HHS Public Access

Author manuscript

*Expert Rev Qual Life Cancer Care*. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

*Expert Rev Qual Life Cancer Care*. 2017 ; 2(1): 23–39. doi:10.1080/23809000.2017.1271981.

# Treating Nicotine Dependence and Preventing Smoking Relapse in Cancer Patients

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## Abstract

**Introduction—**Despite the well-documented harmful effects of smoking, many cancer patients continue to smoke. Smoking cessation is critical to address in this population given the associated increase in treatment toxicity, risk of second primary tumors, decrease in treatment response and higher disease-specific and all-cause mortality with continued smoking following a cancer diagnosis. This review seeks to summarize the latest recommendations and guidelines on smoking cessation treatment for patients diagnosed with cancer, and the evidence behind those recommendations.

**Areas covered—**We reviewed the latest evidence for smoking cessation treatments for cancer patients and the clinical guidelines and recommendation available for oncologists and health care providers. The unique aspects of nicotine dependence among patients diagnosed with cancer, and key challenges and barriers that cancer survivors and health care providers experience when considering smoking cessation treatments, and available clinical resources, are also discussed. Lastly, the authors summarize future directions in the field of smoking cessation treatment for cancer patients.

**Expert commentary—**While there are areas of improvement in research of smoking cessation treatment for cancer patients, critical under-explored areas remain. Nonetheless, providers should

**Declaration of Interest**

B Hitsman receives varenicline and placebo free of charge from Pfizer for use in an ongoing NIH sponsored clinical trial. B Hitsman has served on a scientific advisory board for pfizer. R Schnoll receives medication and placebo free of charge from Pfizer and has provided consultation to Pfizer. R Schnoll has also consulted for GlaxoSmithKline. These companies had no involvement in this work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

adhere to the NCCN guidelines and offer a brief counseling intervention to motivate patients to quit smoking when appropriate resources are not available.

**Keywords**

nicotine dependence; cancer; cancer survivors; oncology; tobacco; smoking; cessation; treatment; intervention

## 1. Introduction

Tobacco is the leading cause of preventable death in the United States and worldwide and is causally linked to several cancers. Despite the well-documented harmful effects of smoking, many patients continue to smoke following their cancer diagnosis. Previous observational studies have reported an estimated current smoking of 45–60% among patients at the time of diagnosis [Berg, 2013; [1]Cooley, 2009; Gritz, 2007]. Furthermore, significantly higher rates (47–60%) of continued smoking following cancer treatment [Gritz, 1991; Ramaswamy, 2016] and relapse rates have been reported among cancer survivors [50% to 83%], compared to the general population [18–23.6%] [Tseng, 2012; Asfar, 2016; Berg, 2013; Land, 2016; Gritz, 2006; Gritz, 2007]. The high rates of persistent smoking among patients diagnosed with cancer is concerning since it has been causally linked to adverse health outcomes such as increased all-cause and cancer-specific mortality as well as reduced survival following cancer treatment [Arnold, 2014; Coker, 2009; Waggoner, 2006; Waggoner, 2010/Ehdaie, 2014]. Furthermore, continued smoking increases the risk for second primary tumors (SPT) at both initial tumor site and other sites [Surgeon General Report, 2014; Do, 2003; Tabuchi, 2013/ Gritz, 2006; Gritz, 2007; Shiels, 2014]. Other potential complications arising from continued smoking following cancer diagnosis include: increased risk of tumor recurrence, poorer response to cancer treatment, and increased treatment-related toxicity, such as increased risk for xerostomia, mucositis, pneumonitis, soft-tissue and bone necrosis and increased risk of infection and other systemic symptoms such as weight loss and fatigue [Surgeon General Report, 2014; Do, 2003; Gritz, 2006; ASCO, 2015]. Smoking can also lessen the efficacy of certain chemotherapy and targeted therapy medications by altering drug clearance time and thus plasma concentration due to the smoking effects on cytochrome P450 [O'Malley, 2014; Hamilton, 2006; van der Bol, 2007].

Given the substantial risks of continued tobacco use and significant health benefits associated with smoking cessation among patients with cancer, the 2014 Surgeon General's Report emphasized the need to urgently address nicotine dependence in patients receiving cancer treatment [Surgeon General Report, 2014; [1]Warren, 2015]. The National Comprehensive Cancer Network (NCCN) established its first clinical practice guideline for smoking cessation treatment in cancer patients in March, 2015 [Shields, 2016]. The guideline recommends that physicians and other health care providers inform patients about the benefits of smoking cessation, educate patients about the specific cancer treatment-related risks and complications related to continued smoking during cancer treatment, and encourage patients to stop using tobacco as soon as possible and well-ahead of cancer treatment initiation.

This review summarizes the current evidence-based treatments and recommendations available for smoking cessation for patients diagnosed with cancer. It is designed to summarize the key recommendations and guidelines on smoking cessation treatments for patients diagnosed with cancer. A comprehensive review of clinical trials and intervention studies on smoking cessation treatment modalities for oncologic patients is undertaken to highlight the areas of deficiencies in our current literature. Key barriers and challenges that are encountered when addressing smoking cessation that may be unique to patients affected by cancer will be examined. Future directions in the field of nicotine dependence treatment to improve the quality of smoking cessation treatment for this population are also discussed.

## 2. Smoking Cessation for Cancer Patients

### 2.1 Current Approach to Nicotine Dependence Treatment for Cancer Patients

To establish an evidence-based, standardized approach to smoking cessation for patients with cancer, the National Comprehensive Cancer Network (NCCN) issued a new set of Clinical Practice Guidelines in Oncology in 2015 [NCCN guidelines, 2015]. The new NCCN Guidelines for Smoking Cessation aims to provide clear steps from patient assessment of tobacco use to recommendations for pharmacotherapy and behavioral therapy for cancer patients with nicotine dependence while emphasizing the importance of close monitoring and follow-up to prevent relapse. Once a patient is identified to be a current smoker (tobacco use within the past 30 days), the guidelines recommend that providers proceed with a thorough evaluation to assess the patient's history of nicotine dependence, prior quit attempts and readiness to quit. The detailed history of tobacco use and prior tobacco cessation attempts helps to formulate a personalized smoking cessation plan to increase the likelihood of success. The evaluation process for former smokers (> 30 days since tobacco use) includes identifying risk factors for relapse such as intensity of tobacco cravings, level of stress and/or depression, history of drug use/abuse, and determining the presence of second hand smoke exposure.

For current smokers who show willingness to engage in treatment, providers should help the patients set a quit date and review the risk of relapse along with a detailed individualized treatment plan. The recommended first-line therapy is a combination of pharmacotherapy and behavior therapy. For pharmacotherapy, either combination nicotine replacement therapy (NRT), such as long-acting nicotine patch plus a short-acting NRT (lozenge, gum, inhaler, or nasal spray), or varenicline, a partial nicotine receptor agonist, for a duration of 12 weeks which may be extended as needed up to one year. For behavior therapy, a minimum of 4 individual or group sessions is indicated. Frequent follow-up monitoring in person or by phone is encouraged during the initial 12 weeks of treatment to determine efficacy and toxicity of the pharmacologic treatment, and to provide support and assess risk for relapse. Ongoing monitoring is encouraged for 12 months from the initial abstinence date.

