National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Smoking Cessation

Version 2.2017 — August 21, 2017

NCCN.org

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017 Panel Members
Smoking Cessation

NCCN Guidelines Index
Table of Contents
Discussion

* Peter G. Shields, MD/Chair †
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

* Roy S. Herbst, MD, PhD/Vice Chair †
Yale Cancer Center/
Smilow Cancer Hospital

Douglas Arenberg, MD Ξ
University of Michigan
Comprehensive Cancer Center

Neal L. Benowitz, MD Þ Σ
UCSF Helen Diller Family
Comprehensive Cancer Center

Laura Bierut, MD θ Σ
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Julie Bylund Luckart, APRN, AOCN, FNP #
Huntsman Cancer Institute
at the University of Utah

Paul Cinciripini, PhD θ
The University of Texas
MD Anderson Cancer Center

Bradley Collins, PhD θ
Fox Chase Cancer Center

Sean David, MD, SM, DPhil Σ Þ
Stanford Cancer Institute

James Davis, MD Þ
Duke Cancer Institute

Brian Hitsman, PhD θ
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Andrew Hyland, PhD θ
Roswell Park Cancer Institute

Margaret Lang, MSN #
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Scott Leischow, PhD θ
Mayo Clinic Cancer Center

* Danielle McCarthy, PhD θ
University of Wisconsin
Carbone Cancer Center

* Elyse R. Park, PhD, MPH θ
Massachusetts General Hospital
Cancer Center

W. Thomas Purcell, MD, MBA †
University of Colorado
Cancer Center

Jill Selzle, MD ¶
Fred & Pamela Buffett Cancer Center

Andrea Silber, MD †
Yale Cancer Center/
Smilow Cancer Hospital

Sharon Spencer, MD §
University of Alabama at Birmingham Comprehensive Cancer Center

Tawee Tanvetyanon, MD, MPH †
Moffitt Cancer Center

Brian Tiep, MD Ξ
City of Hope Comprehensive Cancer Center

Hilary A. Tindle, MD, MPH Þ
Vanderbilt-Ingram Cancer Center

Reginald Tucker-Seeley, MA, ScM, ScD θ
Dana-Farber/Brigham and Women`s Cancer Center

James Urbanic, MD §
UC San Diego
Moores Cancer Center

Monica Webb Hooper, PhD
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Benny Weksler, MD, MBA¶
The University of Tennessee
Health Science Center

C. Will Whitlock, NP, RN # θ
Memorial Sloan Kettering
Cancer Center

Douglas E. Wood, MD ¶
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

NCCN
Jennifer Burns
Jillian Scavone, PhD

[NCCN Guidelines Panel Disclosures]

Continue

Þ Internal medicine
† Medical oncology
¶ Surgery/Surgical oncology
§ Radiotherapy/Radiation oncology
# Nursing
θ Psychiatry/Psychology/Behavioral science
Ξ Pulmonary medicine
Σ Pharmacology/Pharmacogenetics
* Discussion Writing Committee Member

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017 Table of Contents
Smoking Cessation

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017 Updates Smoking Cessation

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 2.2017 of the NCCN Guidelines for Smoking Cessation from Version 1.2017 include:

MS-1

- The Discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 1.2017 of the NCCN Guidelines for Smoking Cessation from Version 1.2016 include:

INTRO

- Addition to third sentence: "It is never too late for patients with cancer to stop smoking cigarettes *and experience health benefits*."
- Clinical recommendations, the last line has been added to the second sub-bullet under the first bullet: "Quitlines may be used as an adjunct, especially in lower-resource settings."
- Footnote "a" added: "Combination NRT = Nicotine patch + short-acting NRT (ie, lozenge, gum, inhaler, nasal spray) for cravings."

SC-1

- Defined long-term former smoker as someone who last smoked ≥1 year ago.

SC-2

- Revised first sub-bullet under nicotine dependency evaluation: "*What is the typical amount you smoked per day within the last 3 months?* ~~, and what is the maximum you ever smoked in a day?~~"
- Management for those not ready to quit within 4 weeks, second bullet revised: "*Consider smoking reduction with a goal of* set*ting* a quit date *in the near future.* Encourage immediate initiation of pharmacotherapy for targeted reduction of cigarettes per day ~~with a goal of cessation in the near future~~."
- Footnote "f" added: "For lung cancer screening recommendations, see NCCN Guidelines for Lung Cancer Screening."

SC-3

- Second bullet revised under management for ≥1 risk factor: "Consider ~~NRT~~ *pharmacotherapy* as clinically indicated to maintain abstinence."
- Footnote "p" added: "When considering pharmacotherapy maintenance options for patients who have been nicotine free for an extended period of time (eg, 30 days or longer), carefully consider the potential effects of re-introducing nicotine through NRT or advocating for the use of combination NRT."

SC-4

- Page heading revised: General Approach to Smoking Cessation For Patients with Cancer and Survivors ~~During Cancer Treatment~~". (Also for SC-5)
- Assessment/follow-up schedule revised: " Within ~~2-~~3 wk after therapy begins *(within 1 wk preferred*) and ~~Following~~ *At* 12 wk ~~of therapy and At end of therapy, if past 12 wk~~." (Also on SC-5)
- After smoke-free
  - Second bullet added: "Extend duration of pharmacotherapy as clinically indicated (ie, > 6 months)." (Also on SC-5)
  - Third bullet revised: "Reassess smoking status *at the end of therapy (if past 12 wk) and* at 6 & 12 mo after therapy."
- Footnote removed: "Therapy may be extended to promote continued cessation (ie, 6 mo–1 y) while attempting to avoid longer periods of time if possible." (Also on SC-5)
- Footnote "w" revised: "Nicotine withdrawal symptoms typically peak within 1–2 weeks of quitting. ~~Encourage continued therapy through brief slips.~~ Patients who do not quit immediately may quit at some later point after withrawal symptoms subside; therefore, encourage continued therapy through brief slips." (Also on SC-5)

SC-5

- Options in first column revised:
  - *Evaluate use of* combination NRT + behavior therapy *if r*elapse or continued smoking ~~following primary therapy with~~."
  - *Evaluate use of* varenicline + behavior therapy *if r*elapse or continued smoking ~~following primary therapy with~~."
- "Sustained released" added where bupropion is listed.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017 Updates Smoking Cessation

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2017 of the NCCN Guidelines for Smoking Cessation from Version 1.2016 include:

SC-A

- Second bullet added: "For patients who are unable or unwilling to quit, one potential strategy is smoking reduction with a goal of quitting. (See SC-2)"
- Third bullet revised: "Encourage the use of evidence-based cessation methods to avoid delays in achieving abstinence. *For patients using alternative approaches, including electronic cigarettes, continue to provide support during quit attempts.* ~~Continue to work with patients who are already using Encourage the use of evidence-based cessation methods to avoid delays in achieving abstinence.~~"

SC-B (1 of 2)

- Under providers should, last two sub-bullets added:
  - "Discuss smoking cessation with all patients who smoke. Patient satisfaction is enhanced when smoking cessation is offered by providers."
  - "Encourage smoking cessation for all members of the household for the benefit of the patient."
- Third bullet under treatment-specific risks, third sub-bullet revised: Increased infection rates, *cardiovascular and* pulmonary complications..."
- Under potential nicotine effects:
  - Following line removed from first bullet: "The use of combination NRT as one type of pharmacotherapy is recommended."
  - Third bullet revised: "~~While myocardial infarction has rarely been reported in NRT users,~~ There is insufficient evidence that NRT increases the risk of myocardial infarction or cardiovascular disease."

SC-C

- Smoking cessation resources have been significantly revised and reorganized. Resources for patients are on SC-C (1 of 2). Resources for health professionals are on SC-C (2 of 2).

SC-D

- Third bullet revised: "Smokers who have planned cancer surgery should be encouraged to quit smoking as soon as possible *before surgery, regardless of how short the time to surgery is. There is no evidence to support delaying a quit attempt at anytime prior to surgery."*

SC-E

- Significantly revised third bullet and content on motivational counseling.

SC-F (1 of 2)

- Revised third bullet for preferred primary therapy options: "*For* patients who continue to smoke or experience relapse, *evaluate use of current therapy and consider* ~~may~~ continu*ing* or resum*ing* the initial pharmacotherapy, or switch to the other primary therapy option before trying the subsequent therapy options."
- Added "sustained release" to bupropion.

SC-F (2 of 2)

- Revised standard dose information for combination NRT:
  - *Begin with* 21 mg patch + short-acting NRT
  - If 21 mg patch is not effective, consider *using more than one patch to* increase the dose to 35 or 42 mg
  - *Short-acting NRT as needed, every 1–2 hours for cravings*
- Added to combination NRT adverse effects: "Patients commonly under-dose when using combination NRT. Nicotine overdose is rare, but possible and usually short-lived."
- Added footnote "d": "Gradually decrease dose over 10 weeks or more. Dose reduction may not be appropriate for patients with limited life expectancy."
- Replaced links to drug label information with the following footnote: "For drug labels and full prescribing information for varencline, buproprion, and NRT products, refer to the National Institutes of Health website at https://dailymed.nlm.nih.gov/dailymed."

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GENERAL PRINCIPLES OF THE SMOKING CESSATION GUIDELINES

These guidelines are focused on smoking cessation recommendations for patients with cancer. There are health benefits to smoking cessation even after a cancer diagnosis, regardless of stage or prognosis, namely improvement in cancer treatment outcomes, disease recurrence, and secondary cancers. It is never too late for patients with cancer to stop smoking cigarettes and experience health benefits. Smoking and nicotine addiction is a chronic relapsing disorder. Patients may slip or relapse, which is expected and can be managed. Smokers with cancer often demonstrate high-level nicotine dependence. The NCCN Panel recommends that treatment plans for all smokers with cancer include the following:

- **Evidence-based motivational strategies and behavior therapy,**
- **Evidence-based pharmacotherapy, and**
- **Close follow-up with retreatment as needed.**

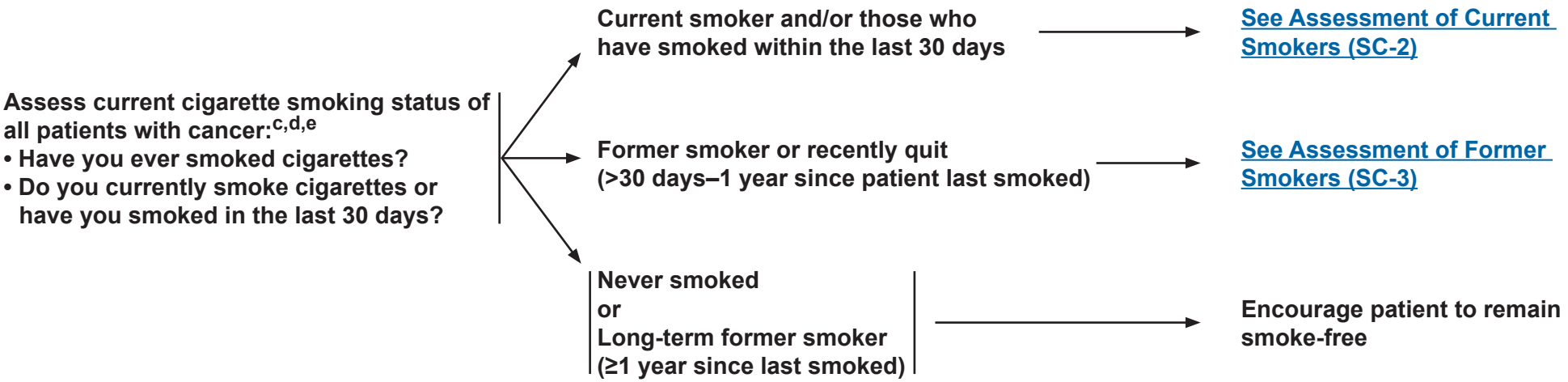
Clinical Recommendations:

- **Combining pharmacologic therapy and behavior therapy is the most effective approach and leads to the best results for smoking cessation.**
  - **The two most effective pharmacotherapy agents are combination nicotine replacement therapy[a] (NRT) and varenicline.**
  - **High-intensity behavior therapy with multiple counseling sessions is most effective, but at least a minimum of brief counseling is highly recommended. Quitlines may be used as an adjunct, especially in lower-resource settings.**
- **Smoking status should be documented in the patient health record. Patient health records should be updated at regular intervals to indicate changes in smoking status, quit attempts made, and interventions utilized.**
- **Smoking relapse and brief slips are common. Providers should discuss this and provide guidance and support to encourage continued smoking cessation attempts. Smoking slips are not necessarily an indication to try an alternative method. It may take more than one quit attempt with the same therapy to achieve long-term cessation.**
- **Smoking cessation should be offered as part of oncology treatment and continued throughout the entire oncology care continuum, including during end-of-life care. An emphasis should be put on patient preferences and values when considering the best approach to fostering smoking cessation during end-of-life care.**

[a]Combination NRT = Nicotine patch + short-acting NRT (ie, lozenge, gum, inhaler, nasal spray) for cravings.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

EVALUATION AND ASSESSMENT OF PATIENT SMOKING[b]



[b]Recommendations in this guideline apply to cessation of cigarette smoking. Patients with cancer should be encouraged to discontinue the use of all combustible products (eg, cigars, hookah, marijuana) and smokeless tobacco products. For information about e-cigarettes, see Principles of Alternative Approaches to Smoking Cessation (SC-A).

[c]Initial evaluation and assessment of patient smoking may be completed by any member of the health care team, including physicians, nurses, medical assistants, health educators, or other dedicated staff.

[d]Smoking status should be documented in the patient health record and assessment should be repeated at every visit (less often for patients with remote smoking histories).

