92 (1.41–2.60)	1.76 (1.11–2.79)	1.65 (1.14–2.38)	3.66 (1.56–8.60)	1.94 (0.79–4.73)	1.17 (0.87–1.58)
Patients with cancer who were current smokers at cancer diagnosis and survived until the next annual follow-up interview							
No. of cases	747	184	135	114	49	32	233
No. of deaths (%)	491 (65.7)	151 (82.1)	72 (53.3%)	73 (64.0%)	23 (46.9%)	15 (46.9%)	157 (67.4%)
Person-years at risk	3,331	547	647	581	311	118	1,126
Average person-years	4.5	3.0	4.8	5.1	6.4	3.7	4.8
Average age at diagnosis	67.0	66.9	69.4	65.4	67.7	70.1	65.9
Median survival time (y) for all patients	4.1	2.1	7.3	4.1	12.4	6.3	4.3
Median survival time (y) for quitters ($r = 0$)	4.4	2.1	3.8	7.9	N/A[c]	9.8	3.3
Median survival time (y) for intermittent smokers ($0 < r < 1.0$)	7.1	2.8	10.9	9.1	12.4	6.0	7.7
Median survival time (y) for continued smokers ($r = 1$)	2.1	1.7	3.8	2.1	2.9	11.1	2.1
HR (95% CI) intermittent smokers vs. quitters[b]	0.89 (0.70–1.12)	0.91 (0.59–1.39)	0.69 (0.38–1.27)	1.35 (0.68–2.67)	1.75 (0.28–11.01)	2.88 (0.22–37.20)	0.76 (0.49–1.17)
HR (95% CI) continued smokers vs. quitters[b]	1.76 (1.37–2.27)	1.89 (1.18–3.02)	1.36 (0.70–2.67)	3.46 (1.69–7.10)	17.29 (2.25–132.64)	0.93 (0.08–11.24)	1.49 (0.92–2.40)
HR (95% CI) time-dependent smoking status[a]	1.79 (1.49–2.16)	2.36 (1.63–3.42)	1.63 (0.98–2.73)	2.31 (1.40–3.81)	2.95 (1.09–7.95)	2.27 (0.40–12.80)	1.34 (0.96–1.88)

[a]Derived from a yearly based time-dependent variable of smoking status (yes vs. no) after cancer diagnosis with the adjustment for age at diagnosis (continuous), level of education (primary school, middle school, or college or above), cumulative number of pack-year of smoking before diagnosis (continuous), and treatment for cancer: surgery (yes/no), chemotherapy (yes/no), and radiation therapy (yes/no). Cox models for all patients were additionally adjusted for cancer site.

[b]All Cox models were adjusted for age at diagnosis (continuous), level of education (primary school, middle school, or college or above), cumulative number of pack-year of smoking before diagnosis (continuous), and treatment modalities: surgery (yes/no), chemotherapy (yes/no), and radiation therapy (yes/no). Cox models for all patients were additionally adjusted for cancer site.

[c]Median survival (50% of the patients died) was not reached in this group of patients with bladder cancer.

administered to patients with cancer was adjusted, which would take into account the potential difference, to some extent, in cancer stage at diagnosis between patients who continued smoking and those who quit smoking after cancer diagnosis. The treatment data available in our study were limited and did not include information on aspects of quality, delays in the timing of care, whether treatment regimens were actually completed, or details on the specific types of surgery, radiation, or chemotherapy agents. Survival differences, especially those we observed between the intermittent smokers and quitters, in these aspects of treatment may exist and may result from either patient or healthcare system issues or from differences in tumor characteristics. Another limitation is that our study included only patients who survived one or more years after cancer diagnosis. Patients who died less than one year after cancer diagnosis ($n = 1,591$; median survival time $= 4.2$ months) were excluded from the present study due to lack of updated information on smoking status after cancer diagnosis. Therefore, the findings of the present study may be only applicable to patients with cancer with at least 1-year survival after diagnosis.

In summary, our study shows that continued smoking after cancer diagnosis increased the risk of all-cause death in male patients with cancer in Shanghai, China by approximately 80%. In current smokers at diagnosis, patients diagnosed with lung, colorectal, or bladder cancers may experience a 2-fold increased risk of death if they continued smoking after diagnosis. These data provide new information about smoking and cancer survival, which should inform future research into the contextual and individual-level factors that may result in inadequate attention of smoking among patients with cancer in the postdiagnosis setting. Our study provides strong support to a smoking cessation intervention program that targets cancer survivors.

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