There are some side effects to consider before choosing appropriate pharmacotherapy options because cancer patients may be more susceptible to the side effects of the medications due to their exposure to cancer treatment [Karam-Hage, 2014]. For example, patients being prescribed varenicline should be warned of the medication's common side

effects including but not limited to nausea, agitation/irritability, insomnia/abnormal dreams, and dry mouth [Price, 2016; Park, 2011]. Overall, data for varenicline indicate that the medication is well tolerated and has been shown to be effective even among cancer patients [Price, 2016; Park, 2011; Karam-Hage, 2014]. Dry mouth from varenicline and short-acting NRT such as lozenges and nicotine gum should be given extra attention especially for head and neck cancer patients undergoing radiotherapy as it may aggravate symptoms of xerostomia that is commonly caused by radiotherapy [Karam-Hage, 2014; Wallstrom, 1999]. There has been substantial concern regarding the neuropsychiatric safety of varenicline. Possible risk of depressed mood and suicidal thinking are some of the possible neuropsychiatric side effects listed on the black-box warning of the medications. A recent large multinational randomized controlled clinical trial by Anthenelli et al. (EAGLES) was performed to determine the safety and efficacy of varenicline among smokers with and without psychiatric disorders [Anthenelli, 2016]. The study results demonstrated no associated increase in neuropsychiatric adverse effects with the medication's use, thus providing further evidence that varenicline is overall safe and well tolerated [Anthenelli, 2016].

The readiness to quit and current tobacco use should be assessed and documented on the medical chart at each patient visit. The guidelines recommend that follow-up assessments be done to monitor progress and the smoking status at 12 weeks, 6 and 12 months from the intervention date at a minimum. Detailed documentation would help the clinicians to determine interventions that seem to be the most effective for the individual. It would also help in identifying pharmacotherapy's side effects and relapses.

Recent data have described the tendency of cancer patients misreporting their tobacco use. High inaccuracy rates [48–80%] in the self-reported tobacco assessments have been described when the information is collected by phone from cancer patients who are current smokers [Klesges, 2015; [2] Warren, 2015]. The misreporting rate seems to be somewhat lower when the tobacco assessment is done in person (11–30%) [Price, 2016; Warren, 2015; Morales, 2013; Warren, 2012], although it still may be somewhat higher overall when compared to the general population (5%) [Martinez, 2009]. Biochemical confirmation may be a necessary adjunctive tool to increase the accuracy of data collected when assessing tobacco status of cancer patients [Warren, 2015; Karam-Hage, 2014]. Additionally, biochemical confirmation may potentially be used as a predictor of post-surgical outcomes among cancer patients [Toll, 2013; Marin, 2008]. Two methods of biochemical verification of abstinence are cotinine (urine or saliva) and expired breath carbon monoxide (CO) analyses. The latter method is more commonly used due to its easier accessibility and lower cost. Furthermore, CO is the method of choice for patients indicating NRT use due to its influence on the systemic cotinine level.

Providers offering smoking cessation treatment for cancer patients should have a thorough knowledge of the oncologic treatment and should be considerate of the treatment's side effects when prescribing smoking cessation pharmacotherapy given side effects when the two therapies are being administered concomitantly. This further highlights the importance of an individualized approach for smoking cessation treatment among cancer patients.

## 3. Comprehensive Review of Treatment Modalities used for Smoking Cessation Treatment for Cancer Patients

For this narrative review of the literature, we conducted a PubMed search in May 2016 with the following key words: tobacco use cessation, smoking cessation, neoplasms, cancer, carcinoma, tumor/tumour and survivor(s). This initial search generated nearly 200 articles. To be comprehensive, we then crosschecked all the references and selected all pertinent articles and publications based on the abstracts. In addition, we reviewed the reference sections of recent relevant papers in this area to ensure that we had not missed suitable papers for this review. All authors reviewed the literature search to determine if there were any missing citations. No weighting was performed for the scientific merit of studies, but we highlight methodological characteristics of studies.

### 3.1 Behavioral Interventions

Evidence-based smoking cessation treatment includes a combination of pharmacotherapy and behavioral therapy. All smokers who are ready to quit smoking should be offered intensive behavioral counseling sessions which typically consist of teaching coping and social skills, contingency management, self control, identification of high-risk situations (i.e., triggers to urge to smoke) and cognitive-behavioural interventions [Stead, 2005; Fiore, 2008]. The NCCN guidelines recommend that four or more counseling sessions be offered either individually or in group [NCCN guidelines, 2015]. Such recommendation is based on the evidence in the current literature to support the effectiveness and efficacy of the combination treatment for non-cancer smokers as data specifically on cancer patients are somewhat limited. Description of literature looking into the efficacy of pharmacotherapy for smokers who are diagnosed with cancer is summarized in the following subsection.

Table 1 summarizes a selected number of studies that have looked into the efficacy of behavioral therapy on smoking cessation for cancer patients. A total of ten studies have been identified. Four of these studies also offered additional pharmacological therapy (NRT) if the treatment was indicated [Schnoll, 2003; Wakefield, 2004; Duffy, 2006], and in one study all participants received a nicotine patch [Schnoll, 2005]. Six of the studies were based on a nurse-delivered behavioral intervention [Stanislaw, 1994; Wewers, 1994; Wewers, 1997; Griebel, 1998; Duffy, 2006]. One study was based on a physician-delivered motivational interviewing session [Schnoll, 2003], and another study looked into the efficacy of interview sessions delivered by a physician or a resident [Gritz, 1993]. The number of counseling sessions varied widely from one study to another, ranging from one to eleven sessions. The duration of follow-up period also varied from 5 weeks to 12 months (Table 1).

The majority of the studies failed to detect any statistically significant differences in the cessation rates between the intervention and the control (i.e., usual care) groups. Two studies did not have any control, and they found 40–43% abstinence rates in their cohort groups at the end of their studies [Wewers, 1997; Smith, 2002]. Only two studies found statistically significant differences in the cessation rates between the intervention and the control groups [Wewers, 1994; Duffy, 2006]. Further, many of the results from these studies were based on

self-reported cessation and therefore may be an over-estimation [Klesges, 2015; Warren, 2015; Price, 2016; Morales, 2013, Warren, 2012].

It is difficult to ascertain the ideal number of behavioral counseling sessions with the currently available data. Furthermore, no study has been done to look into the efficacy of group-based versus individual behavioral therapy sessions. Group therapy sessions may result in improvement of cessation rates when compared to the standard individual therapy sessions since it can provide a confidential space and opportunity where the patients can share their doubts, fears and problems related to nicotine addiction, which may result in additional therapeutic benefit [Stead, 2005].

### 3.2 Pharmacologic Interventions

Table 2 summarizes a selected list of studies that looked into the efficacy of pharmacotherapy treatments for smoking cessation among cancer patients. Research data looking into the efficacy and effectiveness of varenicline, the first-line recommended pharmacotherapy, is lacking for smokers diagnosed with cancer. All five studies identified also offered behavioral therapy sessions. The first two studies looked into the efficacy of bupropion [Browning, 2000; Schnoll, 2010]. In a quasi-experimental study, Browning et al. evaluated the efficacy of a combination NRT and bupropion given for a total of 7 to 8 weeks in addition to a nurse-delivered behavioral counseling sessions to a small group (n=14) of patients who were diagnosed with nonsmall cell lung cancer [Browning, 2000]. The usual care control group patients were accrued via a retrospective chart review. The second study was an RCT conducted by Schnoll et al [Schnoll, 2010]. The patients were randomized to receive either bupropion or placebo for a total of 9 weeks. All patients were offered 5 counseling sessions and 8 weeks of NRT. Biochemical confirmation using CO breath monitoring was performed at 3- and 6-month follow-ups. None of these two studies resulted in statistically significant difference in the abstinence rates.