[e]Smoking cessation should be offered to all smokers with cancer regardless of cancer prognosis. See Smoking-Associated Risks for Patients With Cancer (SC-B).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CURRENT SMOKERS AND THOSE WHO HAVE SMOKED WITHIN LAST 30 DAYS

EVALUATION[f]

Assess and document in the patient health record:

- **Nicotine dependency:**
  - How much do you currently smoke per day? What is the typical amount you smoked per day within the last 3 months?
  - How soon do you smoke after you wake up in the morning?
  - Do you use any other type(s) of tobacco/nicotine products and if so, how much? (eg, pipes, cigars, snuff, e-cigarettes)
- **History of quit attempts:**
  - What is the longest period you have gone without smoking?
  - When was your last quit attempt?
  - Did you use anything to help you quit in the past? If so, what?
    - ◊ Unaided
    - ◊ Medications[g] (eg, varenicline, bupropion, NRT)
    - ◊ Support group
    - ◊ Behavior therapy
    - ◊ Quitlines, websites, smart phone applications, or other media
    - ◊ E-cigarettes[h]
    - ◊ Other
  - Why were previous quit attempts unsuccessful? (eg, side effects, cost, continued cravings, did not work)
- **Patient readiness to quit[i,j]**

MANAGEMENT

Engage patients in motivational dialog about smoking cessation[i]
- Review risks of smoking and benefits of quitting (See SC-B)
- Provide patient education resources (See SC-C)

Ready to quit within 4 weeks[i]
- Establish personalized quit plan based on:
  - Nicotine dependency and prior quit attempts[k]
  - Smoking cessation therapy options (see SC-4)
- Set quit date as soon as possible.
- Encourage smoking cessation as soon as possible if cancer surgery is planned.[l]
- Discuss risk of relapse.[m]

→ **Begin smoking cessation treatment (See SC-4)**

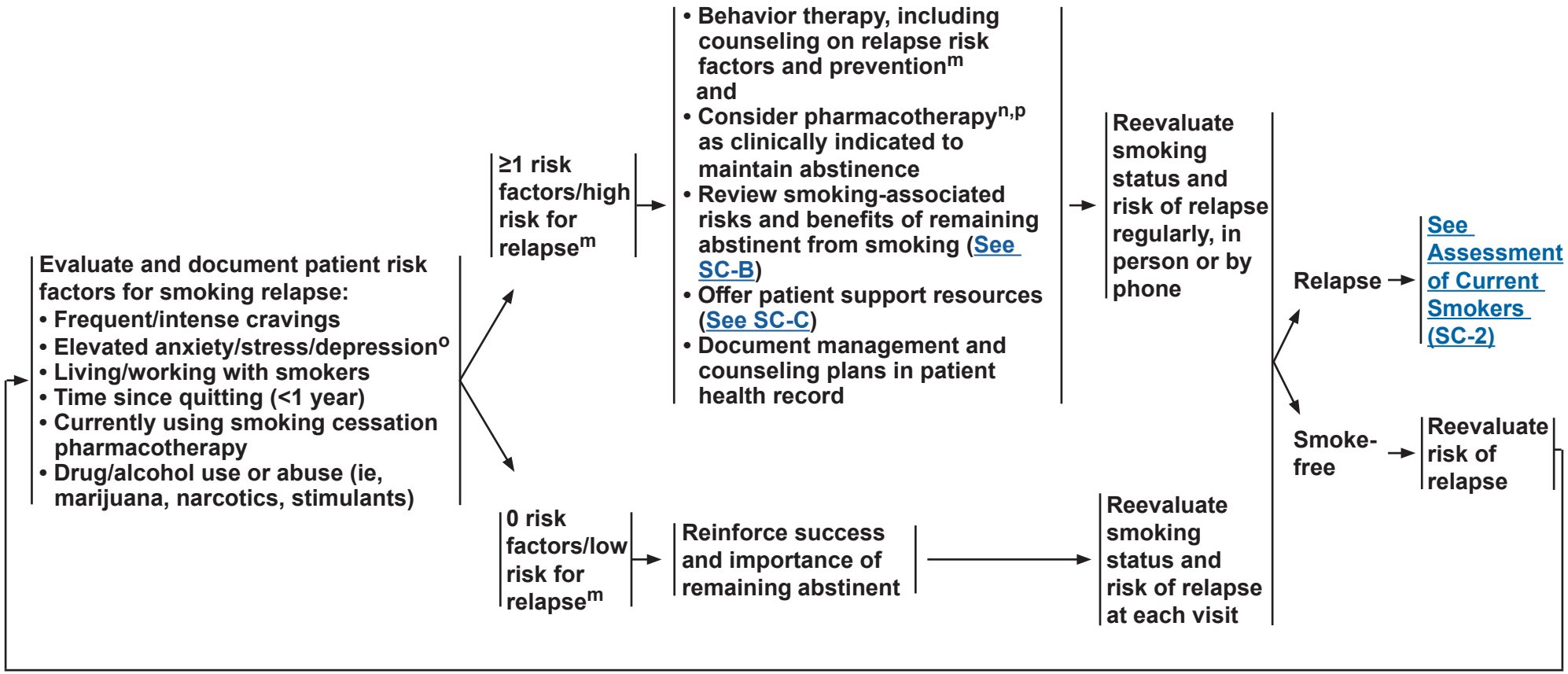
Not ready to quit within 4 weeks[i]
- Assess and address barriers and concerns of patient.
- Consider smoking reduction with a goal of setting a quit date in the near future[j]
  - Encourage immediate initiation of pharmacotherapy for targeted reduction of cigarettes per day[n]

→ **Reassess readiness to quit at each visit**

[f] For lung cancer screening recommendations, see NCCN Guidelines for Lung Cancer Screening.
[g] Document type and dose of medications used during previous quit attempts.
[h] There is currently insufficient evidence to support the use of electronic nicotine delivery systems (e-cigarettes) in smoking cessation for patients with cancer.
[i] Physicians and members of the health care team should discuss potential benefits of quitting with each patient. Readiness to quit is to be determined by both physician and patient.
[j] Making an immediate quit attempt is recommended but smoking reduction may be considered with a goal of cessation at a future quit date (ie, 1–3 mo).
[k] Adjustments to therapy length, intensity, and surveillance may be considered, as clinically indicated, for patients with high nicotine dependency and/or prior unsuccessful quit attempts.
[l] Longer periods of smoking cessation confer better surgical outcomes but should not delay appropriate timing of cancer resection. See Principles of Smoking Cessation and Cancer Surgery (SC-D).
[m] Providers should discuss risk of relapse and smoking slips and provide guidance and support to encourage continued smoking cessation attempts. See Principles of Behavioral Strategies (SC-E).
[n] See Principles of Smoking Cessation Pharmacotherapy (SC-F).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

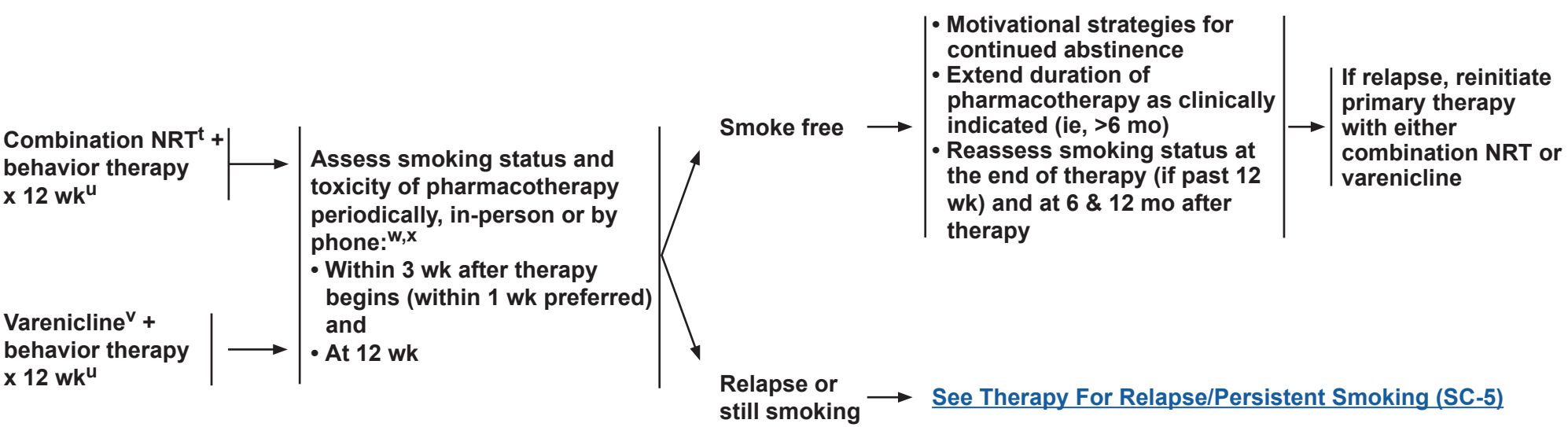
FORMER SMOKERS AND RECENT QUITTERS (>30 Days Since Last Smoked)



[m]Providers should discuss risk of relapse and smoking slips and provide guidance and support to encourage continued smoking cessation attempts. See Principles of Behavioral Strategies (SC-E).
[n]See Principles of Smoking Cessation Pharmacotherapy (SC-F).
[o]Refer to specialist for management of psychiatric comorbidities.
[p]When considering pharmacotherapy maintenance options for patients who have been nicotine free for an extended period of time (eg, 30 days or longer), carefully consider the potential effects of re-introducing nicotine through NRT or advocating for the use of combination NRT.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

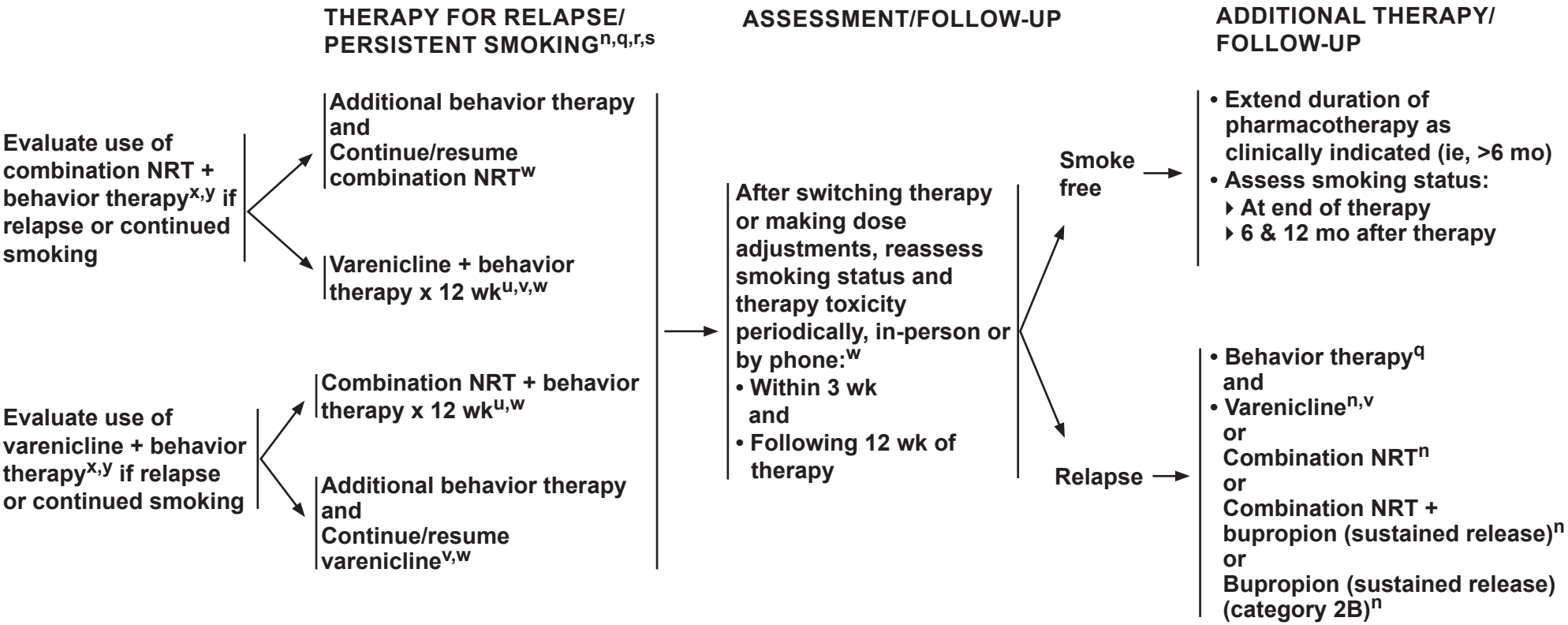
GENERAL APPROACH TO SMOKING CESSATION FOR PATIENTS WITH CANCER AND SURVIVORS



[n] See Principles of Smoking Cessation Pharmacotherapy (SC-F).
[q] See Principles of Behavioral Strategies (SC-E).
[r] Efficacy data are lacking for the use of e-cigarettes and alternative therapies (eg, hypnosis, acupuncture, nutritional supplements). Use of evidence-based cessation methods should be encouraged to avoid delay in achieving smoking abstinence. See Principles of Alternative Approaches to Smoking Cessation (SC-A).
[s] The use of marijuana, or other substances associated with smoking relapse, is discouraged for those attempting to quit smoking.
[t] Combination NRT = Nicotine patch + short-acting NRT (gum/lozenge/inhaler/nasal spray).
[u] A minimum of 4 sessions of individual/group therapy in 12 weeks is preferred, but at least brief counseling is required. See Principles of Behavioral Strategies (SC-E).
[v] Nausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy. Varenicline should be avoided for patients with brain metastases due to seizure risk.
[w] Nicotine withdrawal symptoms typically peak within 1–2 weeks of quitting. Patients who do not quit immediately may quit at some later point after withdrawal symptoms subside; therefore, encourage continued therapy through brief slips.
[x] Adjust behavior therapy frequency as needed, and adjust pharmacotherapy dose for undesirable side effects or if high risk of relapse is suspected.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GENERAL APPROACH TO SMOKING CESSATION FOR PATIENTS WITH CANCER AND SURVIVORS



[n] See Principles of Smoking Cessation Pharmacotherapy (SC-F).
[q] See Principles of Behavioral Strategies (SC-E).
[r] Efficacy data are lacking for the use of e-cigarettes and alternative therapies (eg, hypnosis, acupuncture, nutritional supplements). Use of evidence-based cessation methods should be encouraged to avoid delay in achieving smoking abstinence. See Principles of Alternative Approaches to Smoking Cessation (SC-A).
[s] The use of marijuana, or other substances associated with smoking relapse, is discouraged for those attempting to quit smoking.
[u] A minimum of 4 sessions of individual/group therapy in 12 weeks is preferred, but at least brief counseling is required. See Principles of Behavioral Strategies (SC-E).
[v] Nausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy. Varenicline should be avoided for patients with brain metastases due to seizure risk.
[w] Nicotine withdrawal symptoms typically peak within 1–2 weeks of quitting. Patients who do not quit immediately may quit at some later point after withrawal symptoms subside; therefore, encourage continued therapy through brief slips.
[x] Adjust behavior therapy frequency as needed, and adjust pharmacotherapy dose for undesirable side effects or if high risk of relapse is suspected.
[y] Decision to switch therapy should be based on patient preference, toxicity, and/or a change in clinical status (eg, upcoming surgery).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF ALTERNATIVE APPROACHES TO SMOKING CESSATION

