



Tobacco smoking after diagnosis of cancer: clinical aspects

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Abstract: Tobacco smoking accounts for at least 30% of all cancer deaths and nearly 90% of lung cancer deaths. Smoking cessation significantly reduces the risk of developing tobacco-related malignancies. Smoking after cancer diagnosis is also associated with multiple risks, including worse tolerance of treatment, higher risk of a failure and second primary tumors, and poorer quality of life. Apart from disease site and stage, continued smoking is considered the strongest adverse predictor of survival in cancer patients. However, the benefits of smoking cessation are undervalued: many patients are not aware of harms related to continued tobacco use after cancer diagnosis. Furthermore, health care professionals often do not encourage their patients to quit, and do not provide tobacco cessation assistance for continuing tobacco users. Despite the apparent impact of tobacco use on treatment outcomes, data on current smoking status is only rarely captured in clinical trials. This article reviews the most important clinical aspects of smoking after the diagnosis of cancer.

Keywords: Tobacco use; smoking cessation; cancer

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Introduction

Tobacco smoking remains the main single cause of premature death worldwide, and the most attributable risk factor for cancer. Smoking accounts for at least 30% of all cancer deaths and nearly 90% of lung cancer deaths (1). On average, a lifetime smoker has a 20-fold higher risk of developing lung cancer, compared with a lifetime non-smoker (2). Other cancers strongly attributable to smoking are lung, head and neck, bladder and esophageal cancer. Over 60% of cancer patients are reportedly current smokers, recent quitters or former smokers (3). Smoking cessation significantly reduces the risk of developing tobacco-related malignancies (4), but the benefits of smoking abstinence after a cancer diagnosis are undervalued. Many patients are not aware of harms related to continued tobacco use after cancer diagnosis and believe that once being diagnosed with cancer there is nothing to be gained from quitting. Disappointingly, health care professionals often do not encourage their patients to quit, and do not provide tobacco cessation assistance for continuing tobacco users (5-8). This

attitude may be viewed as a lost opportunity, as a wide and convincing body of literature demonstrates that smoking cessation after cancer diagnosis is associated with multiple benefits, including better tolerance of treatment, reduced risk of a failure and second primary tumor and better quality of life (9). Continued smoking is among the strongest adverse predictors of survival in cancer patients. This article shortly reviews the main clinical aspects of smoking after cancer diagnosis. The examples provided here should be considered illustrative, as no comprehensive analysis of the literature on this topic was attempted.

Prevalence and determinants of continued tobacco use after diagnosis of cancer

The diagnosis of cancer is “the teachable moment”, allowing health care professionals the best opportunity to discuss with patients their lifestyle habits (10-13). Most patients quit or attempt to quit shortly after a cancer diagnosis, but still up to 50% of smoking cancer survivors continue to smoke (5,11,14-16).

The self-reported prevalence of smoking among cancer survivors ranges in particular studies between 9% and 33% (17-24). However, patients with tobacco-related cancers feel guilt and shame resulting from previous smoking and tend to misrepresent their current tobacco dependence (25). Indeed, smoking rates reported by patients are apparently lower than those based on cotinine level verification (26,27). In consequence, the true deleterious effects of continued smoking after cancer diagnosis may be underestimated.

Factors influencing the smoking cessation rates in cancer survivors include tumor type, the causal relationship between smoking and the diagnosed cancer, the nature of cancer treatment (an example is the need to avoid smoking before surgery), the willingness to quit, and comorbid conditions, such as depression, disease-related anxiety and alcohol abuse (5,28-32). The quit smoking rates after cancer diagnosis are higher among patients with tobacco-related than in non-tobacco-related cancers (21). Among lung cancer patients, continued smoking rates are also higher in younger and less educated patients, in those who report greater smoking urges and who quit for a shorter time before surgery (33). Patients with poor, compared to those with favorable, prognosis, are generally less motivated to quit.

With time, smoking abstinence rates among cancer survivors gradually decrease (34,35). For example, the proportion of lung cancer patients who restart cigarette smoking after treatment ranges between 13% and 60% (23,26,28,36). Factors triggering smoking relapse in cancer patients include nicotine withdrawal symptoms, pain, fatigue, nausea, depression and anxiety (37-40).

Consequences of continued smoking after diagnosis of cancer

A wide and convincing body of literature demonstrates that continued tobacco smoking in cancer patients is associated with increased treatment toxicity, higher risk of a treatment failure, higher incidence of second primary tumors, poorer quality of life and shorter survival (9,41,42).