Thomsen et al. conducted a trial to determine the efficacy of NRT given perioperatively with a single motivational counseling session to patients diagnosed with breast cancer [Thomsen, 2010]. The authors detected a significant difference in the abstinence rates between the intervention and the usual care groups (28% vs 11%) at 10 days following surgery, but the difference in the abstinence rates between the two groups was no longer significant at 12-month follow-up (13% vs 9%).

Two studies assessed the efficacy of varenicline [Park, 2011; Price, 2016]. They were both prospective cohort in design, and the pharmacotherapy was given for 12 weeks in addition to behavioral counseling sessions. One study did not have any control group, and the authors found a 40.2% abstinence rate at the end of the study [Price, 2016]. This abstinence rate is comparable to the abstinence rates reported by Wewers et al. and Smith et al. in which the patients received a nurse-delivered counseling sessions with or without additional NRT (Table 1) [Wewers, 1997; Smith, 2002]. The study conducted by Park et al. did have a control arm; however, the authors failed to detect any statistically significant difference in the abstinence rates between the two groups. These last two studies by Park et al and Price et al were the only studies to combine behavioral treatment and varenicline, which is a first-line recommended therapy for cancer patients. Unfortunately, they both suffered from a brief

period of follow-up. The authors concluded that the program was feasible and safe, and they highlighted the need to conduct a larger scale randomized controlled trial looking into the long term benefits and efficacy of combined counseling and varenicline treatment for cancer patients.

### 3.3 Systems-based Interventions

This section describes studies on systems-based interventions. Examples of such would be studies comparing different methods of treatment delivery or intervening on system or organization to change practice patterns (Table 3). There is currently limited evidence of the effectiveness of systems-based smoking cessation for cancer patients. Ostroff et al. sought to evaluate the efficacy of scheduled reduced smoking (SRS) for patients newly diagnosed with cancer [Ostroff, 2014]. Patients in the control group received five individual counseling sessions with NRT. The additional component in the intervention group was the SRS, which is a specific behavioral strategy to help the patients gradually reduce their daily tobacco consumption by adhering to a predetermined smoking schedule. SRS was administered using a handheld, pre-programmed electronic device. Biochemical confirmation was performed using both cotinine and CO levels. The authors failed to demonstrate benefit of SRS with results indicating similar abstinence rates in both groups (32%) at 6 months.

Warren et al. looked into the effectiveness of incorporating electronic health record (EHR) system for automatic referral to tobacco cessation program in oncology clinic setting [[1]Warren, 2014]. Any patients who reported tobacco use within the past 30 days were automatically referred to a dedicated tobacco cessation program using EHR [[1]Warren, 2014]. Once the referral was received, the tobacco cessation service used either mailed invitations and/or telephone calls to contact the patients. If the patients wished to receive treatment, a standardized, evidence-based cessation treatment comprised of behavioral and pharmacological therapies was offered [[1]Warren, 2014]. The authors concluded that an automated referral system using EHR can be useful in identifying a substantial number of patients diagnosed with cancer who are willing to receive treatment [[1]Warren, 2014].

In a recently published study, Klesges et al. examined the efficacy of two common types of tobacco quitlines [Klesges, 2015]. The most common method is Proactive which is based on a counselor-initiated telephone counseling sessions. The other method is Reactive where the patients are asked to call the quitline up to six times over the same duration of eight weeks [Klesges, 2015]. A total of 427 patients were randomized to either Proactive or Reactive arms, and all patients received NRT. A cotinine-verified (< 3 ng/ml) abstinence rate was analyzed at 12-month follow-up. No significant difference in the point prevalence abstinence rates was found in both groups (22% vs 26%). Other forms of system-level interventions, such as the use of mHealth or mobile interventions have not been tested among cancer patients.

### 3.4 Novel approaches for addressing smoking cessation for unmotivated smokers

The patients who are not motivated to quit smoking despite cancer diagnosis are a challenging concern for oncology providers. Given the significant complications and risks associated with continued smoking post-cancer diagnosis, careful consideration must be

given to this vulnerable patient population. For patients who are not ready to quit, providers are recommended to engage the patients in a motivational dialog about smoking cessation by educating the patients on the risks associated with continued smoking and the benefits of quitting during cancer treatment. The guidelines also recommend to address barriers and concerns that patients may have when engaging them in cessation dialog [NCCN guidelines, 2015]. Motivational counseling techniques may be useful for patients who are not yet ready to quit in the hopes of leading them to the state of willingness to quit [NCCN guidelines, 2015]. It encourages the providers to explore the patients' feelings and beliefs on nicotine use and addiction while emphasizing on the benefits and needs of smoking cessation [Fiore, 2008; Miller, 2002; Lindson-Hawley, 2015]. The motivational interview technique consists of building the patients' confidence to quit smoking by increasing self-efficacy while providing empathy [Fiore, 2008; Miller, 2002; Lindson-Hawley, 2015]. Additional resources should be provided to facilitate access to smoking cessation treatment such as quit lines and online support. NRT or varenicline may also be considered to reduce the current amount of tobacco use with a goal of formally readdressing cessation in the near future. In a recent randomized clinical trial by Ebbert et al., the authors determined that the use of varenicline was effective at significantly increasing smoking cessation rates when given to current smokers who are not interested in quitting smoking within the next month but willing to reduce cigarette consumption [Ebbert, 2015]. This pharmacotherapy regimen may be an excellent preparatory treatment for cancer patients who are not yet ready to quit smoking.

In a recent comparative effectiveness study with a randomized factorial experiment design, Cook et al compared different intervention methods to promote abstinence for smokers who are unwilling to quit [Cook, 2015]. The authors compared the following four intervention components: nicotine patch versus none, nicotine gum versus none, motivational interviewing (MI) versus none, and behavioral reduction (BR) counseling versus none. While MI focuses on relevant needs and motives for smoking cessation, BR focuses on reducing the overall cigarette consumption by reducing exposure to high-risk situations and developing appropriate coping skills when experiencing the urge to smoke [Cook, 2015]. The primary outcome of the study was the percentage change in cigarettes smoked per day at 26 weeks since enrollment. The point-prevalence abstinence was also recorded at 12 and 26 weeks as secondary outcome measures. Two following component combinations resulted in the most significant smoking reduction: nicotine gum combined with BR and BR combined with MI ($p=0.01$, $\beta=0.12$). The authors also found that nicotine gum and possibly BR combined with nicotine gum could improve long-term abstinence.

These novel approaches to promote abstinence among smokers who are unwilling to quit are promising. However, these studies were based on general population, and their effectiveness may be limited when used for patients diagnosed with cancer. Future studies looking into the efficacy and effectiveness of these novel approaches for cancer patients who are not interested in smoking cessation are warranted.

## 4. Unique Clinical Aspects and Challenges for Cancer Patients

### 4.1 Stronger nicotine dependence among cancer patients

It is important to understand that nicotine dependence is often relatively high in patients with a smoking-related cancer, as with other tobacco-related disease patient populations (e.g., COPD or CVD), and it may not change so readily even with the cancer diagnosis [NCCN. 2015; Morgan, 2011; Emery, 2000; Schnoll 2002; Karam-Hage 2014, Gritz, 2007]. Long-term smoking history, early age of smoking initiation, and continued use in patients with cancer are often associated with a greater degree of nicotine dependence which is particularly difficult to treat [Gritz, 2007; Waggoner, 2010]. The ongoing deleterious use of nicotine in the setting of life-threatening disease attests to the severity of nicotine dependence in this population [Tseng, 2012; Asfar, 2016; Berg, 2013; Land, 2016] and is consistent with standard definitions of drug addiction [APA DSM, 2000]. It is therefore important to gauge the severity of nicotine dependence to guide decision making about treatment intensity and duration. The high levels of nicotine dependence in individuals with cancer and cancer survivors suggests the potential need for extended duration or combination treatments when compared to the general population [Morgan, 2011; Emery, 2000; Karam-Hage, 2014; Schnoll, 2002]. Head and neck cancer patients as a group in particular have been shown to be heavy users of nicotine, with long histories of nicotine dependence, which enhances the difficulty of smoking cessation interventions [Lewin, 1998; Schildt, 1998; Sharp, 2008].