- **Offer motivational and behavioral support to all patients attempting to quit smoking, regardless of what smoking cessation method(s) is/are being used. See Principles of Behavioral Strategies (SC-E)**
- **For patients who are unable or unwilling to quit, one potential strategy is smoking reduction with a goal of quitting. (See SC-2)**
- **Encourage the use of evidence-based cessation methods to avoid delays in achieving abstinence. For patients using alternative approaches, including electronic cigarettes, continue to provide support during quit attempts.**
- **Relapse and smoking slips are common. Remind patients that repeated attempts with evidence-based methods are frequently needed to achieve longer-term abstinence.**

Electronic Nicotine Delivery Systems (ENDS) or "E-Cigarettes"

- **ENDS are not FDA-approved smoking cessation devices.**
- **There is currently insufficient evidence to support the use of e-cigarettes in smoking cessation, alone or in combination with evidence-based smoking cessation methods. There is also insufficient evidence regarding the safety and efficacy of e-cigarette use in patients with cancer.**
  - **The American Heart Association, American Association for Cancer Research (AACR), and American Society of Clinical Oncology (ASCO) recognize the potential for ENDS to alter existing smoking behaviors, as well as the lack of definitive data regarding associated benefits and harms.[1,2] However, ENDS are not recommended by these associations because of the insufficient data on efficacy and safety.**
  - **According to the US Preventative Services Task Force (USPSTF), "Current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation in adults, including pregnant women. The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety."[3]**

Other Alternative Methods

- **There is currently insufficient evidence to support the use of alternative methods (eg, hypnosis, acupuncture, nutritional supplements) when used alone and in combination with standard smoking cessation methods.[4,5]**
- **Prior unsuccessful quit attempts with conventional therapies do not justify the use of unproven alternative cessation methods because multiple attempts with evidence-based methods may be necessary to achieve abstinence.**
- **There are very limited, low-quality data regarding the efficacy of exercise-based interventions.[6]**

[1]Brandon TH, Goniewicz ML, Hanna NH, et al. Electronic nicotine delivery systems: a policy statement from the American Association for Cancer Research and the American Society of Clinical Oncology. J Clin Oncol 2015;33:952-963.
[2]Bhatnagar A, Whitsel LP, Ribisl KM, et al. Electronic cigarettes: a policy statement from the American Heart Association. Circulation 2014;130:1418-1436.
[3]Final Update Summary: Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions. U.S. Preventive Services Task Force. September 2015. http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1?ds=1&s=tobacco
[4]Barnes J, Dong CY, McRobbie H, et al. Hypnotherapy for smoking cessation. Cochrane Database Syst Rev 2010:CD001008.
[5]White AR, Rampes H, Liu JP, et al. Acupuncture and related interventions for smoking cessation. Cochrane Database Syst Rev 2014;1:CD000009.
[6]Ussher MH, Taylor AH, Faulkner GE. Exercise interventions for smoking cessation. Cochrane Database Syst Rev 2014;8:CD002295.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SMOKING-ASSOCIATED RISKS FOR PATIENTS WITH CANCER (1 OF 2)

- The 2014 Surgeon General's Report[1] stated that:
  - Sufficient evidence exists to support a causal relationship between smoking and adverse health outcomes, increased all-cause mortality and cancer-specific mortality, and increased risk for secondary primary cancers.
  - Existing evidence is suggestive of a link between smoking and increased risk of cancer recurrence, poor treatment response, and increased treatment-related toxicity.
- Providers should:
  - Inform patients of the potential benefits of smoking cessation, including improved survival, treatment outcomes, and health-related quality of life, as well as decreased treatment-related toxicity, drug side effects, and surgical complications.
  - Educate patients on the specific risks of smoking during treatment for their particular cancer.
  - Encourage smoking cessation as far in advance as possible before initiating cancer treatment.
  - Consider patient smoking status prior to initiating treatment and when making decisions regarding treatment selection, dosage, and timing of initiation.
  - Discuss smoking cessation with all patients who smoke. Patient satisfaction is enhanced when smoking cessation is offered by providers.
  - Encourage smoking cessation among all members of the household for the benefit of the patient.

Treatment-Specific Risks (see Discussion for additional information)

- Smoking can impact the metabolism of chemotherapy and targeted therapy.
  - Smoking effects on cytochrome P450 enzymes may include altered drug clearance time and plasma concentration, potentially impacting the efficacy of certain drugs for patients who smoke. Providers should consider whether patients are at risk for altered drug metabolism due to smoking and determine if medication or dose adjustments may be required. Drugs whose metabolisms are known to be affected include erlotinib, irinotecan, and bendamustine.[2-6]
- Smoking increases risk of radiation therapy (RT)-associated treatment complications during RT and may decrease treatment response.[7-9]
- Smoking is associated with increased rates of postoperative complications and mortality after cancer surgery.
  - Compared with nonsmokers, patients who smoke may experience decreased health-related quality of life after cancer surgery (eg, dyspnea, fatigue, pain).[10-12]
  - Smoking may impair wound healing following surgery for cancer.[13,14]
  - Increased infection rates, cardiovascular and pulmonary complications, and longer postoperative hospital stays are more commonly observed in patients who smoke.[15]
  - Postoperative mortality rates are higher among patients who smoke.[16]

Potential Nicotine Effects on Cancer and Cardiovascular Risks (see Discussion for additional information)

- Blood nicotine levels from NRT, including combination NRT, are significantly less than from smoking cigarettes. Therefore, providers and smokers should not be dissuaded from using NRT to foster quitting and long-term cessation.
- There is insufficient evidence that NRT causes cancer in humans.[17-21]
- There is insufficient evidence that NRT increases the risk of myocardial infarction or cardiovascular disease.

References on next page

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SMOKING-ASSOCIATED RISKS FOR PATIENTS WITH CANCER (2 of 2)

REFERENCES

[1]The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General. Atlanta (GA); 2014. Available at: http://www.surgeongeneral.gov/library/reports/50-years-of-progress/. Accessed March 20, 2017.

[2]Li H, Shi Q. Drugs and diseases interacting with cigarette smoking in US prescription drug labeling. Clin Pharmacokinet 2015;54:493-501.

[3]O'Malley M, King AN, Conte M, et al. Effects of cigarette smoking on metabolism and effectiveness of systemic therapy for lung cancer. J Thorac Oncol 2014;9:917-926.

[4]Hamilton M, Wolf JL, Rusk J, et al. Effects of smoking on the pharmacokinetics of erlotinib. Clin Cancer Res 2006;12:2166-2171.

[5]van der Bol JM, Mathijssen RH, Loos WJ, et al. Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropenia. J Clin Oncol 2007;25:2719-2726.

[6]Darwish M, Bond M, Hellriegel E, et al. Pharmacokinetic and pharmacodynamic profile of bendamustine and its metabolites. Cancer Chemotherapy and Pharmacology. 2015;75(6):1143-1154. doi:10.1007/s00280-015-2727-6.

[7]Eifel PJ, Jhingran A, Bodurka DC, et al. Correlation of smoking history and other patient characteristics with major complications of pelvic radiation therapy for cervical cancer. J Clin Oncol 2002;20:3651-3657.

[8]Browman GP, Wong G, Hodson I, et al. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Engl J Med 1993;328:159-163.

[9]Zevallos JP, Mallen MJ, Lam CY, et al. Complications of radiotherapy in laryngopharyngeal cancer: effects of a prospective smoking cessation program. Cancer 2009;115:4636-4644.

[10]Balduyck B, Sardari Nia P, Cogen A, et al. The effect of smoking cessation on quality of life after lung cancer surgery. Eur J Cardiothorac Surg 2011;40:1432-1437; discussion 1437-1438.

[11]Erhunmwunsee L, Onaitis MW. Smoking cessation and the success of lung cancer surgery. Curr Oncol Rep 2009;11:269-274.

[12]Mason DP, Subramanian S, Nowicki ER, et al. Impact of smoking cessation before resection of lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database study. Ann Thorac Surg 2009;88:362-370; discussion 370-361.

[13]Chang DW, Reece GP, Wang B, et al. Effect of smoking on complications in patients undergoing free TRAM flap breast reconstruction. Plast Reconstr Surg 2000;105:2374-2380.

[14]Kuri M, Nakagawa M, Tanaka H, et al. Determination of the duration of preoperative smoking cessation to improve wound healing after head and neck surgery. Anesthesiology 2005;102:892-896.

[15]Ehlers SL, Gastineau DA, Patten CA, et al. The impact of smoking on outcomes among patients undergoing hematopoietic SCT for the treatment of acute leukemia. Bone Marrow Transplant 2011;46:285-290.

[16]Sharma A, Deeb AP, Iannuzzi JC, et al. Tobacco smoking and postoperative outcomes after colorectal surgery. Ann Surg 2013;258:296-300.

[17]Stepanov I, Carmella SG, Briggs A, et al. Presence of the carcinogen N'-nitrosonornicotine in the urine of some users of oral nicotine replacement therapy products. Cancer Res 2009;69:8236-8240.

[18]Murray RP, Connett JE, Zapawa LM. Does nicotine replacement therapy cause cancer? Evidence from the Lung Health Study. Nicotine Tob Res 2009;11:1076-1082.

[19]Murphy SE, von Weymarn LB, Schutten MM, et al. Chronic nicotine consumption does not influence 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis. Cancer Prev Res (Phila) 2011;4:1752-1760.

[20]Maier CR, Hollander MC, Hobbs EA, et al. Nicotine does not enhance tumorigenesis in mutant K-ras-driven mouse models of lung cancer. Cancer Prev Res (Phila) 2011;4:1743-1751.

[21]Shields PG. Long-term nicotine replacement therapy: cancer risk in context. Cancer Prev Res (Phila) 2011;4:1719-1723.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SMOKING CESSATION RESOURCES FOR PATIENTS AND HEALTH PROVIDERS (1 of 2)

CANCER-RELATED RESOURCES FOR PATIENTS[a]

Organization	Website	Quitline/Contact Info	Guides for Quitting/Additional Resources
American Cancer Society (ACS)	https://www.cancer.org/healthy/stay-away-from-tobacco.html	1.800.227.2345	Guide to quitting smoking: http://www.cancer.org/healthy/stayawayfromtobacco/guidetoquittingsmoking/index
American Lung Association	http://www.lung.org/stop-smoking/	Lung Cancer Helpline: 1.844.252.5864	
National Cancer Institute (NCI)	http://www.cancer.gov/cancertopics/tobacco/smoking	• Quitline: 1.877.448.7848 • LiveHelp (Online Chat): https://livehelp.cancer.gov/app/chat/chat_launch	• "Clear Horizons: A Quit-Smoking Guide for People 50 and Older": http://smokefree.gov/sites/default/files/pdf/clear-horizons-accessible.pdf • "Clearing the Air: Quit Smoking Today": http://smokefree.gov/sites/default/files/pdf/clearing-the-air-accessible.pdf
Smokefree.gov	• Springboard Beyond Cancer: https://smokefree.gov/springboard/wellness/quit-smoking • https://www.smokefree.gov/	• NCI Quitline: 1.877.448.7848	• QuitGuide App: https://smokefree.gov/apps-quitguide • SmokeFreeTxt: https://smokefree.gov/tools-tips/smokefreetxt-signup ▸ SmokefreeMOM: http://smokefree.gov/smokefreemom ▸ SmokefreeVET: http://smokefree.gov/vet ▸ SmokefreeESPANOL: http://espanol.smokefree.gov/smokefreetxt-espanol

GENERAL RESOURCES FOR PATIENTS[a]

Organization	Website	Quitline/Online Support
American Heart Association	http://www.heart.org/HEARTORG/GettingHealthy/QuitSmoking/Quit-Smoking_UCM_001085_SubHomePage.jsp	
American Indian Commercial Tobacco Program	https://americanindian.quitlogix.org	1.855.372.0037
Asian Smokers' Quitline	http://www.asiansmokersquitline.org/	• Mandarin/Cantonese: 1.800.838.8917; Korean: 1.800.556.5564; Vietnamese: 1.800.778.8440
Centers for Disease Control and Prevention (CDC) and National Network of Tobacco Cessation Quitlines	https://www.cdc.gov/tobacco/quit_smoking/cessation/pdfs/1800quitnow_faq.pdf	• English: 1.800.QUIT.NOW (1.800.784.8669) • Spanish: 1.855.335.3569
Ex: A New Way To Think About Quitting Smoking	http://www.becomeanex.org/	ExCommunity Online: https://excommunity.becomeanex.org
TRICARE (Military and their families)	http://www.tricare.mil/HealthWellness/Tobacco.aspx	North: 1.866.459.8766; South: 1.877.414.9949; West: 1.888.713.4597
Quit Tobacco: UCANQUIT2.org	https://www.ucanquit2.org/	• Live chat quit coach: http://www.ucanquit2.org • SmokefreeMIL text support: http://www.ucanquit2.org/en/HowToQuit/SmokefreeMIL.aspx

[a]Free or low-cost support is sometimes available for uninsured or underinsured patients. Resources may vary by organization and location. Contact each organization to learn more about the availability of free and low-cost smoking cessation resources offered regionally.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued on next page

SMOKING CESSATION RESOURCES FOR PATIENTS AND HEALTH CARE PROVIDERS (2 OF 2)

CANCER-RELATED RESOURCES FOR HEALTH PROFESSIONALS

Organization	Guidelines and Resources
American Association for Cancer Research (AACR)	Policy Statement: http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Documents/AACRStatement_TobaccoUseCancerPatients_2013_CCR___f3f578.pdf
American Society of Clinical Oncology (ASCO)	http://www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/tobacco-cessation-control
NCCN Guidelines for Lung Cancer Screening	http://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf
NCCN Guidelines for Survivorship	http://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf
NCI- Physician Data Query:	https://www.cancer.gov/about-cancer/causes-prevention/risk/tobacco/quit-smoking-hp-pdq
U.S. Department of Health and Human Services, Public Health Service	Treating Tobacco Use and Dependence: 2008 Update. Content last reviewed June 2015. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html