Increased risk of second primary cancer

Many reports indicate that smoking increases not only the incidence of a first, but also a second primary cancer. Most data on the relation between continued tobacco use after cancer diagnosis and the risk of a second primary cancer refers to tobacco-related malignancies, such as lung, and head and neck cancer. Richardson *et al.* (43) assessed the

potential effect of smoking cessation on the incidence of second primary cancers in 540 small-cell lung cancer patients. Among patients surviving free of cancer for two or more years, the relative risk for any second primary cancer compared with that in the general population was 4.4 [95% confidence interval (CI), 2.5–7.2], with a relative risk of 16 (95% CI, 8.4–27) for a second primary non-small-cell lung cancer. Among patients who stopped smoking at the time of small cell lung cancer diagnosis, the relative risk of a second lung cancer was 11 (95% CI, 4.4–23), compared to 32 (95% CI, 12–69) in patients who continued to smoke. A systematic review and meta-analysis of randomized and longitudinal observational studies also demonstrated a fourfold higher risk of developing a second primary tumor for small cell lung cancer patients who continued smoking, than for those who quit at diagnosis [hazard ratio (HR) 4.3; 95% CI, 1.09–6.98] (44). Rice *et al.* (45) examined prospectively the risk of second primary cancer in 569 stage I non-small cell lung cancer patients who had undergone complete pulmonary resection. Within the median follow-up of 5.9 years, second primary tumors developed in 15% of patients, 56% of these were second primary lung cancers (incidence =1.99/100 patient-years). Second primary lung cancer did not develop in any patient who had never smoked. Current, compared to former smokers had almost doubled incidence of second primary lung cancers (HR 1.91, P=0.03). Data from the Japanese population-based cancer registry including 29,795 patients demonstrates 59% and 102% higher risk for all and smoking-related second primary cancers, respectively in ever, compared to never smokers (46). Regardless of the first cancer site, second primary malignancies most attributable to continued smoking included oral/pharyngeal, esophageal, stomach, lung, and hematological cancers. Notably, patients who had stopped smoking prior to cancer diagnosis had 18% and 26% less risk, respectively, for any or tobacco-related second primary cancer, compared to those who smoked at the diagnosis.

In the Retinoid Head and Neck Second Primary (HNSP) Trial including 1,384 patients, the annual rates of tobacco-related second primary cancers in current, former and never smokers were 4.2%, 3.2%, and 1.9%, respectively (P=0.03; current *vs.* never smokers, P=0.02) (47). An adverse impact of continued smoking on the risk of primary cancers in head and neck cancer was also demonstrated in earlier studies (48-50).

Increased risk of developing new cancer as a result of continued smoking is not confined to tobacco-related malignancies. For example, smoking considerably increases

the risk of lung cancer in breast cancer patients who underwent radiotherapy (51), in Hodgkin lymphoma patients managed with chemotherapy and/or radiotherapy (52,53) and in testicular cancer patients (54).

Increased risk of postoperative complications

Tobacco smoking significantly increases the risk of complications in patients undergoing surgery. In a meta-analysis comprising 140 cohort studies and 479,150 patients, the pooled adjusted odds ratios were 3.60 (95% CI, 2.62–4.93) for necrosis, 2.07 (95% CI, 1.53–2.81) for healing delay and dehiscence, 1.79 (95% CI, 1.57–2.04) for surgical site infection, 2.27 (95% CI, 1.82–2.84) for wound complications, 2.07 (95% CI, 1.23–3.47) for hernia, and 2.44 (95% CI, 1.66–3.58) for lack of fistula or bone healing. An overview of 18 unique studies comprising 26,297 patients demonstrated that continued use of tobacco results in healing delay and dehiscence with an odds ratio of 2.86 (95% CI, 1.49–5.49), whereas 4 to 8 weeks of preoperative abstinence from smoking significantly reduced surgical site infections (55). Another meta-analysis showed that smoking cessation results in an overall reduction of postoperative complications by 24% (relative risk 0.76; 95% CI, 0.69–0.84, $P < 0.0001$) (56). A meta-analysis of 11 randomized studies demonstrated that preoperative smoking cessation interventions including individual counselling initiated at least 4 weeks before operation and nicotine replacement therapy significantly decreases the risk of postoperative complications (risk ratio 0.56; 95% CI, 0.41–0.78; $P < 0.0001$) (57). Continued smoking is one of the most important factors increasing the risk of chest surgery in lung cancer patients (58,59). A spectacular effect of smoking cessation intervention (counselling and nicotine replacement therapy) prior to pulmonary resection was shown in a Danish randomized study including 120 lung cancer patients (60). The overall complication rate in the smoking intervention and control groups was 18% and 52%, respectively ($P < 0.01$); 5% *vs.* 31% ($P = 0.001$) for wound-related complications, 0% *vs.* 10% ($P = 0.08$) for cardiovascular complications, and 4% *vs.* 15% ($P = 0.07$) for secondary surgery.