### 4.2 Treatment of Depression and Addressing Pain

The psychological impact of a cancer diagnosis presents an additional consideration in addressing smoking cessation for cancer patients. Smokers diagnosed with cancer have been reported to have a greater incidence of depression, anxiety, and stress than the general population (10–25% prevalence rates of MDD among cancer patients vs 2.2% prevalence of depression among general population) [Pirl, 2004]. Symptoms of depression are associated with not only the lower likelihood of a smoking cessation attempts but also a higher risk of relapse following a cessation attempt [Weinberger, 2016; Berg, 2013; Pirl, 2004; Boyes, 2011; Martinez, 2009]. The need for cessation prior to the initiation of therapeutic treatment for cancer patients can further increase their level of physiological stress which can, in turn, decrease their likelihood to attempt smoking cessation [Shields, 2015; Gritz, 2007]. Berg et al. previously reported that patients who continued to smoke following the cancer diagnosis were much more likely to have depression symptoms, compared to patients who successfully quit smoking (63.8% vs 26.7%) [Berg, 2013]. Furthermore, depressed smokers are less likely to quit smoking than non-depressed patients [Hitsman et al. 2013]. Given the significant impact of depression on the patients quit attempt and their likelihood of success, it is critical to address and treat depression for cancer patients when detected. Selective serotonin reuptake inhibitors and tricyclic antidepressants have been suggested to be effective in treating depression in patients with cancer [Pirl, 2004]. Additionally, varenicline has been shown to have antidepressant-like effects in animal models, and bupropion's anti-depressant properties are considered to be particularly helpful for cancer patients with concurrent depression [Rollema, 2009, Schnoll, 2010].

Similarly, pain as a component of cancer treatment may be an important consideration in smoking cessation. A recent study described the efficacy of nicotine as a pain modulator in the setting of chemotherapy-induced neuropathies [Di Cesare, 2014]. Pain was shown to be marginally associated with smoking relapse during recovery in a retrospective study [[1]Cooley, 2009]. A recent study reported that, similar to depression, greater daily pain ratings were associated with lower likelihood of cessation attempts and greater use of nicotine among cancer patients [Aigner, 2016]. Additionally, continued smoking following a cancer diagnosis was associated with higher levels of pain among cancer patients, compared to former and non-smokers [Daniel, 2009; Florou, 2014]. Previous research studies have identified tobacco addiction to be a risk factor for chronic pain among general population [Shiri, 2010; Sugiyama, 2010]. In fact, patients with chronic pain conditions are thought to be more likely to be dependent on nicotine [Cook, 2007; Plesner, 2016; Bakhshaie, 2016]. A recent Cochrane review was conducted to determine the effect of NRT on postoperative pain [Matthews, 2016]. The authors concluded that based on low quality research data currently available, nicotine may possibly reduce postoperative pain at 24 hours when compared to placebo but its effect was thought to be relatively small [Matthews, 2016]. The authors also determined that nicotine failed to reduce postoperative use of opioids and was more likely to increase presence of nausea [Matthews, 2016]. In conclusion, the current evidence is unclear whether greater levels of pain makes quitting smoking more difficult for cancer patients, or whether the smoking itself is causally associated with increased levels of pain for the patients affected with cancer. Special attention should be given to pain control in cancer patients for improvement in quality of life and to possibly increase the likelihood of smoking cessation.

## 5. Prevention of Relapse

### 5.1 Rates of Relapse and Continued Smoking among Cancer Patients

Approximately 50% of Americans diagnosed with cancer have smoked at some point, and 30% of those with cancer report continued smoking despite the cancer diagnoses being an ideal opportunity for smoking intervention [Ramaswamy, 2016; Gritz, 2006; Tang, 2014; ASCO, 2012]. Continued smoking proportions have been reported as high as 47% at 1-year and 60% at 2-years among cancer survivors [Ramaswamy, 2016; Gritz, 1991; Davison, 1982]. Among the individuals diagnosed with tobacco-related cancers, as many as 86% report quit attempts at the time of diagnosis, but the relapse rates are high (up to 60%) [Simmons, 2013; Ramaswamy, 2016]. For example, 70–86% of patients diagnosed with lung or head and neck cancer quit smoking immediately following their cancer diagnosis, but unfortunately the relapse rate is as high as 50% within the first six months of smoking cessation [Simmons, 2013; Toll, 2013]. These quit rates have not been found to be similar to the rates observed among the general population [Ramaswamy, 2016; Gritz, 1991; Ostroff, 1995; Vander Ark, 1997; Dresler, 1996; Walker, 2004]. According to these recent data, the diagnosis of cancer did not appear to be a significant factor influencing cessation rates, possibly illustrating the generally higher degree of nicotine dependence among cancer patients.

Patients with a tobacco-related cancer diagnosis such as lung and head and neck cancers have been observed to have higher quit rates when compared to patients diagnosed with non-tobacco cancers [Gritz 2007; Schnoll, 2003; Berg, 2013; Bryant, 2016]. In a recent cross-sectional study, Bryant et al. determined that lung cancer patients specifically had up to four times greater odds of quitting smoking than patients diagnosed with other cancer types [Bryant, 2016]. However, patients with tobacco-related cancers also tend to exhibit higher relapse rates [Berg, 2013; [1]Cooley, 2009; Walker, 2006; Schnoll, 2011]. Previous studies have indicated that the timing of smoking cessation intervention is a crucial factor behind successful cessation [Gritz, 2007; Sanderson Cox, 2002; Garces, 2004]. Higher abstinence rates were found for both lung and head and neck cancer patients who received treatment within three months of their diagnosis compared to those who were treated beyond three months post diagnosis [Gritz, 2007; Sanderson Cox, 2002; Garces, 2004].

### 5.2 Factors Associated with Smoking Persistence

The prognosis of smoking cessation varies depending on a number of factors. More salient predictors of failed smoking cessation or relapse include: younger age at which cancer patients started smoking [Waggoner, 2010; Schnoll, 2003, Gritz, 1999], concurrent symptoms or diagnosis of depression [Waggoner, 2010,; Berg, 2013; Pirl, 2004; Boyes, 2011; Martinez, 2009], second hand smoke exposure (e.g. from spouse, home, or workplace) [Waggoner, 2010; Kim, 2015; Kashigar, 2013; Eng 2014], decreased desire to quit [Waggoner, 2010, Schnoll, 2013, Park 2011], and concurrent alcohol use [Kim, 2015; Kashigar, 2013]. Lung cancer survivors exposed to second hand smoke at home were found to have a 6-times greater odds of continued smoking, a 2.5 times greater odds was observed among lung cancer survivors exposed to smoking at work, and a combination of these exposures had an additive effect of 10 times greater odds of continued smoking when compared to the lung cancer survivors without such exposures [Eng, 2014]. Continued smoking following cancer diagnosis has been associated with lower perceived social support and exposure to second hand smoke [Burke, 2009 l Westmass, 2015; Berg, 2013; McBride, 2003]. Many of these aforementioned risk factors of relapse convey similar risks of relapse among non-cancer patients [Yasin, 2012; Lee, 2007; Yang, 2006]. Lung cancer patients who quit smoking more than 6 months prior to their diagnoses were also less likely to relapse than those who quit less than 6 months prior to diagnosis [[1]Cooley, 2009]. Previous quit attempts during the year prior to diagnosis were associated with better quit rates in patients regardless of the cancer type [Wakefield, 2004].