GENERAL RESOURCES FOR HEALTH PROFESSIONALS

Organization	Website/Resource
American Academy of Family Physicians (AAFP)	Ask and Act Smoking Cessation Program: http://www.aafp.org/about/initiatives/ask-act.html
American College of Chest Physicians (ACCP)	Toolkit: http://tobaccodependence.chestnet.org/
Association for the Treatment of Tobacco Use and Dependence (ATTUD)/Council for Tobacco Treatment Training Programs (CTTTP)	• http://www.attud.org/ • Accredited training programs: http://ctttp.org/accredited-programs/
RxForChange: Clinician-Assisted Tobacco Cessation	http://rxforchange.ucsf.edu/
Smokefree.gov	http://smokefree.gov/health-care-professionals
Treatobacco.net	http://www.treatobacco.net/en/index.php
U.S. Department of Health and Human Services-Surgeon General Reports	http://www.surgeongeneral.gov/priorities/tobacco
U. S. Preventative Services Task Force	Final Update Summary: Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions. U.S. Preventive Services Task Force. September 2015. https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1?ds=1&s=Tobacco smoking cessation in adults

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SMOKING CESSATION AND CANCER SURGERY

- **Smoking increases the risk of pulmonary complications, surgical site infection, and poor wound healing in patients undergoing surgery. See Smoking-Associated Risks for Patients With Cancer (SC-B)**
- **Access to cancer surgery should not be restricted for smokers, although smoking cessation may be deemed mandatory for some elective non-cancer surgeries (ie, reconstructive procedures).**
- **Smokers who have planned cancer surgery should be encouraged to quit smoking as soon as possible before surgery, regardless of how short the time to surgery is. There is no evidence to support delaying a quit attempt at anytime prior to surgery.**
- **Longer periods of smoking cessation confer better surgical outcomes but should not delay appropriate timing for cancer resection.**
- **Elective procedures, such as plastic surgery reconstruction, may benefit from delaying surgery for 60–90 days after smoking cessation.**

- **Preoperative pharmacotherapy options are consistent with the smoking cessation options for all patients with cancer who smoke. See Primary Therapy (SC-4). Primary therapy options for preoperative smoking cessation include:**
  - **Combination NRT + behavior therapy**
    - **There is no clear evidence that NRT degrades the wound healing benefits of smoking cessation. NRT offers benefits over continued smoking.**
    - **NRT is a valuable adjunct to perioperative smoking cessation.**

  or
  - **Varenicline + behavior therapy**

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF BEHAVIORAL STRATEGIES (1 of 2)

- **Pharmacotherapy is most effective when combined with behavior therapy.[1] Population-level studies of smoking cessation treatment modalities indicate that counseling by a smoking cessation specialist plus medication results in a significant improvement in cessation rates relative to no counseling or medication (OR = 3.25; CI, 2.05–5.15).[2] In addition to the benefits of enhancing motivation and knowledge of the addiction process, behavior therapy assists patients with medication use and strategies since adherence to tobacco treatment medication recommendations is often inadequate. Therefore, pharmacotherapy alone without some form of counseling may not be better than unaided cessation.**
- **Through behavior therapy, smokers are provided with problem-solving skills, support, and encouragement. Behavior therapy, tailored somewhat to the patient's nicotine dependence and previous quit attempts, provides strategies for:**
  - **Coping with nicotine withdrawal symptoms and cravings (Note: Symptoms typically peak within 1–2 weeks after quitting and then subside.)**
  - **Identifying smoking triggers**
  - **Coping with stressful and difficult situations in which smoking is likely**
  - **Avoiding high-risk situations**
  - **Addressing other patient-specific barriers to and facilitators of smoking behavior change.**
- **Motivational counseling is beneficial for all patients, but is essential for those not yet ready to quit.[2-4]**
  - **Motivational counseling involves first establishing a connection with the patient and then exploring the smoker's feelings (eg, distress), beliefs (eg, fatalistic), and values (eg, importance of family) in order to help him/her work through ambivalence or conflicting motivations about quitting. Clinicians use a guiding and empathetic style to help the smoker: 1) understand his/her reasons for quitting and smoking; 2) understand the relation of these to his/her values and goals; and 3) build his/her confidence to quit and stay quit. To achieve this, clinicians ask open-ended questions, reflect back patient comments, affirm patient strengths, and summarize discussion. Clinicians should express acceptance for the patient and validate his/her worth, strengths, and independence.**
  - **Physicians and health professionals use four basic strategies, commonly referred to as OARS, for motivational interviewing: Open-ended questions; Affirmations; Reflective listening; and Summary statements.**
  - **For patients who struggle to identify reasons to quit, the clinician can also use the 5 R's strategy focusing on: the personal Relevance of quitting; personal Risks of continuing smoking; personal Rewards of quitting; identifying Roadblocks to quitting; and Repeating the message at every contact.[2]**
- **In smokers with cancer, there is a high incidence of depression, anxiety, and stress, all of which are common causes of relapse. It may be optimal to enroll patients in a behavior therapy program with specific interventions designed to ameliorate these conditions and other cancer-related relapse challenges. This may require referral to specialized smoking cessation programs that have staff trained to treat mental health disorders, or referral to behavior therapists who have expertise in treating comorbid substance dependence and mental health disorders.**
- **Specialized treatment centers may consider providing smoking cessation therapy targeted specifically to patients with cancer (eg, individual therapy and group support that focuses on challenges specific to cancer survival and treatment) with access to counselors or group leaders experienced in the treatment of patients with cancer.**

References on next page

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF BEHAVIORAL STRATEGIES (2 of 2)

Behavior Therapy/Counseling Recommendations:

- **Four or more sessions during each 12-week course of pharmacotherapy. The first session is recommened within the first 2–3 weeks.**
  - **Duration: 10–30+ minutes per session. Research suggests that longer, more frequent sessions are linked to higher success rates.**
  - **At a minimum, brief advice should be delivered. Brief advice of about 3 minutes by physicians or other health care providers results in a small but important increase in quit rates.[2]**
- **Individual or group therapy, in-person and/or by phone, in coordination with a smoking cessation clinic if available.**
  - **For those in active cancer treatment, behavior therapy can occur during scheduled oncology visits to avoid the need for additional appointments.**
  - **Refer to a smoking cessation quitline, in addition to providing brief counseling from a health care provider, if face-to-face or group intervention is not available. See Smoking Cessation Resources (SC-C).**
- **Should be performed by a tobacco treatment specialist or a dedicated staff member (ie, nurse, medical assistant, health educator) trained in smoking cessation motivational and behavior strategies.**
- **Therapy should include skills training, social support, and motivational interviewing with print- or web-based patient education materials.**
- **For more information on behavior therapy for smoking cessation, see Discussion.**

[1]Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev 2012;10:Cd008286.
[2]Fiore MC, Jaen CR, Baker TB, et al. Treating tobacco use and dependence: 2008 Update, Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service, 2008. (Treating Tobacco Use and Dependence. April 2013. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/index.html.)
[3]Miller WR, Rollnick S. Motivational interviewing: Helping people for change (3rd edition). New York, NY: Guilford Press; 2013.
[4]Lindson-Hawley N, Thompson TP, Begh R. Motivational interviewing for smoking cessation. Cochrane Database of Systematic Reviews 2015, Issue 3. Art. No.: CD006936.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SMOKING CESSATION PHARMACOTHERAPY (1 OF 2)

- **Smoking cessation is important for improving clinical outcomes for patients with cancer. Therefore, the included agents and methodologies should be made available to all patients with cancer who smoke.**
- **A minimum of 12 weeks of combination NRT or varenicline[a] is recommended for the initial quit attempt. Therapy may be extended to promote continued cessation (ie, 6 months–1 year) while attempting to avoid longer periods of time if possible.**
  - **Follow-up is recommended (in-person or by phone) within 2 weeks after starting pharmacotherapy, but can be extended to within 3 weeks to coordinate with regularly scheduled oncology appointments as needed. Additional periodic follow-up during therapy (at a minimum of 12-wk intervals), and after completion of therapy, is recommended.**
  - **Nicotine withdrawal symptoms typically peak within 1–2 weeks of quitting and then subside. Encourage continued therapy through brief slips. Patients who do not quit immediately may quit at some later point after withdrawal symptoms subside.**
  - **Pharmacotherapy dose adjustments may be considered as clinically indicated.**
- **Track attempts at smoking reduction. If reduction efforts stall, or reaching total abstinence seems unlikely, consider switching to a different pharmacotherapy.**
- **As patients progress through multiple lines of treatment, behavior therapy should be progressively intensified with referral to specialty care (eg, psychiatrist, psychologist) as indicated.**

Preferred Primary Therapy Options	• **Combination NRT: Nicotine patch + short-acting NRT for cravings (lozenge/gum/inhaler/nasal spray) or** • **Varenicline[a,b]** • **For patients who continue to smoke or experience relapse: Evaluate use of current therapy and consider continuing or resuming the initial pharmacotherapy, or switch to the other primary therapy option before trying the subsequent therapy options.**
Subsequent Therapy Options*	• **Combination NRT + bupropion (sustained release)[b]** • **Bupropion (sustained release)[b] (category 2B)**

***Additional pharmacotherapy options are currently being evaluated. See Discussion for details.**

Continued on next page

[a]Nausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy.
[b]Varenicline and bupropion should be avoided for patients with brain metastases due to seizure risk.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SMOKING CESSATION PHARMACOTHERAPY (2 of 2)

	Standard Dose[c]	Duration	Adverse Effects and Contraindications[f,g]
Combination NRT (preferred)	• Begin with 21 mg patch + short-acting NRT[d] • If 21 mg patch is not effective, consider using more than one patch to increase the dose to 35 or 42 mg • Short-acting NRT as needed, every 1–2 hours for cravings	12 wk[e]	Blood nicotine levels from NRT, including combination NRT, are significantly less than from smoking cigarettes. NRT is well tolerated and nicotine toxicity is rare and transient, even when used with smoking. Patients commonly under-dose when using combination NRT. Nicotine overdose is rare, but possible and usually short-lived.
Varenicline (preferred)	• Initiate dosing 1–2 wk prior to quitting • Days 1–3: 0.5 mg orally, once daily • Days 4–7: 0.5 mg orally, twice daily • Week 2–12: 1 mg orally, twice daily, if tolerated	12 wk[e]	• Nausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy. • Although these side effects are uncommon, providers should monitor for the development or worsening of serious neuropsychiatric issues (ie, depression and suicidal ideation/behavior), including those without a previous history, and discontinue use if these signs occur. See Manufacturer Black Box Warning, and weigh the substantial benefits of immediate smoking cessation versus risks of increased hostility, depression, or suicidal behavior. • Contraindicated for patients with brain metastases due to seizure risk.
Bupropion (sustained release) ± NRT (category 2B for bupropion alone)	• Initiate dosing 1–2 wk prior to quitting • Days 1–3: 150 mg orally, once daily ▸ Adjust dose for hepatic insufficiency. • Day 4–12 wk: 150 mg orally, twice daily, if tolerated • Maximum 300 mg per day	7–12 wk[e]	• Although these side effects are uncommon, providers should monitor for the development or worsening of serious neuropsychiatric issues (ie, depression and suicidal ideation/behavior), including those without a previous history, and discontinue use if these signs occur. See Manufacturer Black Box Warning, and weigh the substantial benefits of immediate smoking cessation versus risks of increased hostility, depression, or suicidal behavior. • Bupropion is contraindicated for patients with seizure risks (ie, stroke, brain metastases), those taking MAO inhibitors (increased risk of hypertensive reactions) or tamoxifen, or those with closed-angle glaucoma.

- **In most circumstances, the side effects related to preferred smoking cessation medications are minimal and are considered an acceptable risk compared to smoking. Serious side effects are extremely rare. Refer to manufacturer inserts for exhaustive lists of potential side effects and warnings.[e,f]**
- **A recent multicenter randomized controlled trial (RCT) examined the neuropsychiatric safety of varenicline and bupropion in 2 cohorts of patients: those with diagnosed psychiatric disorders (n = 4074) and those without (n = 3984). Rates of neuropsychiatric adverse events in individuals receiving varenicline or bupropion were not significantly increased relative to those receiving nicotine patches or placebo in either cohort.[g]**

[c]Dose adjustments may be considered if clinically indicated.
[d]Gradually decrease dose over 10 weeks or more. Dose reduction may not be appropriate for patients with limited life expectancy.
[e]Therapy may be extended to promote continued cessation (ie, 6 mo–1 y).
[f]For drug labels and full prescribing information for varencline, buproprion, and NRT products, refer to the National Institutes of Health website at https://dailymed.nlm.nih.gov/dailymed.
[g]Anthenelli RM, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet 2016;387:2507-2520.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

Table of Contents

Overview

Nearly 40 million adults in the United States currently smoke cigarettes, accounting for approximately 15% of the adult population in 2015—16.7% of males and 13.6% of females.[1] Cigarette smoking results in over 480,000 premature deaths yearly, and 1 in every 5 deaths are smoking-related.[2] Tobacco smoking has been implicated in causing cancers of mouth, lips, nose, sinuses, larynx, pharynx, esophagus, stomach, pancreas, kidney, bladder, uterus, cervix, colon/rectum, ovary, and myeloid leukemia.[3] Cancers linked to tobacco use comprise 40% of all cancer diagnoses and cigarette smoking is linked to 30% of all cancer deaths nationwide.[4] State-level data suggest that cigarette smoking is responsible for as high as 40% of cancer deaths in some geographic regions.[5] Lung cancer is the leading cause of cancer death in both men and women.[4]

These guidelines emphasize the importance of smoking cessation in all patients with cancer and seek to establish evidence-based, standard-of-care recommendations tailored to the unique needs and concerns of patients with cancer. The recommendations contained herein describe interventions for cessation of cigarette smoking. However, the panel recommends that patients with cancer be encouraged to discontinue use of all combustible products (eg, cigars, hookah, marijuana) as well as smokeless tobacco products.

In a 2014 report from the Surgeon General, *The Health Consequences of Smoking—50 Years of Progress*, a comprehensive review of the evidence revealed the following important findings for patients with cancer and cancer survivors:[2]

- Sufficient evidence exists to infer a causal relationship between cigarette smoking and adverse health outcomes, increased all-cause mortality (ACM), and cancer-specific mortality.
- Sufficient evidence exists to infer a causal relationship between cigarette smoking and second primary cancer.
- Evidence is suggestive of a causal relationship between cigarette smoking and risk of recurrence, poorer response to treatment, and increased treatment-related toxicity.