Decreased efficacy and tolerance of radiation

Continued smoking in patients with head and neck cancer considerably increases radiotherapy-induced complications, such as oral mucositis, weight loss, fatigue xerostomia, loss

of taste and voice problems (42,61). Patients with head and neck cancer who continue smoking have lower rates of complete response to radiation therapy and poorer survival, compared to nonsmokers and those who quit prior to treatment (62,63). Current, compared to never smoking prostate cancer patients were demonstrated to experience an increased risk of radiotherapy-caused defecation urgency, diarrhea, sensation of incomplete emptying and abdominal cramps, whereas there was no increased prevalence ratio for these symptoms among former smokers (64). In the study of Eifel *et al.* (65) including cervical cancer patients managed with radiotherapy, heavy smoking was the strongest independent predictor of overall complications (HR 2.30; 95% CI, 1.84–2.87), with over three times higher incidence of small bowel complications (HR for smokers of one or more packs per day 3.25; 95% CI, 2.21–4.78).

Of particular importance are the long-term consequences of smoking in patients managed with radiotherapy. For example, breast cancer patients administered radiotherapy who continued smoking experienced a more than additive effect on the risk of myocardial infarction (HR 3.04; 95% CI, 2.03–4.55) (66).

Decreased efficacy and tolerance of systemic therapy

Preclinical studies using *in vitro* and animal models suggest that nicotine may impair the efficacy of chemotherapy (67,68). This effect has been attributed to activating cell growth pathways, stimulating survival pathways and conferring resistance to apoptosis (69–71).

Continued tobacco use has an adverse impact on the liver metabolism of many cytotoxic agents, thus affecting their outcomes and increasing the complications rates. Polycyclic aromatic hydrocarbons present in tobacco smoke induce accelerated clearance of key cytochrome P450 enzymes, which metabolize several systemic anti-cancer compounds (72,73). Given a narrow therapeutic index of systemic therapy for various solid tumors, even small changes in plasma concentrations or exposure in smokers may affect treatment efficacy. Lung cancer patients who continue smoking exhibit higher clearance of erlotinib and gefitinib than nonsmokers (epidermal growth factor receptor inhibitors) and may require higher doses of both compounds to reach equivalent systemic exposure (74–80). The study of Hughes *et al.* (81) showed that pharmacokinetic and toxicity profiles for smokers receiving erlotinib at a 300 mg daily dose is similar to that in nonsmokers receiving 150 mg daily. Based on these findings, it was postulated that the daily dose

erlotinib in current smokers should be increased to 300 mg.

Tobacco smoke was also demonstrated to affect the pharmacokinetics and toxicity of irinotecan, a topoisomerase-I inhibitor used in small-cell lung cancer (82). Irinotecan is a substrate for several cytochrome P450 and UGT1A1 isoenzymes, which are induced by components of tobacco smoke. Smoking lung cancer patients treated with gemcitabine and taxanes (docetaxel and paclitaxel) were shown to have a lower incidence of grade 3 to 4 neutropenia compared with nonsmokers (83,84). Although cigarette smoking does not seem to impact clearance of these drugs, the question of whether a lesser degree of chemotherapy-induced neutropenia may predict poor therapeutic response warrants further investigation.

Decreased health functioning and quality of life

Lung and head and neck cancer patients who quit smoking prior to their cancer diagnosis (recent quitters and former smokers) have better quality of life indices than survivors who continue smoking or quit smoking after their cancer diagnosis (85-87). Compared to never or former smokers, cancer patients who continued smoking have also poorer physical health, self-perception of their general health, emotional and social functioning, and vitality.

Patients who continue smoking after a diagnosis of cancer experience higher levels of cancer-related symptoms than nonsmokers or former smokers. For example, Ditre *et al.* (88) demonstrated that compared to former smokers, patients with advanced cancer who continued smoking experienced greater pain severity and decreased normal activities. Additionally, among former smokers, pain severity was decreasing with increasing time since smoking cessation. Likewise, in a study of Daniel *et al.* (89) moderate to severe pain was reported by 60% and 37% of persistent smokers and nonsmokers with lung cancer, respectively ($P < 0.001$). In that study, persistent smoking was also associated with higher levels of fatigue, shortness of breath and difficulty eating. These findings are consistent with those of Garces *et al.* (85). Lung cancer patients who quit smoking may also maintain a better performance status than those who continue smoking (90).