### 5.3 Prevention of relapse

Cancer patients are thought to be at a “teachable moment”, when their cancer diagnosis increases receptivity to health promotion advice [Gritz, 2006; McBride, 2003; ASCO, 2015]. Although the motivation to stop using tobacco may be high initially following a new diagnosis of cancer, the motivation level will fluctuate with time even during the cancer treatment. Given the higher abstinence rates observed among patients who received cessation treatment early (i.e.. within three months of their cancer diagnosis), starting cessation treatment as soon as possible may be critical [Gritz, 2007; Sanderson Cox, 2002; Garces 2004].

Timing of relapse is another important factor to consider with smoking cessation efforts in this population. Generally, relapse among cancer patients tends to be delayed compared to the general population [Gritz, 2014]. It is important to keep in mind that the relapse can occur even after a long period of abstinence. In an observational study by Krall et al., up to a 20% relapse rate over the 20 years of follow-up among patients who had remained abstinent for two years at the start of the study was noted [Krall, 2002]. The majority of the relapse occurred in years 3 to 10 in this cohort. Head and neck cancer patients are expected to show a delay in smoking relapse beyond 1 month of cessation compared to their healthy counterparts who tend to relapse within 1 month of cessation [Gritz, 1993, 1999, & 2000]. Therefore, interventions should be developed and targeted to this critical period of relapse and prolonged for up to a year [Lee, 2008]. Effective relapse prevention strategies should also be identified specific to patients diagnosed with cancer.

Clinicians may be unaware of relapse, and patients may not disclose their smoking behaviors at the time of diagnosis or after surgery, further complicating enrollment and sustainment of smoking abstinence [[1]Cooley, 2009; Chapple, 2004]. Early enrollment in smoking cessation programs has been shown to be essential in the prevention of smoking relapse. Cessation treatment provided closer to the time of diagnosis is associated with greater health benefits such as reduced perioperative morbidity and greater likelihood for continued abstinence [Park, 2011; Dresler, 1996; Garces, 2004; Gritz, 1991; Schnoll, 2003; Cox, 2002]. Furthermore, cancer survivors who continue to smoke seem to need frequent, brief contacts and social support to promote tobacco abstinence, which often exceed USPHS guidelines [Park, 2011]. Therefore, the implementation of evidence-based interventions with frequent and long-term follow-up may help ensure adherence to treatment and increase chance of cessation and abstinence [Warren, 2015].

A recent randomized trial conducted by Donny et al determined that usage of reduced-nicotine cigarettes resulted in significant reductions in smoking and nicotine dependence when compared to the conventional cigarettes use among general population [Donny, 2015]. The authors also observed minimal degree of nicotine withdrawal symptoms when reduced-nicotine cigarettes were used instead of conventional cigarettes with much higher nicotine contents [Donny, 2015]. Reduced-nicotine cigarettes may be beneficial for cancer patients to treat symptoms of nicotine withdrawal which may be stronger when compared to the general population.

Home environment is both critical for sustained abstinence from smoking and a fertile ground for further intervention. Targeting smoking cessation efforts towards household members and spouses may benefit both family members and the patient. Relatives of lung cancer patients have been described as receptive to discussing smoking cessation [Butler, 2011]. Indeed, Patterson et al. determined that the perceived risk of individuals with a family member with cancer was increased and these individuals were 36% more likely to report an intention to quit than individuals without a family member with a cancer diagnosis [Patterson, 2010]. In addition, Schnoll et al. examined if a cancer diagnosis, vs. orthopedic surgery, could serve as a teachable moment for recruiting smokers and treating nicotine dependence among cancer patient relatives [Schnoll, 2013]. As predicted, relatives of oncology patients were significantly more likely to enroll in the smoking cessation program

when compared to orthopedic patients' relatives. However, contrary to expectations, oncology patients' relatives were not significantly more likely to remain in the program or quit smoking when compared to the orthopedic patients' relatives. The authors determined that relatives of oncology patients exhibited significantly greater levels of depression and anxiety symptoms, which are barriers to cessation [Berg, 2013; Pratt, 2010]. Therefore, attention to address possible psychological distress symptoms among relatives of oncology patients may also be beneficial for smoking cessation. An approach to smoking cessation that is inclusive to the cancer survivors' family members may increase not only the cancer survivors' chance of cessation but may also benefit the health of the family members and the public.

## 6. Patients' Barriers to Access to Treatment

Cancer patients need to overcome many barriers for successful smoking cessation. Enrollment in cessation programs has been shown to be hindered by various factors such as medical contraindication to pharmaceutical intervention, lack of interest, and language barriers [Martinez, 2009]. Additionally, it has been postulated that perception of disease course and severity play large roles in severity of depressive symptoms, self-efficacy, and perceived benefit of quitting smoking among cancer patients [Martinez, 2009]. Motivation to quit has been associated with elevated self-efficacy, perception of risk, perceived benefits of cessation, lower tobacco use and level of addiction, and more recent diagnosis [Miller, 2002; Lindson-Hawley, 2015; Schnoll, 2004]. According to the 2005 National Health Interview Survey, among cancer patients who had attempted to quit within the previous year, only 3.8% used evidence-based behavioral treatment and 33.5% used pharmacotherapy [Coups, 2009]. This current situation can be improved by developing and implementing simple motivational techniques among health care providers in oncology settings or by implementing systems to identify current tobacco users among cancer survivors (see [2]Warren et al., 2014).

## 7. Barriers to Delivery of Treatment in the Clinical Setting

Many practical and perceived barriers to smoking cessation may hinder a provider's intervention efforts. Lack of time has often been cited as a principal barrier to in-office smoking cessation interventions [Shields, 2015; Warren, 2015; Morgan, 2011]. Survey-based studies previously illustrated that only between 50% and 72% of cancer patients had been advised to quit smoking at some point during their treatment [Ramaswamy, 2016; Coups, 2009; Burke, 2009] and only 44% of patients' expressed being informed of the additional dangers of smoking with a concurrent cancer diagnosis [Burke, 2009]. Lack of available smoking cessation resources and dedicated staff are a common obstacle along with perceived complexity of interventions [Warren 2015; Morgan, 2011; Shields, 2015]. These factors possibly feed into the perception that there is little benefit to smoking cessation and little consequence of continued tobacco use among cancer patients who continue to smoke, especially among those with advanced disease [Westmaas, 2015; Martinez, 2009; McBride, 2003].

Clinicians may be aware of the practice guidelines on smoking cessation treatment for cancer patients but are often unable to follow the recommendations due to the following barriers and challenges. Various factors such as inadequate time and resources dedicated to smoking cessation in cancer patients, low provider reimbursement for cessation treatment, a lack of expertise and training prevent clinicians from addressing smoking cessation [Shields, 2015; Warren, 2015; Morgan, 2011; Toll, 2013; Warren, 2013; Shelley, 2012; Frazier, 2001]. Although the provider reimbursement for offering smoking cessation have improved over the past decade largely for the medical settings [McMenamin, 2008], it is still perceived to be low and inadequate especially for providers running a busy practice. This perception of poor incentives is further complicated by the significant deficiency of the providers in the knowledge of smoking cessation treatment [Bjurlin, 2010; Toll, 2013; [2]Cooley, 2009; Toll, 2013]. Specific training and education on the importance of smoking cessation for cancer patients is also demonstrated in the lack of content not only in the medical school and residency training curriculums but also in oncology professional examinations and education [Frazier, 2001; Morgan, 2011]. This educational gap possibly feeds a misguided perception that physician intervention is not efficacious [Shields, 2015; Toll, 2013; Warren, 2013], although evidence indicates that even brief advice from physicians is effective in promoting smoking cessation [Stead, 2008]. Furthermore, fear of increasing patient stress [Lina, 2016] and patient resistance to intervention [Toll, 2013; Warren, 2013] have also been cited as barriers to delivery of smoking cessation intervention by clinicians. Given these significant barriers, the practice guidelines may unfortunately be inadequate and ineffective in real-world clinical settings.