Although the harmful effects of smoking after a cancer diagnosis have been clearly demonstrated, many patients continue to smoke cigarettes during treatment and beyond. The prevalence of continued smoking among those who have received a cancer diagnosis has been examined in recent studies. The rate of smoking post-diagnosis varies widely by cancer type and with other factors such as gender, race, and age.

Smoking Prevalence in Patients with Cancer

Using data from the National Health and Nutrition Examination Survey (NHANES), of the 566 cancer survivors who regularly smoked prior to their diagnosis, 64% continued to smoke post-diagnosis. Those identified at higher risk for continued smoking included female, younger, and Hispanic individuals.[6] In the Cancer Care Outcomes Research and Surveillance (CanCORS) cohort of patients with lung (n = 2456) and colorectal (n = 3063) cancers, 90% of patients with lung cancers and 55% of patients with colorectal cancer reported a history of smoking. At diagnosis, 39% of those with lung and 14% of those with colorectal cancer were current smokers, and of these individuals 14% of patients with lung and 9% of patients with colorectal cancer continued to smoke at 5 months post-diagnosis.[7]

Smoking often persists beyond cancer treatment and well into survivorship. In a population-based study using the Behavioral Risk Factor Surveillance System, survivors of tobacco-related cancers had a

smoking prevalence of 27% compared with 16% and 18% for other cancer survivors and those without a history of cancer, respectively.[8] Based on prospectively collected data from 772 individuals with cancer in the Cancer Prevention Study-II Nutrition Cohort, persistent smoking was observed in 68.7% and 57% of the cohort at 2 and 4 years post-diagnosis, respectively.[9] One study revealed smoking prevalence to be highest among survivors of bladder, lung, and ovarian cancers.[10] Other studies have found high prevalence of continued smoking in survivors of cervical cancers.[11]

Health Care Community Response

Given the adverse health effects and prevalence of smoking in patients with cancer and survivors, several leading national organizations have called upon the oncology community for improved smoking cessation efforts. In 2013, the American Association for Cancer Research (AACR) released a policy statement calling for provision of evidence-based smoking cessation assistance to all patients with cancer, outlining the following objectives:

- "Universal assessment and documentation of tobacco use by cancer patients in all clinical settings;
- Development of universal standards for measurement of tobacco use and exposure in clinical and research settings;
- Incorporation of evidence-based tobacco interventions into review criteria used by research and health care quality and accreditation bodies; and
- Recognition and support of the value of tobacco cessation interventions by health systems, payers, and research funders through provision of appropriate incentives for infrastructure development and intervention delivery."[12]

Additionally, in a recent policy statement update, ASCO called upon oncology professionals to treat tobacco dependence as aggressively and compassionately as cancer and to advocate for the wide availability of tobacco cessation services.[13]

However, despite general consensus on the importance of smoking cessation, particularly for patients with cancer, many cancer centers and oncology practices report that they fall short of providing consistent, high-quality smoking cessation services. In a survey of 58 NCI-designated cancer centers, 20% reported offering no smoking cessation services for their patients, 38% did not routinely provide tobacco education materials to patients, and only half reported that they effectively identified tobacco use in their patients.[14] The AACR Task Force on Tobacco and Cancer found that few cancer care institutions utilize systematic and consistent mechanisms to foster cessation among patients with cancer.[12]

Several studies have linked increased patient satisfaction to the delivery of smoking cessation advice or intervention.[15,16] Data from large surveys of oncologists practicing in academic medical centers, non-academic hospitals, and oncology practices depict generally high rates of smoking assessment and providing initial advice to quit.[17-20] However, smoking assessment rates were weaker outside of the academic/university setting (ie, for those practicing in a hospital-based, nonacademic, or private setting).[20] Regardless of work setting, only 30% to 44% of respondents reported discussing specific interventions or providing subsequent follow-up. Moreover, the majority of respondents report inadequate training and/or a lack of confidence in ability to provide effective smoking cessation counseling and intervention.[17-20] A dearth of smoking assessment and documentation has also been demonstrated in oncology trials.[21,22]

Issues regarding insurance coverage and provider reimbursement for smoking cessation assessment, counseling, and cessation aids have also presented a challenge for the oncology community in the past. However, implementation of the Affordable Care Act has led to changes designed to increase access to smoking cessation interventions.[23]

Barriers to Smoking Cessation in Oncology Patients

Patients may have limited awareness about the harms associated with continued smoking upon a diagnosis of cancer. A recent survey assessed knowledge of the harms of continued smoking in 985 current or former smokers with a cancer diagnosis.[24] Across the board, one half to three-quarters of the respondents were unaware of the negative impact that smoking can have on chemotherapy, radiation, surgery, overall treatment efficacy, survival, and development of second primary cancers. The knowledge gap was most prevalent among those with non-tobacco–related cancers and those who were actively smoking at diagnosis.

Although over 68.8% of current smokers in the United States express a desire to quit and 52.5% report making a quit attempt within the past year, only 6.2% report recent smoking cessation.[25] In the general population, individuals who smoke report a number of different barriers to quitting, including stress; dependence; home, work, and social environmental factors; and lack of resources and support for quitting.[26] Importantly, patients and providers in the oncology setting face additional life challenges that can amplify the magnitude of these barriers.

In a population-based analysis of individuals recently diagnosed with cancer who actively smoked, health professional-provided cessation counseling was provided to only 52% of individuals in the past 12 months.[27] Surveys of oncology providers have identified common themes among barriers to smoking cessation for patients with cancer. Inadequate provider training and lack of time are often cited by oncology providers as barriers to successful intervention.[18] Providers have also cited patient-related factors such as inability to quit, lack of motivation, or resistance to treatment.[17,18] However, pain, second-hand smoke exposure, guilt over smoking, fear of stigmatization, and fatalism regarding disease also represent obstacles unique to oncology patients, particularly those with advanced disease.[28-33]

Notably, clinical trial research on smoking cessation for patients with cancer is limited, particularly for patients thought to have non-tobacco–related cancers. Barriers that limit or prevent enrollment in smoking cessation trials include smoking rate, medical history, contraindicated medications, lack of interest, and language barriers.[34] Ongoing randomized controlled trials (RCTs) are examining smoking cessation interventions designed specifically for patients with cancer. [35,36]

Given the complexity of smoking cessation interventions for patients with cancer, there is a great need for resources that provide guidance on smoking cessation specifically for this patient population. The inaugural NCCN Guidelines for Smoking Cessation have been created to establish a standard of care for smoking cessation in patients with cancer. The NCCN Guidelines panel has developed these guidelines in order to facilitate implementation of this standard, to allow for quality control monitoring, to fill a gap among existing treatment guidelines, and ultimately, to improve the health and outcomes for patients with cancer.

Literature Search Criteria and Guidelines Update Methodology

Prior to the development of this inaugural version of the NCCN Guidelines® for Smoking Cessation, an electronic search of the PubMed database was performed to obtain key literature in smoking

cessation for patients with cancer, published from December 2015 through December 2016, using the following search terms: (smoking cessation[Title/Abstract] OR quit smoking[Title/Abstract) AND (cancer[Title/Abstract] OR oncology[Title/Abstract]). The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[37]

The search results were narrowed by selecting studies in humans published in English. The PubMed search resulted in 220 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the NCCN Guidelines update meeting as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

General Principles of the Smoking Cessation Guidelines

The recommendations in these guidelines apply to cessation of cigarette smoking for patients with cancer; however, the panel strongly recommends that patients also discontinue use of all combustible products, including cigars, hookah, marijuana, as well as smokeless tobacco products. Smoking cessation has health benefits even after a cancer diagnosis, regardless of stage or prognosis—namely improvement in cancer treatment outcomes, disease recurrence, and secondary cancers. Importantly, a diagnosis of cancer may present a teachable moment and valuable opportunity for providers to encourage smoking cessation.[9,38-40] It is the view of the NCCN Guidelines panel that it is never too late for patients with cancer at any stage to stop smoking cigarettes and experience health benefits.

Because smokers with cancer often demonstrate high-level nicotine dependence, the panel recommends a multimodal approach to cessation therapy. The NCCN Panel recommends that treatment plans for all smokers with cancer include the following 3 tenets: evidence-based motivational strategies and behavior therapy (counseling), which can be brief; evidence-based pharmacotherapy; and close follow-up with retreatment as needed.

The panel asserts that a smoking cessation approach combining pharmacologic therapy and behavior therapy is the most effective and leads to the best results for smoking cessation. The two most effective pharmacotherapies are combination nicotine replacement therapy (NRT) (combined long- and short-acting NRT) and varenicline. There is a dose-response relationship for the success of counseling; high-intensity behavior therapy with multiple counseling sessions is most effective, but at least a minimum of brief counseling is needed and effective.[41-44] Quitlines may be used as an adjunct, especially in lower-resource settings.[45,46]

The panel also emphasizes the importance of documenting smoking status and treatment plans in the patient health record. Patient health records should be updated at regular intervals to indicate changes in smoking status, quit attempts made, and interventions utilized.

The panel emphasizes that smoking relapse and brief slips are common. Providers should discuss this with patients and provide guidance and support to encourage continued smoking cessation

attempts despite slips. Additionally, providers should be aware that smoking slips do not necessarily indicate a need for an alternative intervention. More than one quit attempt with the same therapy may be necessary to achieve long-term cessation.

Finally, smoking cessation interventions should be offered and continued throughout the oncology care continuum, including during end-of-life care. Emphasis on patient preferences and values is important when considering the best approach to fostering smoking cessation in that setting.

Smoking-Associated Risks for Patients with Cancer

Exposing cancer cells to cigarette smoke has been shown to promote a more malignant phenotype through its effects on angiogenesis and cell proliferation, migration, invasion, and survival. For a review of the preclinical data, see Sobus and Warren (2014).[47] These data have been corroborated by clinical studies. Per the Surgeon General's Report, *The Health Consequences of Smoking—50 Years of Progress*[2], sufficient evidence exists to support a causal relationship between smoking and adverse health outcomes, increased ACM and cancer-specific mortality, and increased risk for secondary primary cancers. Additionally, existing evidence is suggestive of a link between smoking and increased risk of cancer recurrence, poor treatment response, and increased treatment-related toxicity.

NCCN recommends that providers should inform patients of the potential benefits of smoking cessation, including improved survival, treatment outcomes, and health-related quality of life, as well as decreased treatment-related toxicity, drug side effects, and surgical complications. Patients should receive education on the specific risks of smoking during treatment for their particular cancer and should be encouraged to stop smoking as far in advance as possible before initiating cancer treatment. All members in the household who smoke should be encouraged to quit for the benefit of the patient. Prior to initiating treatment, when making decisions regarding treatment selection, dosage, and timing of initiation, providers should consider patient smoking status and potential smoking-related effects.

Overall Survival and Mortality

Smoking has been linked not only to the development of disease in tobacco-related cancers, but also to prognosis upon diagnosis and risk of death during treatment. Evidence suggests that current smoking increases risk of death and negatively impacts survival for patients with cancer in a variety of disease sites, including bladder,[48-51] breast,[52-54] cervix,[55,56] colon/rectum,[57-59] endometrium,[60] esophagus,[61,62] head and neck,[63-66] kidney,[67-69] lung,[70-73] ovarian,[74] pancreas,[75,76] and prostate,[77] as well as hematologic malignancies.[78]

Prospective studies of smoking at cancer diagnosis offer insight into the negative effects of smoking on overall survival (OS), disease-specific mortality (DSM), and ACM. In the 2014 Surgeon General's report, a comprehensive review of the data assessing smoking and ACM in patients with cancer revealed that 87% of the studies (139/159) indicated increased risk, while 62% of all studies (99/159) demonstrated a statistically significant risk increase.[2] Additionally, over half of the reviewed studies found at least a 50% increase in risk of death.[2] Additionally, among the studies examining OS in patients with cancer who smoke, 77% (48/62) were indicative of shortened survival, with 42% (26/62) revealing statistical significance.[2] Finally, smoking in patients with cancer was associated with higher DSM in 79% of studies reviewed (46/58), with a statistically significant link between cancer-related mortality and patients' smoking status in 59% (34/59).[2]

Risk of Recurrence or Secondary Primary Tumor

A number of studies have linked cigarette smoking and heightened risk of recurrence (ie, recurrent cancer in the same anatomic location as the original primary cancer). The 2014 Surgeon General's Report identified a positive association between smoking and risk of recurrence in 82% of the reviewed studies (42/51), with 53% of studies revealing significantly increased risk.[2] Among the studies that compared relative risk (RR) of recurrence between never smokers, former smokers, and current smokers, the median RR was 1.42 and 1.15 for current and former smokers, respectively.[2]

Disease sites with data linking current patient smoking to increased risk of recurrence include the anus,[79] bladder,[48,80,81] breast,[82] lung,[70] stomach,[83] and prostate.[77,84-86]

Studies have also examined the impact of continued smoking in patients with cancer on the risk of second primary tumor formation. The 2014 Surgeon General's Report identified a positive association between smoking and risk of second primary tumor in all studies examined (n = 26). The association was strongest when considering the effects of smoking on RR of developing a smoking-related second primary cancer (eg, lung cancer). Among 5 studies classifying smoking status into "never," "former," and "current," the median elevated RR of a second primary tumor was 1.20 and 2.20 for former and current smokers, respectively. Data from a large retrospective series and pooled data analyses have continued to provide support for smoking and increased risk of second primary malignancy, especially smoking-associated cancers.[87,88] Additionally, data also suggest that smoking interacts synergistically with radiation therapy (RT) to elevate the risk of second primary cancers.[2,89,90]

Smoking-Related Effects on Treatment Efficacy, Side Effects, and Outcomes

A majority of the existing data establishes and supports the detrimental impact of persistent smoking during cancer treatment. In a 2014 report from the Surgeon General, 80% of the evaluated studies (66/82) demonstrated a statistically significant association between active smoking and increased anticancer treatment-related toxicity.[2] Smoking has implications across the spectrum of cancer treatment, including surgical outcomes, RT efficacy and toxicity, chemotherapy metabolism and side effects, and overall symptom burden. This discussion also addresses the developing evidence base for the benefits of smoking cessation after receiving a cancer diagnosis.

Smoking-Associated Risks

Surgery

Smoking has been shown to negatively impact outcomes from cancer surgery, affecting postoperative complications, quality of life, length of hospital stay, and mortality risk.