Increased overall mortality

Apart from disease site and stage, abstinence from smoking is considered the strongest predictor of survival in cancer patients who have ever smoked (41). Smokers remain

at increased risk of all-cause mortality (91) due to both poorer cancer outcomes, and higher rates of cardiovascular, respiratory and other non-cancer-related deaths caused by smoking.

Several observational studies and overviews demonstrated decreased overall mortality among patients continuing smoking after a cancer diagnosis compared with recent quitters. In the single institutional study of Warren *et al.* (3), the overall mortality rate among all cancer patients who continued smoking was 20% higher, compared with those who stopped smoking within one year before diagnosis. In the study of Videtic *et al.* (92) small cell lung cancer patients who continued smoking during chemotherapy or radiotherapy had poorer survival rates than former smokers (median 18 *vs.* 13.6 months; 5-year actuarial overall survival 8.9% *vs.* 4%). An overview of 10 lung cancer studies demonstrated that patients who quit smoking at the time of diagnosis had 5-year survival rates of 63% and 70% for small-cell and non-small-cell lung cancer, respectively, *vs.* 29% and 33%, respectively, among those who continued smoking (44). In the authors conclusion, most of the benefit from smoking cessation was due to a lower risk of cancer progression rather than a reduction in cardiorespiratory deaths. An apparently decreased risk of mortality by virtue of quitting tobacco use around the time of diagnosis was also shown in head and neck cancer patients. In the study of Browman *et al.* (62) patients who continued to smoke during radiotherapy or chemoradiotherapy, compared to those who did not smoke, had a lower rate of complete response (45% *vs.* 74%, $P = 0.008$) and poorer two-year survival (39% *vs.* 66%; $P = 0.005$). A risk reduction for patients who had quit less than 12 weeks and more than one year before cancer diagnosis (relative to that for patients who continued to smoke) was 40% and 70%, respectively. In the Radiation Therapy Oncology Group 9003 trial, patients with oropharyngeal cancer who did not smoke during radiotherapy had significantly better overall survival than those who smoked (HR 2.48; 95% CI, 1.70–3.60; $P < 0.001$). The absolute 5-year survival difference between both groups was 24.6% (93). A meta-analysis of 15 studies comprising 10,192 bladder cancer patients demonstrated that current, compared with a never smoking status significantly increased the relative risk of recurrence (relative risk 1.23; 95% CI, 1.05–1.45) and mortality (1.28; 95% CI, 1.07–1.52) (94).

Reduced cancer-specific and overall survival was also demonstrated in malignancies less associated with tobacco, such as prostate, colorectal, esophageal, cervical,

endometrial, and ovarian cancer (95-100).

The consequences of continued smoking are particularly important in cancer types with good prognosis, in which non-cancer-related mortality, particularly cardiovascular and respiratory deaths, may dominate survival outcomes. In the study including 5,892 breast cancer patients the association between smoking exposure variables and all-cause mortality was highly significant ($P \leq 0.0001$) and stronger than that for breast cancer-specific mortality (101). Likewise, in the study of Izano *et al.* (102) including 975 breast cancer patients, smoking impact was higher on non-cancer-related *vs.* breast cancer-related mortality (HR 1.47; 95% CI, 1.13–1.90 *vs.* 1.06; 95% CI, 0.81–1.40, respectively). Increased all-cause mortality associated with tobacco use has also been reported in testicular, prostate and colorectal cancers (54,98,103,104).

Notably, tobacco use can affect primary endpoints and treatment compliance in clinical trials, and may result in their misinterpretation. For example, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT) (investigating the role of adjuvant tamoxifen), current tobacco smoking was significantly associated with reduced protocol adherence (odds ratio 0.75; $P < 0.0003$) (105). Despite this, data on current smoking status is captured in only one-third of clinical trials, and assessment methods are not standardized (106). Only recently, Cancer Patient Tobacco Use Assessment Task Force of the National Cancer Institute-American Association for Cancer Research developed recommendations for assessment of tobacco smoking status in cancer clinical trials (107).

Conclusions

Quitting smoking after diagnosis of cancer represents an important opportunity to decrease the risk of secondary cancers, alleviate cancer treatment complications, improve survival, general health and quality of life, and decrease mortality from non-cancer tobacco-related diseases. Enhanced focus on smoking cessation, and its active promotion, may increase patients' motivation to quit. There is a sore need of addressing tobacco use in patients with cancer. All patients should be screened for tobacco use and advised on the benefits of tobacco cessation. In patients who continue smoking after diagnosis of cancer evidence-based tobacco cessation assistance should be integrated into multidisciplinary cancer care (108). Prospective clinical studies are required to determine the most effective smoking cessation interventions.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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