Improvement of the providers' knowledge on tobacco cessation treatment alone may be insufficient at improving effective delivery and access to smoking cessation treatment given the practical barriers mentioned above. To diminish the impact of clinic and patient-level barriers, Vidrine et al. suggested a new approach to smoking cessation treatment delivery called Ask Advise and Connect (AAC) [Vidrine, 2013]. In this method, nurses and medical assistants were trained to determine current tobacco use at every patient visit and briefly advised patients who were active smokers to quit. If the patients showed willingness to receive treatment, an automatic connection to the quitline was provided via the electronic health record (EHR). The quitline would then actively contact the patients for counseling and treatment. The authors determined that the AAC approach resulted in a 13-fold increase in enrollment when compared to the recommended 5As approach where the patients are simply provided with information on available resources [Vidrine, 2013]. This method would indeed shift the burden away from the providers who have cited lack of time as the main barrier to offering smoking cessation [Shields, 2015; Warren, 2015; Morgan, 2011] and may be a convenient and cost-effective approach for institutions who are using an EHR system.

Transitions to care from inpatient to outpatient, family involvement, and follow-up visits have also been suggested as underused intervention opportunities [McBride, 2013]. In a recent study of NCI Cooperative Group trials only 5% collected data on tobacco use at follow-up [Toll, 2013; Peters, 2012]. The lack of data from these trials on tobacco use indicates a failure to quantify the effect and potential confounding of tobacco use in cancer patients participating in clinical trials [Toll, 2013]. Incorporation of the new guidelines and

recommendations into clinical oncology practice and research may fill in these gaps as they stress the importance of close follow-up, adequate documentation, and using variety of resources for patients and providers [Shields, 2015]. Dedicated resources, continual assessment, incorporating multi-lingual approaches, better referral mechanisms, improving provider incentives and addressing gaps in education on the importance of smoking cessation and resources available will result in the improvement of provider adherence to clinical treatment guidelines and will ultimately increase provision of evidence-based cessation interventions for cancer patients [Martinez, 2009; Warren, 2015; Morgan, 2011].

## 8. Expert commentary

The number of new cancer cases in the United States is expected to increase to roughly 1.9 million cases per year by 2020 [CDC, New Cancer Cases]. Although the overall cancer incidence rates are expected to remain stable, the increasing aging white population and a growing black population are thought to be the key factors behind this expected increase in cancer diagnosis [CDC, New Cancer Cases]. Because the majority of cancer patients are expected to survive longer after the cancer diagnosis due to early disease detection and improved treatment, the projected number of cancer survivors by the year 2020 is approximately 18 million, which is an over 50% increase in the number of cancer survivors in 2007 [CDC, New Cancer Cases; Demark-Wahnefried, 2008]. It is imperative for public health professionals to understand the importance of disease prevention and health promotion behavior and education for cancer patients and survivors. Smoking cessation and relapse prevention are essential to improving the likelihood of cancer treatment success and quality of life [Karam-Hage, 2014].

Despite the clear treatment recommendations set by the recent guidelines [NCCN, 2015], very few smoking cessation interventions have been tested to determine the efficacy among patients diagnosed with cancer. The recommendations were derived from the efficacy trials performed mostly in the general population who may have different characteristics such as the level of nicotine dependence, readiness to quit and medical comorbidities than cancer patients. Further research is needed to determine the most effective evidence-based smoking cessation intervention that is specific to this highly vulnerable patient population.

In order to improve the quality of smoking cessation research among cancer patients, a comprehensive and repetitive documentation of tobacco use has been strongly advocated by the previous AACR Policy Statement and the NCI-AACR Task Force recommendations [Toll, 2013; Land, 2016]. In the policy statement, Toll et al. advocate the frequent assessment of tobacco use and its documentation for all cancer patients regardless of their clinical trial participation status [Toll, 2013]. In the recent recommendations by the NCI-AACR Task Force, Land et al. recommend a standardized timing of tobacco use assessment [Land, 2016]. At a minimum, the Task Force advocates tobacco use assessment be done at the study or patient registration and at the end of protocol therapy [Land, 2016]. Additional recommended time points for tobacco use assessments are: immediately before or after cancer surgery, day 1 of every chemotherapy cycle, beginning and end of radiotherapy, beginning and end of other systemic therapy, or monthly. The Task Force also recommends that the assessments be done at 6 to 12 months after the end of therapy [Land, 2016].

Standardized, valid and reliable approaches to tobacco use measurement in clinical trials and the oncology setting would help to improve our knowledge of cancer treatment toxicity, disease progression and prognosis, the impact of cessation on these factors, as well as on survival outcomes. It would also allow data pooling and comparison between different patient populations.

All providers involved in the care and management of cancer patients are encouraged to advocate smoking cessation [NCCN, 2015; ASCO, 2012]. However, given the various challenges and barriers such as lack or paucity of resources, the providers may not be able to offer evidence-based smoking cessation assistance despite their interests and efforts. If the assistance and recommended treatment cannot be provided within the oncology practice setting, then all efforts should be made to provide patients resources such as toll-free quitlines that are available in all 50 states [Toll, 2013].

There are very little data on the use of e-cigarettes in the treatment of smoking cessation among cancer patients. Providers should be aware that electronic nicotine products are not regulated and their safety and efficacy has not been tested and therefore unknown [Harrell, 2014]. Thus far, a single study looked into the impact of electronic cigarettes (e-cigarettes) for the treatment of smoking cessation for head and neck cancer patients [McQueen, 2016]. The authors determined that the use of e-cigarettes has not decreased tobacco use among head and neck cancer patients and the patients using e-cigarettes were less likely to achieve smoking cessation [McQueen, 2016]. The evidence is still lacking on the effectiveness of e-cigarettes in the treatment of smoking cessation, and further research is required to determine its efficacy for patients diagnosed with cancer desiring to quit smoking.

It can be challenging for providers without dedicated tobacco treatment specialists to offer a comprehensive treatment approach for smoking cessation treatment given the numerous barriers discussed above. However, the evidence shows that even an intervention from a clinician that is as brief as 3 minutes can be effective at motivating patients to stop smoking [Raw, 1999] and the AAC model can identify smokers and substantially increase treatment engagement. Therefore, providers are encouraged to mention the topic of smoking cessation during each visit at the very least to increase the likelihood of success for their patients.

In summary, smoking cessation is a critical component of treatment for patients diagnosed with cancer. While there are areas of improvement in the research of smoking cessation for cancer patients, the authors recommend that providers adhere to the NCCN guidelines and offer a brief counseling intervention to motivate patients to quit smoking when appropriate resources are not available.