In lung cancer, studies show that smoking impacts the success of surgical resection, decreases postoperative quality of life, and increases persistent dyspnea and thoracic pain at 12 months postoperatively.[91,92] Analysis of data from 7990 patients who had primary resections for lung cancer (Society of Thoracic Surgeons General Thoracic Surgery Database) revealed increased risk of hospital death and pulmonary complications associated with smoking.[93]

The adverse effects of smoking on postoperative outcomes was examined in more than 20,000 patients with gastrointestinal (n = 12,432), lung (n = 4490), and urinary tract cancers (n = 3491) using the Veteran's Health Administration Surgical Quality Improvement Program

(VASQIP) database for 2002 through 2008.[94] Surgical complications examined included surgical site infections, vascular complications (ie, venous thromboembolism, stroke/cerebrovascular accident, myocardial infarction), and composite pulmonary outcomes (CPO: pneumonia, failure to wean from ventilator >48 hours, or re-intubation for cardio-respiratory failure). Across all three cohorts, never smokers had fewer complications than former and current smokers. Compared with prior smokers, current smokers in the gastrointestinal cancer cohort had higher postoperative rates of pneumonia, failure to wean from ventilator, reintubation, and CPO. In the lung cancer cohort, current smokers had higher rates of pneumonia, failure to wean from the ventilator, reintubation, CPO, and return to surgery compared with former smokers. Current smoking status was associated with an increased length of hospital stay across all cancer sites when compared with never smokers; never smokers and prior smokers did not differ on this measure.

Postsurgical outcomes (ie, incisional infections, infectious and major complications, and mortality at 30 days) were compared between cohorts of never smokers, former smokers, and current smokers using data from over 26,000 patients with colorectal cancer in the American College of Surgeon's National Surgical Quality Improvement Program database (2005–2010). Postoperative morbidity and mortality rates were higher among current smokers and a significant dose-dependent effect was observed when stratifying risk of major complications by pack-years of smoking.[95]

In patients undergoing hematopoietic stem cell transplantation to treat acute leukemias, pulmonary complications, and longer postoperative hospital stays were more commonly observed in patients who smoked.[96]

Smoking can also impair wound healing and predispose patients to surgical complications for those undergoing reconstructive surgeries after cancer treatment. Among patients with breast cancer who underwent transverse rectus abdominis myocutaneous (TRAM) flap breast reconstruction surgery, smoking was associated with significantly higher risk of flap complications and delayed healing,[97,98] and evidence suggested that complication risk was reduced by smoking cessation of at least 4 weeks prior to surgery.[97] In patients with stage III or IV squamous cell carcinoma of the head and neck, serum cotinine concentration was dose-dependently linked to increased risk of wound complications following reconstructive head and neck surgery.[99]

Radiation

Studies have shown that prior smoking and active smoking during RT may decrease treatment response and increase complication rates, particularly for patients with head and neck cancers, but also in cervical, lung, breast, or prostate cancers.

In patients with head and neck cancer receiving RT, current smokers had poorer rates of locoregional control.[64,100] In another cohort, patients with head and neck cancer who continued to smoke during RT had lower rates of complete response and worse survival times than nonsmokers or those who quit prior to treatment.[101] Continued smoking during RT in patients with head and neck cancer has also been shown to increase the rates of treatment-related complications. In patients with laryngopharyngeal cancers, smoking during treatment was associated with significantly elevated incidence of osteoradionecrosis and hospitalization during treatment.[102] Another study demonstrated a significantly greater decline in several health-related quality-of-life measures in patients who continued to smoke during therapy compared with patients who quit beforehand.[103]

Among 3,489 patients receiving RT as part of treatment for stage I or II cervical cancer, heavy smoking (defined as at least 1 pack/day) was the strongest independent factor in predicting long-term major bladder, rectal, or small bowel complications, with even light/moderate smoking (less than 1 pack/day) predisposing patients to small bowel complications.[104] In another study of 565 patients with cervical cancer who were receiving primary RT, patients who smoked during treatment had lower cure rates, higher frequency of RT side effects, and higher rates of severe, irreversible complications.[105]

Smoking during RT for non-small-cell lung cancer was associated with significantly decreased locoregional control.[106] Active smoking may also decrease the efficacy of RT for prostate cancers and increase the prevalence of long-lasting treatment-related effects on the bowel and anal sphincter.[107-109] Concurrent smoking and RT increased the risk of cardiovascular disease in 4414 10-year survivors of breast cancer.[110]

Chemotherapy/Systemic Therapy

Data on the impact of smoking on chemotherapy are much more limited than that for surgery and RT, in part because smoking quantity during treatment is often left out of the medical record.[21] Many of the purported effects of smoking during chemotherapy are extrapolated from what is known about the impact of chemotherapy and smoking as individual factors of health. Smoking has the potential to exacerbate the risk of anticancer drug-related pulmonary and cardiac toxicities such as cardiomyopathy and pulmonary fibrosis.[111] Combining neoplastic agents with radiation while smoking may lead to further toxicity. Additionally, cancer drug side effects such as weight loss, cachexia, and fatigue may also be increased by smoking during treatment.[111,112]

Many systemic anticancer agents result in some degree of immune suppression/compromise, and smoking during chemotherapy may further compromise immune function in an already vulnerable patient population.[21,111] Preclinical and clinical studies suggest that smoking and nicotine exposure can be detrimental to the function of both the adaptive[113-116] and innate immune system.[117-121] Similarly, cigarette smoking may increase the incidence of infection, particularly for smoking-related infectious diseases such as pneumonia and influenza.[122]

Preclinical studies also suggest a potential link between nicotine exposure from smoking and the development of chemoresistance, [123-127] although no clinical data are currently available to support these findings.

Smoking can also impact the metabolism of certain cytotoxic chemotherapies and other systemic therapy. Smoking effects on cytochrome P450 enzymes may alter drug clearance time and plasma concentration, potentially impacting the efficacy of certain drugs for patients who smoke.[128] Providers should consider whether patients are at risk for altered drug metabolism due to smoking and determine if medication or dose adjustments may be required.

Drugs with metabolisms that are known to be affected include erlotinib and irinotecan. Rapid drug clearance has been observed in smokers who were receiving erlotinib therapy, such that higher doses may be required to achieve equivalent systemic exposure to standard dosing in nonsmokers.[129,130] Similarly, smoking increases the clearance time of irinotecan, potentially lessening systemic exposure.[129,131] Given the narrow therapeutic index of systemic therapy for lung cancer, small changes in drug exposure due to smoking could affect treatment efficacy and patient outcomes.[129] Bendamustine metabolism is also likely to be impacted by smoking, resulting in decreased drug plasma concentration and increased concentration of its active metabolites.[132,133]

However, smoking does not appear to alter the pharmacokinetic properties of taxane chemotherapeutics (eg, docetaxel, paclitaxel) despite its paradoxical protective effects on drug-induced neutropenia and leukopenia.[134]

Symptom Burden

In a study of 947 patients who were undergoing chemotherapy and/or RT, smoking during treatment was linked to a higher overall burden of symptoms commonly experienced among patients with cancer. In analyses that controlled for age, gender, race, education, occupation, treatment, cancer site, and Karnofsky performance score, current smokers had a significantly higher symptom burden compared with nonsmokers, both during treatment and 6 months afterwards.[135] Active smoking in patients with advanced lung cancer was associated with greater symptom burden on diagnosis and poorer health-related quality of life post-diagnosis.[136] Additional studies suggest that current smokers with cancer may experience more severe or frequent pain than nonsmoking counterparts.[137-140]

Benefits of Smoking Cessation for Patients with a Cancer Diagnosis

For many smokers, the benefits of smoking cessation can be appreciated immediately through reduced blood carbon monoxide levels, decreased irritative respiratory symptoms (eg, cough, shortness of breath), and improved lung function. In the long term, cessation is associated with reduced risk of smoking-related disease, development of malignancy, and smoking-related mortality.[141] Although the deleterious effects of smoking after a cancer diagnosis are well documented and understood, research on the benefits of cessation post-diagnosis is much more limited.[12,142] For patients with cancer, the potential benefits and risk reductions associated with cessation are of critical importance.

Studies have begun to assess the impact of smoking cessation at or near the time of a cancer diagnosis by comparing outcomes of patients who continue to smoke during cancer treatment to those who quit prior to treatment ("recent quitters"). Studies generally show that recent quitters have survival outcomes intermediate to that of never-smokers and current-smokers, suggesting a measurable benefit of cessation post-diagnosis. The data to support this survival pattern are derived primarily from cohorts of patients with lung or head and neck cancers,[70,72,101,143-145] but similar patterns have been observed for other disease sites.[51,72,146]

A recent study of cancer registry data from Japan (n = 30,658) compared the risk of ACM in never smokers, former smokers (>3 years), recent quitters (≤3 years; 85% within the past year), and current smokers.[147] When combined results were weighted by disease site prevalence, risk of death in recent quitters was reduced by 11% compared with current smokers (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.81–0.97). Risk of death in never/former smokers was found to be 15% to 16% lower than current smokers. Over the course of 10 years, adjusted survival rates were consistently higher among recent quitters, former smokers, and never smokers. When comparing recent quitters to former smokers, a small but significant difference in survival rate was observed (+1.8%–2.9%).[147]

A prospective longitudinal study examined the impact of smoking at diagnosis in 5185 patients with cancer across 13 disease sites over the course of at least 12 years.[72] In this study, recent quitters were examined as a specific subset of former smokers who quit within 1 year of the study's structured smoking assessment, allowing for comparisons to individuals who actively smoked during cancer treatment. For disease sites with larger recent quit cohorts (ie, lung, head/neck cancers), recent quitters had lower overall mortality risk compared with continued

smokers (current smoker vs. recent quitter: lung cancer HR, 1.38–1.42; head/neck cancer HR, 2.11–2.15).[72] Similarly, a systematic review and meta-analysis of 10 observational studies pointed to a 5-year survival benefit for patients with lung cancer who quit smoking compared to patients who continued smoking (70% vs. 33%).[70] In a comprehensive cancer center study that controlled for disease characteristics, smoking history, and patient demographics, 250 patients with lung cancer who quit smoking had statistically improved survival time of 9 months over those who continued to smoke through treatment and beyond.[148]

Smoking cessation is linked to reduced risk of recurrence and second primary tumor formation. Data from patients with lung and head and neck cancers showed that rates of second primary cancers were lower for patients who quit smoking than for those who continued to smoke after diagnosis.[144,149,150] In a cohort of patients with colon cancer, active smokers were at significantly greater risk for baseline metastasis, but interestingly, rates among former smokers and never smokers were similar and significantly less in comparison.[151]

Cessation at or near cancer diagnosis appears to reduce treatment-related complications compared to patients who continued smoking. In patients undergoing lung cancer resection, preoperative cessation mitigated the risk of pulmonary complications and in-hospital mortality. Risk-adjusted odds ratios (ORs) for mortality and pulmonary complications decreased as preoperative cessation time increased from 14 days to 1 month, to 1 to 12 months, and to more than 12 months.[93] A retrospective study of 188 patients undergoing reconstructive surgery after treatment for head and neck cancer revealed that preoperative smoking cessation of at least 3 weeks led to lower incidence of wound healing complications than patients who continued smoking.[152]

Cessation has been shown to lead to improvements in various measures of general health and well-being for patients with cancer. Smoking cessation improved performance status at 6 and 12 months post-lung cancer diagnosis over that of continued smokers when adjusting for disease stage, patient demographics, therapy, and comorbidity.[153] Additionally, patients with cancer who quit smoking benefited from lower rates of smoking-related cardiovascular and pulmonary disease.[154]

Evaluation and Assessment of Patient Smoking

These guidelines highlight the importance of evaluating and assessing smoking status and history in patients with cancer. In a recent policy statement, the AACR emphasized the need for universal assessment and documentation of tobacco use by patients with cancer both in the standard clinical setting and in oncology clinical trials.[12] The NCI-AACR Cancer Patient Tobacco Use Assessment Task Force recently published proposed core and extension items to be used for the assessment of tobacco use in patients with cancer enrolled in research trials.[155] However, current practice is suboptimal, as inadequate or inconsistent assessment and documentation of smoking status has been reported both in the care setting and in the context of clinical trials.[14,22]

Despite the demonstrated adverse effects of smoking during cancer treatment, a large proportion of cancer clinical trials do not collect adequate, up-to-date information regarding patient smoking status and history, particularly for malignancies other than well-known tobacco-related cancers (eg, lung, head and neck cancers).[21,22] Such assessments are needed to make evidence-based determinations of the impact of smoking on patients, treatment efficacy, and side effects.

In a large study conducted at a comprehensive cancer center, a smoking assessment questionnaire was integrated into the electronic health record (EHR) in order to automatically identify and refer appropriate candidates for onsite cessation services. The smoking assessment items incorporated into the EHR were refined based on analysis of responses from an initial patient screen containing 23 items. Response analysis revealed that the most effective questions for generating referrals included whether 1) patients smoked cigarettes every day, some days, or not at all; and 2) if/what other types of tobacco products were used. For former smokers, it was important to assess the last time a patient smoked a cigarette, "even a puff," and for established enrollees to the cessation program, what type(s) of cessation aids were being employed.[156] The study revealed that just 3 assessment questions made it possible to efficiently and accurately identify the vast majority (over 98%) of current smokers or those at risk for smoking relapse.

Determining Smoking Status

The NCCN Guidelines for Smoking Cessation advocate for smoking status to be updated in the patient's health record at regular intervals to indicate any status changes or quit attempts. To do so, the panel recommends the providers initially ascertain: 1) whether the patient has ever smoked, and if so, then regularly assess; 2) whether the patient is a current smoker; and 3) whether the patient has smoked within the past 30 days. All information should be recorded in the medical record. As a follow-up to the initial evaluation, these guidelines direct providers to a tailored patient assessment based on smoking status and history. Specific algorithms for current smokers (patient smoked within the last 30 days), recent quitters (30 days to 1 year prior), and former smokers (≥1 year since patient last smoked) are included. For never smokers or longer-term former smokers, providers should urge patients to remain smoke-free, explaining the benefits of remaining smoke-free. For recommendations regarding lung cancer screening for current/former smokers, see the NCCN Guidelines for Lung Cancer Screening at www.NCCN.org.