## 9. Five Year View

A priority for the coming years is the implementation of clinical trials focusing on the effectiveness of smoking cessation treatments targeting cancer patients. There has been more interest in determining the effects of genetic factors and the role of pharmacogenetics in the individualized treatment especially among a high nicotine dependence patient population. More research is warranted to determine novel treatment approaches in order to identify the

most effective, evidence-based treatment approach specific for patients diagnosed with cancer. Furthermore, there is a deficit in the current literature on the effectiveness of smoking cessation treatment on the survival for advanced stage cancer patients and its impact on their quality of life. Given the lack of data, the NCCN and ASCO guidelines do not offer any specific advice or recommendations on the influence of the cancer stage when approaching smoking cessation. Further research needs to be done to determine the impact of smoking cessation on the prognosis, survival and quality of life especially for the patients diagnosed with end-stage cancer. Additional research would help us determine a tailored, individualized management approach to smoking cessation based on the cancer stage that takes into account of the patient's autonomy and quality of life.

Furthermore, there is a deficit in our knowledge on how to effectively approach patients who are active smokers and who are not interested in cessation treatment despite their cancer diagnosis. Clinical trials to determine effective methods for addressing this vulnerable population to increase willingness to quit are much needed. For example, a trial of NRT and/or reduced-nicotine cigarettes similar to the ones performed by Becker et al and Rose et al may be an interesting clinical study to determine whether these methods could successfully increase cessation rates among cancer patients who are not interested in quitting smoking [Becker, 2008; Rose, 2006]. Furthermore, clinical trials looking into some of the novel treatment tools for smoking cessation, such as cytisine and e-cigarettes, should be considered. More research looking into the ideal concentration levels of nicotine in e-cigarettes and its safety and effectiveness for smoking cessation treatment should be entertained.

Additionally, our knowledge on possible associations between level of nicotine dependence and the duration of relapse as well as the ideal duration of therapy for cancer survivors is currently lacking. More clinical trials are needed to determine the ideal duration of treatment especially for the pharmacotherapy for cancer patients and survivors. Further research should also focus on the cost-effectiveness of smoking cessation treatment for cancer patients which may encourage institutions to invest more in smoking cessation programs especially in the setting of oncology practices.

More novel methods to improve smoking cessation among cancer patients are needed. Various health communication methods such as warning labels and advertisements, larger-scale distribution of free NRT, mHealth and text-messaging, and family-based interventions should be tested to determine their effectiveness to increase cessation among cancer patients. Additionally, public health research on reduced-nicotine cigarettes targeting cancer patients may be beneficial to determine its efficacy.

## 10. Key issues

- Tobacco has been causally linked to over fourteen cancers and numerous chronic conditions.
- There is evidence to support improvement in diagnosis and treatment outcomes with smoking cessation among cancer patients.

- Despite the harmful effects of smoking during and following cancer treatment, many patients continue to smoke. Nicotine dependence is often strong for patients diagnosed with cancer and is therefore more challenging to treat as compared to the general population.
- The National Comprehensive Cancer Network (NCCN) issued a new set of Clinical Practice Guidelines in Oncology in 2015 for smoking cessation treatment targeting patients diagnosed with cancer. The guidelines recommend an individualized approach to evidence-based treatment for smoking cessation which consists of combination pharmacotherapy and behavioral therapy. The first-line treatment is combination nicotine replacement therapy or nicotine receptor agonist (varenicline) for a duration of 12 weeks with a minimum of 4 individual or group behavior therapy sessions. Close monitoring and frequent follow-up is strongly recommended during the treatment period.
- Standardized tobacco use measurement is strongly recommended by the National Cancer Institute (NCI) and the American Association for Cancer Research (AACR) for clinical research related purposes to improve the quality of research on smoking cessation treatments. The readiness to quit and current tobacco use should be assessed and documented at each visit. At a minimum, the Task Force advocates tobacco use assessment be done at the registration and at the end of therapy.
- There are many practical and perceived barriers to smoking cessation. Some of the most commonly cited barriers are the lack of the following: time, available smoking cessation resources and education on smoking cessation treatment. Dedicated resources, continual assessment, incorporating multi-lingual approaches, better referral mechanisms, improvement in provider reimbursement and addressing gaps in provider education on smoking cessation are needed. All patients should be provided at minimum easily accessible resources such as toll-free quitlines that are available in all 50 states.
- There is currently a lack of clinical research dedicated to smoking cessation treatment specific for cancer patients. More research is needed to determine the most efficacious and effective evidence-based treatment for this population. Some of the recommended topics for future research are: determining the ideal duration of cessation treatment, effective treatment modalities for cancer patients who are not willing to quit, pharmacogenetics, the impact of cessation on prognosis and clinical outcomes, public health research to promote primary and tertiary preventions, and the cost-effectiveness of the cessation treatment for cancer survivors.

## Acknowledgments

**Funding**

Support for this manuscript was provided by National Cancer Institute grants R01 CA184211 and R01 CA165001.

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*-Papers of interest

**-Papers of considerable interest


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**Table 1**

Selected published studies on behavioral therapy for smoking cessation for cancer patients.

| Author(s), year | Study Design | Sample size, Type of cancer | Intervention(s) | | Mean followup | Confirmation of non-smoking status | Results |
|---|---|---|---|---|---|---|---|
| | | | Behavioral | Pharmacological | | | |
| Gritz et al. 1993 | RCT | N = 186, Head and neck squamous cell carcinoma | Educational material to both the patient and his/her family member/caretaker, reminder postcards, abstinence contract; 7 counseling sessions (monthly meeting) by provider (physician or resident), quit date and tobacco journal vs usual care | None | 12 months | Cotinine (urine, < 50ng/ml) | No significant difference in the abstinence rates between the intervention vs usual care groups (63.8% vs 76.8%). |
| Stanislaw et al. 1994 | RCT | N = 26, Head and neck (80%), breast (8%), prostate (8%), cervical (4%) | Nurse-delivered intervention during post-operative period in surgical oncology unit;3 consecutive daily 20–30-minute counseling sessions followed by five weekly calls post-discharge. Additional educational material provided vs usual care | None | 5 weeks | Cotinine (saliva, <10 ng/ml) | 75% of intervention vs 43% of usual care group patients abstinent ($x^2$=2.735, df=1, p<0.10). |
| Wewers et al. 1994 | RCT | N = 80 (*n=30 with the following cancer diagnosis: head and neck (83.3%), breast (6.7%), prostate (6.7%), cervical (3.3%) | Nurse-delivered intervention consisting of 3 consecutive 20–30-minute counseling sessions followed by five weekly calls post-discharge. Additional educational material provided vs usual care | None | 5–6 weeks | Cotinine (saliva, <10ng/ml) | Significant difference in the abstinence rates between the intervention and the usual care groups (64.3% vs 50.0%), respectively. |
| Wewers et al. 1997 | Prospective, descriptive (cohort) | N = 15, Lung cancer | Nurse-delivered counseling sessions (3 daily sessions during hospitalization followed by 5 weekly sessions via telephone), provision | None | 6 weeks | Cotinine (saliva, < 14 ng/ml) | 40% abstinence rate |