Assessing Smokers

In patients who are current smokers (or those who have smoked in the last 30 days), providers should assess nicotine dependency to understand the chances for success and risk of relapse, and document the findings in the patient's health record. To assess nicotine dependency, providers should query patients regarding the amount of cigarettes currently smoked per day, the typical amount smoked within the last 3 months, how soon the patient smokes after waking up in the morning, and whether the patient uses other forms of tobacco (eg, pipes, cigars, snuff, e-cigarettes). The Fagerstrom Test for Nicotine Dependence is an alternative standardized tool for assessing nicotine dependence.[157] However, the panel has opted to recommend a more streamlined assessment for use in the oncology setting.

In order to best tailor treatment, providers should also gather information regarding the patient's history of quit attempts and why they were or weren't successful. Specifically, providers should ascertain the longest period of abstinence achieved, the date of the most recent quit attempt, what cessation aids were employed, and why these failed. It is important to document the patient's previous experience with smoking cessation aids, including any medications, behavior therapy, e-cigarettes, quit-lines, websites, smart phone applications, or other media aids. The patient's perspective on why these aids were unsuccessful—such as medication side effects, continued cravings, or inefficacy—are important pieces of information.

Patient readiness to quit within the next month should be determined. Providers are encouraged to engage patients in a motivation dialog

about smoking and to ensure patients are aware of the disease-specific risks of smoking and benefits of quitting. Educational resources should be provided. The panel recommends that clinicians provide patients with reasons, ideas, and needs for smoking cessation, emphasizing the importance of both encouragement and directness with patients who smoke. When incorporating motivational interviewing (MI) to promote willingness to quit, the panel emphasized the importance of the following general principles: 1) express empathy, 2) develop discrepancy, 3) roll with resistance, and 4) support self-efficacy.[158,159] For a summary of the methods and data on MI for smoking cessation, see the *Principles of Behavior Therapy* section below.

If patients are not ready to quit within the next month, providers should assess and address patient-reported barriers and concerns regarding cessation. When possible, providers should work with patients to set a near future quit date and/or consider smoking reduction with the goal of cessation in the near future. The panel encourages immediate initiation of pharmacotherapy for targeted smoking reduction with a goal of cessation in the near future. A meta-analysis of 10 randomized trials in 3760 patients with cancer found quit rates to be comparable when comparing abrupt cessation to gradual smoking reduction.[160,161] Therefore, both options can be used after discussions with the patient. Trial data since then have continued to mirror this trend of comparable success rates with abrupt cessation and gradual reduction.[162] At each visit, providers should reassess readiness to quit and engage in motivational dialog as indicated.

Assessing Former Smokers/Recent Quitters

To evaluate patients who recently quit (30 days to 1 year prior), providers should assess and document the patient's risk of relapse. The panel suggests the following characteristics to identify patients at high risk for relapse: frequent/intense cravings; elevated anxiety, stress, or depression; cohabitating or working with smokers; quitting within the past year; use of ongoing smoking cessation treatment; and drug/alcohol use or abuse. The panel considers patients demonstrating at least one of these characteristics to be at higher risk for relapse and recommends a management plan tailored to prevent relapse. Providers should discuss risk of relapse with patients and provide guidance and support to promote continued smoking cessation attempts. As indicated, refer patients with anxiety and/or depression to a specialist to manage psychiatric comorbidities.

Management of patients who demonstrate an elevated risk of relapse includes behavior therapy with counseling on relapse risk factors and relapse prevention. Pharmacotherapy can be considered to promote maintenance of abstinence. However, the panel recommends careful consideration of the potential effects of nicotine re-introduction via NRT in patients who have been nicotine free for an extended period of time (ie, ≥30 days). Providers should review smoking-associated risks for patients with cancer as well as the health benefits of abstinence. All management plans and counseling should be documented in the patient health record. For patients deemed to be at low risk for relapse, providers should reinforce success and highlight the importance of continued abstinence. Risk of relapse should be reevaluated at subsequent visits.

It is important to regularly reevaluate patients' smoking status and risk of relapse, which can be accomplished in person or by phone. If relapse occurs, patients should be evaluated per the recommendations for current smokers. Additionally, providers should remain aware that patient self-report of smoking status may underestimate the rate of active smoking among patients with cancer, as is evidenced by research comparing self-reported and objective measures.[163-165] Patients

who remain smoke free should regularly undergo reevaluation with documentation of any risk factor changes.

Smoking Cessation During or After Cancer Treatment

The following recommendations are appropriate for patients who are currently undergoing cancer treatment as well as cancer survivors.

Devising a Treatment Plan

Following assessments, providers should establish a personalized quit plan for each patient that takes into account the patient's nicotine dependency, prior quit attempts and any cessation aids used, and smoking cessation therapy options. Providers should work with patients to set a quit date as soon as possible. Risk of relapse and smoking slips should be discussed with the patient along with reassurance and support for continued cessation efforts should slips occur.

Smoking Cessation and Cancer Surgery

Smoking has been shown to increase the risk of pulmonary and cardiovascular complications, surgical site infection, and poor wound healing in patients undergoing surgery. For an overview of the data, see section on *Smoking-Related Effects on Treatment Efficacy, Side Effects, and Outcomes* in this Discussion. Study findings generally support the benefits of preoperative smoking cessation, which has been shown to reduce postoperative morbidity in patients undergoing surgery for various cancer types.[93,166-168]

For patients with planned cancer surgery, cessation should occur as soon as possible before surgery, regardless of how short the time to surgery is. There is no evidence to support a harmful effect of quitting any time before surgery. Although longer periods of preoperative smoking cessation may confer better surgical outcomes,[167,169] the panel emphasizes that patient smoking should not delay appropriate timing for cancer resection, and access to cancer surgery should not be restricted based on smoking status. Preoperative smoking cessation interventions that combine pharmacotherapy with behavioral therapy may be most effective.[170-173] NRT at the normal doses has not been shown to negatively affect acute wound healing,[174-176] and therefore functions as a valuable adjunct to perioperative smoking cessation.

Elective procedures, such as plastic surgery reconstruction, may benefit from delaying surgery for a period of time after smoking cessation. At this time, consensus on an optimal time period of preoperative cessation has not been demonstrated through the existing literature.[169] Providing surgery-specific resources and advice for smoking cessation may facilitate smoking reduction or cessation in patients undergoing elective (non-cancer) surgery.[177,178]

Preferred Primary Therapy Options

Based on clinical trial data of smoking cessation in patients with cancer, the panel recommends a combination frontline approach including pharmacotherapy and behavior therapy for smoking cessation for patients with cancer. Population studies and meta-analyses of randomized or quasi-randomized trial data support the addition of behavior therapy to pharmacotherapy to enhance the rate of success.[179-181]

Preferred primary therapy options in these guidelines are 1) combination NRT; or 2) varenicline (typical initial duration of 12 weeks). The combination NRT approach includes the use of a nicotine patch plus a short-acting NRT for breakthrough cravings, such as nicotine gum, lozenge, inhaler, or nasal spray. Patients commonly underdose when using combination NRT.[182-184] Patients should be advised that nicotine overdose is rare but possible, and usually short-lived. Providers should also note that nausea is a common side effect of varenicline and

may need to be managed in patients with cancer who are receiving chemotherapy. Additionally, varenicline and bupropion should be avoided in patients with brain metastases due to increased seizure risk. For discussion of the evidence for individual pharmacotherapeutic regimens, see the section below on *Principles of Pharmacotherapy*.

As a general principle, the panel recommends trying both preferred primary therapy approaches (combination NRT and varenicline) before proceeding to any of the subsequent pharmacotherapy options. See section below on *Treatment for Persistent Smoking or Relapse* for additional details. Pharmacotherapy regimens should always be paired with behavioral counseling.

Follow-up

Assessment of smoking status and toxicity of pharmacotherapy should be performed within 3 weeks of initiating therapy (within 1 week preferred), at 12 weeks. Assessment should continue on a periodic basis moving forward, including within about 12 weeks following completion of pharmacotherapy. Nicotine withdrawal symptoms typically peak within 1 to 2 weeks of cessation before subsiding. Initial follow-up within 2 weeks of initiating smoking cessation therapy is important in order to assess efficacy and toxicity of pharmacotherapy. Patients who do not quit immediately may quit at a later point once withdrawal symptoms subside. Therefore, providers should encourage continued treatment adherence through brief slips, with adjustments to dose or behavior therapy frequency as indicated. Undesirable side effects may also warrant dose adjustments.

When possible, in-person follow-up during planned clinical visits or individual/group therapy sessions is preferred. To minimize the burden on patients in active cancer therapy, behavior therapy can be provided by a trained member of the health care team during oncology visits. Alternatives include phone contact. During follow-up, providers should assess risk of relapse and, as indicated, consider adjusting the dose and or type of pharmacotherapy. Patients may slip or relapse, which is expected and can be managed. Maintain close follow-up through the duration of therapy. At 12 weeks, assessment of smoking status should be made in person or by phone. For pharmacotherapy courses exceeding 12 weeks duration, assessment should be repeated at the end of the course of therapy.

If patients remain smoke free, additional follow-up should take place at 6 and 12 months, either in person or by phone. Motivational strategies should be employed to promote continued abstinence. Duration of pharmacotherapy can be extended beyond 6 months if clinically indicated. Patients who experience smoking relapse can be considered for second-line therapy.

Treatment for Persistent Smoking or Relapse

For patients who continue to smoke or experience relapse, reevaluate the use of pharmacotherapy and provide additional behavior therapy. The panel recommends continuation of initial pharmacotherapy or switching to the alternate preferred option (combination NRT or varenicline). These regimens should always be paired with continued behavior therapy. Both preferred primary therapy approaches (combination NRT and varenicline) should be tried before proceeding to any of the subsequent pharmacotherapy options.

Subsequent options for pharmacotherapy include combination NRT with bupropion sustained release (SR), or bupropion SR alone (category 2B). Bupropion should be avoided in patients with brain metastases due to increased seizure risk. For further relapse, extended duration of pharmacotherapy can be considered. Additional or more intensive behavior therapy is also an option.

After switching therapy or adjusting the dose of an existing regimen, follow-up should occur within 3 weeks and after 12 weeks of therapy. Smoking status should be re-evaluated. For patients who are smoke-free, the course of pharmacotherapy can be extended as clinically indicated. Additional follow-up at 6 and 12 months after successful quitting is recommended.

Principles of Pharmacotherapy

General

A minimum of 12 weeks of combination NRT or varenicline is recommended for the initial quit attempt. Duration of therapy can be extended to promote continued cessation, but providers should attempt to avoid unnecessarily long treatment duration when possible. Research suggests that longer courses of certain cessation regimens may be associated with higher rates of 7-day point-prevalence abstinence.[185]

Follow-up is recommended 2 weeks after starting pharmacotherapy but can be extended to 3 weeks to coordinate with scheduled oncology appointments. For relapse or continued smoking, options include continuation of the initial agent or a switch to the alternative preferred agent. Dose adjustments should be considered as clinically indicated. Attempts at smoking reduction should be tracked. If reduction efforts stall or if complete abstinence seems unlikely, providers should consider an alternative pharmacotherapy regimen.

In most circumstances the side effects related to primary smoking cessation medications are minimal and are considered an acceptable risk compared to smoking. A review of post-marketing case reports on adverse neuropsychiatric effects from smoking cessation medications have generated some safety concerns in the past,[186] but recent large-scale analyses of the data support the safety of these regimens.[187,188]

Although serious side effects of primary cessation approaches are extremely rare, providers should refer to manufacturer inserts for exhaustive lists of potential side effects and warnings.

Adherence to pharmacotherapy is important to promote optimal outcomes and success, and numerous studies have tested interventions designed to promote and improve medication adherence.[189]

Below, data from various clinical trials are discussed. Included in this discussion are findings from a 2013 Cochrane network meta-analysis that included data on pharmacologic interventions across 267 individual studies in 101,804 participants.[190] The authors characterized positive treatment outcome as continuous or prolonged abstinence at least 6 months from the start of smoking cessation therapy. Harm outcomes were measured by the incidence of serious adverse events associated with treatment.

Primary Therapy Options

For patients with cancer, the guidelines recommend primary therapy with either combination NRT or varenicline. If smoking persists or relapse occurs while a patient is on an initial primary therapy regimen, providers should continue therapy with that initial regimen or switch to the alternate primary therapy option. Both preferred primary therapy options should be used before trying any subsequent therapy options. The efficacy and safety data on preferred primary regimens are summarized below.