| Author(s), year | Study Design | Sample size, Type of cancer | Intervention(s) | | Mean followup | Confirmation of non-smoking status | Results |
|---|---|---|---|---|---|---|---|
| | | | Behavioral | Pharmacological | | | |
| | | | of educational material, | | | | |
| Griebel et al. 1998 | RCT | N = 28, Gynecologic (21%), breast (18%), Gastrointestinal (14%), thoracic (14%), urologic (14%), neurologic (11%), head and neck (7%) | Nurse-delivered, one-time 20 minute counseling, provision of educational material and free community smoking cessation resources; followed by short five weekly calls vs usual care | None | 6 weeks | Cotinine (saliva <or= 14ng/ml) | No significant difference in the abstinence rates between the intervention vs usual care groups (21% vs 14%). |
| Smith et al. 2002 | Prospective, descriptive (cohort) | N = 124, Type of cancer not specified | Nurse-delivered counseling sessions during hospitalization followed by 4 additional counseling telephone sessions post-discharge with additional education material | NRT if indicated | 12 months | None | 43% (intention to treat) cessation rate observed among cancer patients. |
| Schnoll et al. 2003 | RCT | N = 432, Stage I–II of any cancer or Stage III–IV breast, prostate, testicular cancer or lymphoma | Physician-based intervention quit advice and assistance (motivational interviewing, counseling, provision or educational booklet, referral to a cessation program and/or to 1-800-4-CANCER QL - i.e. the 5As model) vs usual care | NRT if indicated | 6 and 12 months | None | At 6-month follow-up, 14.4% of intervention vs 11.9% of the usual care group patients reported abstinence. At 12-month follow-up, 13.3% of intervention vs 13.6% of usual care group patients reported abstinence. No significant difference in quit rates observed at 6- and 12-month follow-ups. |
| Wakefield et al. 2004 | RCT | N = 137, Lung (12%), head and neck (17%), bladder (2%), breast (13%), prostate (9%), colon (10%), leukemia (10%), lymphoma (15%), testicle (4%), others (8%) | Motivational interviewing, counseling, provision or educational booklet; additional assistance (referral to a cessation program and/or to 1-800-4-CANCER QL (i.e. the 5A model) vs usual care | NRT if indicated | 6 months | Cotinine (urine sample, <400 nmol/mmol) or carbon monoxide (CO) breath monitoring. | No significant difference in the abstinence rates between the intervention vs usual care groups (7% vs 6%). |

| Author(s), year | Study Design | Sample size, Type of cancer | Intervention(s) | | Mean followup | Confirmation of non-smoking status | Results |
|---|---|---|---|---|---|---|---|
| | | | Behavioral | Pharmacological | | | |
| Schnoll et al. 2005 | RCT | N = 109, Lung (65.5%), Head and neck (34.5%) | Four counseling sessions (one in-person, three over the phone) consisting of cognitive behavioral therapy (CBT) based on self-efficacy and risk perception vs usual care | NRT (nicotine patch) for 8 weeks (for both intervention and usual care arms) | 1 and 3 months | None | No significant difference in the abstinence rates between the intervention vs usual care groups at 3 months (43.2% vs 39.2%). |
| Duffy et al. 2006 | RCT | N = 184, Head and neck (61% of the patients had Stage III/IV disease) | Nurse-delivered, 9 to 11 CBT telephone sessions with provision of educational material vs usual care | As needed (NRT +/− bupropion (150mg BID)) | 6 months | None | Significant difference in the abstinence rates between the intervention vs usual care groups (47% vs 31%) ($p<0.05$). |

*Expert Rev Qual Life Cancer Care*. Author manuscript; available in PMC 2018 January 01.

**Table 2**

Selected published studies on pharmacotherapy for smoking cessation for cancer patients

| Author(s), year | Study Design | Sample size, Type of cancer | Intervention(s) | | Mean follow-up | Confirmation of non-smoking status | Results |
|---|---|---|---|---|---|---|---|
| | | | Behavioral | Pharmacological | | | |
| Browning et al. 2000 | Quasi-experimental | N = 25, Non-small cell lung cancer | Nurse-delivered, 8 AHCPR-based (the 4 A's approach) counseling sessions – 3 during hospitalization and 5 post-discharge - provision of educational material, additional contacts by a clinician on the set quit date and two weeks following the quit date vs usual care | NRT (8 weeks) and bupropion (7 weeks) | 6 months | CO breath monitoring (< or = 8 ppm) | 71% and 55% abstinence rates seen in the intervention and usual care groups, respectively. Not statistically significant. |
| Schnoll et al. 2010 | RCT | N = 246, Lung/Head and Neck (35%), Breast (21%), prostate (15%), lymphoma (9%), colorectal (5%), kidney/ pancreas/liver (4%), genitourinary (3%), esophageal (3%), Others (5%) | All patients received 5 counseling sessions | Bupropion vs placebo for 9 weeks (all patients received 8 weeks of NRT) | 3 and 6 months | CO breath monitoring (abstinence <or =10 ppm) | No significant difference in the abstinence rates between the intervention vs the control groups at 6 months (18.4% vs 17.4%). |
| Thomsen et al. 2010 | RCT | N = 130, Breast cancer only | One 45–90 minute motivational counseling vs usual care | NRT to intervention group only (given perioperatively) | 10 days and 12 months post-operatively and 12 | CO breath monitoring (*only at 10 days post-operatively) | Significant difference in the abstinence rates between the intervention vs usual care groups (28% vs 11%) at 10 days following surgery, but no statistically significant difference seen in both groups at 12-month follow-up (13% vs 9%). |
| Park et al. 2011 | Cohort | N = 432, Suspected diagnosis of thoracic cancer | The 5 As, motivational sessions (7) | Varenicline | 12 weeks | Cotinine (saliva, < 15 ng/ml) | 28.1% and 14.3% abstinence rates in the intervention and the control groups, respectively. Not statistically significant. |
| Price et al. 2016 | Cohort | N = 132, Genitourinary (24.2%), Breast (20.5%), Lung (15.2%), Skin (11.4%), Hematological (10.6%), Head and neck (6.8%), Gastrointestinal | 5 brief counseling cessions | Varenicline | 12 weeks | CO breath monitoring (<10 ppm) | 40.2% abstinence |

| Author(s), year | Study Design | Sample size, Type of cancer | Intervention(s) | | Mean follow-up | Confirmation of non-smoking status | Results |
|---|---|---|---|---|---|---|---|
| | | | Behavioral | Pharmacological | | | |
| | | (6.1%), Kidney/ Pancreas/Liver (5.3%) | | | | | |

**Table 3**

Selected published studies on system-based interventions for smoking cessation for cancer patients

| Author(s), year | Study Design | Sample size, Type of cancer | Intervention(s) | | Mean follow-up | Confirmation of non-smoking status | Results |
|---|---|---|---|---|---|---|---|
| | | | **Behavioral** | **Pharmacological** | | | |
| Ostroff et al. 2014 | RCT | N = 185, Lung (30%), Head and neck (9%), Breast (12%), Gynecology (12%), Urology (20%), Other (17%) | Five individual counseling sessions to all patients ("best practices only" group); the intervention arm also received the five counseling sessions PLUS a handheld electronic device ("QuitPal") for administration of Scheduled Reduced Smoking program | NRT offered to all patients | 3 and 6 months | Cotinine (saliva, < 15ng/ml) and CO breath test (< 10 ppm) | Similar abstinence rates observed in both groups (34% and 36% at 3 months; 32% for both groups at 6 months). (p>0.05) |
| [1]Warren et al. 2014 | Cohort | N = 2765 | Automatic referral to a tobacco cessation service generated by EHR screening system; motivational counseling offered to patients | Appropriate pharmacotherapy given | N/A | N/A | EHR can be used to identify a substantial number of smokers who are receptive to receive cessation treatment |
| Klesges et al. 2015 | RCT | N = 427, Any histologic subtype | Proactive (counselor-initiated, 6 counseling sessions over 8 weeks) vs Reactive (participant-initiated: participants were asked to call the QL (1.877.4SJ.QUIT) up to 6 times over 8 weeks) | Proactive: given up to 7 weeks of nicotine patch if eligible at no cost vs Reactive: given two weeks of free nicotine patch ("starter kit") and the patients were encouraged to purchase more patches afterwards at a discounted rate | 12 months | Cotinine (saliva, < 3 ng/ml) | No significant difference in the point prevalence abstinence for proactive and reactive groups (22% vs 26%). |