Combination Nicotine Replacement Therapy

Efficacy

NRT offers an alternative nicotine delivery method and can be used to ameliorate nicotine withdrawal symptoms during cessation attempts. Combination NRT incorporating long-term and fast-acting NRT offers the greatest potential benefits for smokers.[170,190-192] Cochrane network meta-analysis data published in 2013 support the superiority of combination NRT over single forms of NRT such as nicotine patch (OR, 1.43; 95% CI, 1.08–1.91), nicotine gum (OR, 1.63; 95% CI, 1.21–2.2), and various other forms that collectively include inhaler, lozenge, spray, or tablets (OR, 1.34; 95% CI, 1.0–1.8).[190] All forms of NRT were superior to placebo, but smokers using combination NRT were almost three times as likely to succeed (OR, 2.73; 95% CI, 2.07–3.65).[190] Compared with single forms of NRT, combination NRT using a patch plus short-acting NRT improved the odds of quitting (OR 1.34; 95% CI, 1.18–1.51).[190,193]

The success of NRT may be contingent on concurrent behavior therapy to support cessation. In a large population study, over-the-counter NRT resulted in similar rates of cessation to those who used no aid. The addition of behavior therapy to NRT increased the odds of success nearly three-fold.[179]

Safety

The safety of combination NRT for use in humans has been demonstrated and benefits are considered to outweigh potential risks.[194] Importantly, providers should be aware that blood nicotine levels from NRT, including combination NRT, are significantly less than that from smoking cigarettes.[195-197] In fact, patients commonly underdose when using combination NRT,[182-184] and although nicotine overdose is possible, it is rare and usually short-lived. Therefore, providers and smokers should not be dissuaded from using NRT to foster quitting and long-term cessation. Recent reviews of the data suggest that NRT is not linked to increased serious cardiovascular adverse events when used for smoking cessation.[198] While myocardial infarction has rarely been reported in NRT users, there is insufficient evidence that NRT increases the risk of myocardial infarction or cardiovascular disease.[193,199] Data from large case series have not shown elevated risk with the use of NRT in patients with acute coronary syndromes.[200,201]

In the past, the safety of NRT has been evaluated in light of the bioactivity of nicotine and evidence that this drug can promote cell growth in certain types of cancer cells.[202] Some *in vitro* data suggested that nicotine increased the malignant potential of small cell lung cancer cells[203]; induced chemoresistance in models using lung cancer cells[123-125] and nasal epithelial cells[126]; and promoted chemoresistance and metastasis in pancreatic cancer cell and mouse models.[127] However, other studies suggested no effects of physiological levels of nicotine exposure on tumorigenesis in mouse lung cancer models.[204,205] Moreover, there is insufficient evidence that NRT causes cancer in humans.[204-208] Evaluation of data from 3320 participants in the Lung Health Study, which recorded in-study NRT use and smoking exposure, found that NRT was not a significant predictor of lung cancer, while smoking was.[207]

Varenicline

Efficacy

Varenicline is a non-nicotinic partial agonist of the alpha4beta2 subtype of the nicotinic acetylcholine receptor. Varenicline partially mimics the effects of nicotine in the brain's reward center and competitively inhibits the binding of nicotine from cigarettes.[209]

Systematic reviews/meta-analyses have identified varenicline as the most effective single pharmacotherapy option for smoking cessation.[190,210,211] Cochrane network meta-analysis data report that varenicline increases the odds of smoking cessation by almost three-fold compared with placebo (OR, 2.88; 95% CI, 2.40–3.47).[190] Direct comparison of the cumulative data suggest that varenicline was more efficacious than bupropion (OR, 1.59; 95% CI, 1.29–1.96) and single forms of NRT such as nicotine patch, nicotine gum, and other formulations (OR, 1.57; 95% CI, 1.29–1.91).[190] Varenicline appeared to be equally as likely to promote smoking cessation as combined treatment with more than one form of NRT (OR, 1.06; 95% CI, 0.75–1.48), so that both may be offered depending on patient circumstances.[190]

Results recently published from the double-blind EAGLES RCT (n = 8144) revealed that varenicline-treated patients achieved higher abstinence rates than patients receiving placebo (OR, 3.61; 95% CI, 3.07–4.24), nicotine patch (OR, 1.68; 95% CI, 1.46–1.93), or bupropion (OR, 1.75; 95% CI, 1.52–2.01).[212] A recent study investigated the efficacy of varenicline specifically for patients with cancer, revealing 84% retention and 40% abstinence at 12 weeks. Side effect profiles mimicked those observed in the general population, and abstinence improved cognitive function and reduced negative affect over time.[213]

Varenicline may also be efficacious for smoking reduction. A clinical trial enrolling 1510 individuals revealed that a 24-week course of varenicline effectively promoted smoking cessation in patients who were unwilling to quit but willing to gradually reduce cigarette consumption.[214] Therefore, this agent provides an alternative for patients who cannot or will not attempt abrupt cessation. A clinical trial in 1236 smokers showed that an additional 12 weeks of varenicline maintenance therapy helped to sustain continued abstinence in those who successfully quit during initial treatment.[215]

One study examined whether varenicline dose increases would boost treatment efficacy in patients who had a low or no response to standard dosing. A double-blind RCT of 503 smokers found no evidence to suggest that gradual dose titration beyond the standard 2-mg dose (up to a maximum 5 mg/d) lessened frequency of urges and nicotine withdrawal symptoms, or increased cessation rates.[216] However, nausea and vomiting were increased in the treatment group receiving more than 2 mg/d. Additionally, another RCT showed that varenicline was effective and well-tolerated for retreating patients who had previously received this agent (n = 498).[217]

A recent RCT (n = 1246) examined whether a biomarker of nicotine clearance (nicotine metabolite ratio, NMR) was predictive of nicotine patch versus varenicline efficacy in “slow” versus “normal” metabolizers of nicotine. The findings showed that varenicline was more effective than nicotine patch in normal metabolizers, but varenicline superiority was not observed among slow metabolizers, suggesting the possibility in the future to optimize treatment selection based on this biomarker.[218]

Safety

Varenicline safety has been extensively examined to determine the risk of adverse effects, particularly serious cardiovascular events and neuropsychiatric changes. Initial phase III studies found varenicline to be safe and generally well-tolerated compared with bupropion or placebo; common side effects included nausea, insomnia, and abnormal dreams with rates of approximately 28% to 29%, 14%, and 10% to 13%, respectively.[219,220]

Concerns regarding neuropsychiatric adverse effects of varenicline have been extensively investigated in smokers with comorbid mental illness.[190] Despite reviews of case reports that raised concern,[186] a 2015 systematic review and meta-analysis of 39 randomized controlled smoking cessation trials identified no evidence to suggest that varenicline increases risk of suicide or suicide attempts, suicidal ideation, depression, or death.[188] Another trial showed that varenicline increased smoking cessation rates without exacerbating anxiety and depression symptoms in adults with stably treated current or past depression.[221] Results were recently published from a large double-blind RCT (EAGLES trial) that enrolled 2 cohorts: individuals with psychiatric disorders (n = 4116) and those without psychiatric disorders (n = 4028). No significant increase in neuropsychiatric events was observed for varenicline relative to nicotine patch or placebo. Varenicline was associated with significantly higher abstinence rates than bupropion plus nicotine patch, as well as placebo.[212]

Cardiovascular risks have also been examined. Importantly, recent systematic reviews and meta-analyses of RCT data have not identified a significant link between varenicline and increased risk of serious cardiovascular adverse events.[190,198,222,223] However, the cardiovascular safety of varenicline has remained a topic of interest and concern.[224-226]

In a 2015 retrospective review of 164,766 individuals who received pharmacotherapy for smoking cessation (varenicline, n = 51,450; NRT, n = 106,759; bupropion, n = 6557), neither varenicline nor bupropion posed an elevated risk of cardiovascular or neuropsychiatric (depression, self-harm) events compared with NRT.[227] Based on the current evidence base for safety risks, the panel considers varenicline to be safe and to have a favorable risk/benefit ratio for use in patients with cancer who smoke.

Although rare, elevated seizure risk is a concern with varenicline therapy.[228,229] In patients with brain metastases who have a history or elevated risk of seizure, varenicline should be avoided.

Subsequent Therapy Options

Recommended subsequent therapy options in these guidelines include combination NRT with bupropion SR or bupropion SR alone (category 2B). Currently, other regimens are not recommended in this treatment setting. However, the panel acknowledges ongoing evaluation of alternative regimens (eg, varenicline plus combination NRT; varenicline plus bupropion, nortriptyline, or clonidine). The panel regularly reviews the evidence base for alternative regimens when updating these guidelines. The data for various regimens are summarized below.

Recommended Regimens

Bupropion + NRT

A large trial in the United Kingdom (n = 1071) examined the efficacy of NRT alone, bupropion alone, and NRT plus bupropion.[230] All participants received 7 weeks of behavior therapy support in addition to the pharmacologic interventions. Abstinence rates at 6-month follow-up ranged from 24.2% to 27.9% and did not differ significantly between cohorts. Several unwanted side effects were more common with bupropion than NRT (eg, disturbed sleep, dry mouth, headaches, nausea), and side effects of combination therapy were not significantly different versus bupropion alone. Five serious adverse events occurred in the bupropion group, including allergic reaction (n = 3), neuropsychiatric symptoms (n = 1), and chest pain (n = 1). A trend toward improved efficacy of bupropion in patients with a history of depression was noted ($\chi^2 = 2.86$, $P = .091$).

A double-blind RCT compared bupropion + NRT, bupropion alone, nicotine patch alone, and placebo in 893 individuals who smoked at least 15 cigarettes per day. At 12 months, the highest abstinence rates were observed for the bupropion + NRT group (35.5%) and bupropion only group (30.3%), although these groups did not differ significantly.[231] A smaller RCT studying the addition of bupropion to combination NRT and behavior therapy in patients with schizophrenia suggested that combination pharmacotherapy promoted smoking reduction and cessation, but also demonstrated a high relapse rate after discontinuation of treatment.[232] A 2014 meta-analysis of 12 trials examining this combination revealed a nonsignificant trend in improved cessation with the addition of NRT to bupropion.[233]

Bupropion

Bupropion was first approved to treat depression but its efficacy as a cessation aid also became apparent. In addition to its effects on the dopaminergic and adrenergic systems, this agent also acts as an inhibitor of nicotinic acetylcholingeric receptors. A 2014 Cochrane review of 44 trials examined bupropion efficacy, revealing an RR of 1.62 (95% CI, 1.49–1.76).[233] Recent results from the EAGLES trial (n = 8144) revealed that patients receiving bupropion achieved superior abstinence rates compared with placebo (OR, 2.07; 95% CI, 1.75–2.45).[212] Efficacy was similar to nicotine patch but less than that for varenicline. Some evidence suggests that bupropion may be particularly beneficial as a smoking cessation agent for persons with depression.[230,234] Additionally, longer duration of bupropion treatment may help to prevent relapse in those who have successfully quit.[235]

Bupropion reduces the seizure threshold and meta-analyses of trial data have found a 0.1% seizure risk among those receiving the drug for smoking cessation.[233] In patients with brain metastases who have a history or elevated risk of seizure, bupropion should be avoided.

Neuropsychiatric effects have also been identified as a safety concern with bupropion, although to a lesser extent than varenicline.[186] However, recent systematic reviews of the data have found that serious neuropsychiatric adverse events were rarely associated with bupropion prescribed for smoking cessation, including studies of bupropion in patients with mental illness.[190,236] In the EAGLES trial, no significant increase in neuropsychiatric events was observed for bupropion relative to nicotine patch or placebo.[212]

Similarly, regarding risk of serious adverse cardiovascular effects, recent meta-analyses do not show elevated risk as a result of bupropion use for smoking cessation.[190,198,233]

Other Regimens

Several other pharmacotherapy regimens for smoking cessation have been studied in clinical trials but are not recommended by the panel at this time based on the existing data. Data from these studies are summarized below for informational purposes.

Varenicline + NRT

A study in 435 smokers found that the addition of nicotine patch to varenicline therapy significantly increased the cessation rates at the end of treatment (12 weeks), at 24 weeks, and at 6-month follow-up.[237] No significant differences were noted for side effect incidence between varenicline/NRT and varenicline/placebo with the exception of skin reactions, which were increased with combination therapy (14.4% vs. 7.8%; $P = .03$). However, one RCT of 341 smokers did not find enhanced cessation rates at 12- and 24-week follow-up among individuals receiving a combination of varenicline and nicotine patch, versus varenicline alone.[238] The addition of nicotine patch to varenicline did not cause significant changes in side effect profiles. Similarly, a trial in 117 participants did not find evidence that the addition of NRT to

varenicline increased abstinence rates at 1, 4, or 12 weeks after the targeted quit date, and no between-group differences in adverse effects were found.[239]

Varenicline + Bupropion

In an RCT of smokers who demonstrated an inadequate response to front-line nicotine patch treatment (n = 222), combination therapy with varenicline and bupropion appeared to be more efficacious than varenicline alone as a second-line therapy option.[240] This observation was more pronounced among male smokers and those with a high level of nicotine dependency. Although no significant differences in side effects were observed between varenicline and bupropion versus varenicline alone, dose reductions were required for 11.5% and 24.8% of patients, respectively. Common side effects were vivid dreams, change in taste perception, thirst, insomnia, and irritability. Another study of varenicline + bupropion therapy versus varenicline alone (n = 316) demonstrated that combination therapy increased prolonged abstinence but did not affect 7-day point prevalence at 12 and 26 weeks follow-up, and no significant differences were observed between the groups at 52 weeks.[241] In this study, anxiety (7.2% vs. 3.1%; $P = .04$) and depressive symptoms (3.6% vs. 0.8%; $P = .03$) occurred more frequently in patients receiving combination therapy versus varenicline alone.

Nortriptyline and Clonidine

Studies have also suggested some efficacy of off-label use of nortriptyline, a tricyclic antidepressant, as well as the antihypertensive agent clonidine.

A Cochrane network review identified 6 trials comparing nortriptyline with placebo, finding a pooled RR of 2.03 (95% CI, 1.48–2.78).[102,133] However, as an adjunct to NRT, clear-cut benefits were not observed.[190,242]

Clonidine is recommended as a third-line smoking cessation option. Although several studies have produced data in favor of clonidine as a cessation aid versus placebo, not all study data reveal a statistically significant effect. Additionally, clonidine's benefits can be counteracted by dose-dependent increases in drug side effects. A 2013 Cochrane network review of data from 6 studies resulted in a pooled RR of 1.63 (95% CI, 1.22–2.18).[102]

Principles of Behavior Therapy

General Principles

The guidelines provide the following guiding principles on behavior therapy, which have been developed in consideration of the existing evidence base, clinical practice guidelines, and expert consensus.[180,181,194]

The panel recommends a combination of behavior therapy with pharmacotherapy for best outcomes. In fact, studies suggest that counseling for smoking cessation may enhance patient satisfaction.[15,16] A 2012 systematic review of 41 studies provided support for the efficacy of this approach.[180] The "real world effectiveness" of adding a behavior therapy component to smoking cessation therapy was further supported by a large population study published in 2014.[179] Additionally, a 2016 meta-analysis of data from 1239 patients with head and neck cancer showed improved smoking cessation rates with the addition of counseling to usual care (NRT).[243]

Behavior therapy may enhance motivation and support optimal medication strategies and adherence to pharmacotherapy. When possible, therapy should be provided by a tobacco treatment specialist

or dedicated staff member (ie, nurse, medical assistant, health educator) with training in motivational and behavior strategies for smoking cessation.

As a general principle, more intensive behavior therapy is preferred over brief advice or counseling.[181] The evidence supports a measurable dose-response effect of behavior therapy with more numerous and/or longer sessions delivering improved outcomes. The panel defines intensive behavioral therapy as at least 4 sessions within 12 weeks (in person; group or individual) lasting at least 10 minutes but typically 30 minutes or longer. As patients progress through multiple lines of pharmacotherapy, behavior therapy should be progressively intensified with referral to specialty care (eg, psychiatrist, psychologist) as indicated. Studies have also demonstrated additional benefit for relapse prevention of extending behavioral therapy for six months or more.[244-246] Importantly, if intensive therapy is not feasible, brief counseling should still be given. Studies have demonstrated a small but significant benefit of counseling lasting only a few minutes.[41-44]

The most successful behavior therapy strategies employ practical counseling, which addresses problem solving and skills training, as well as social support and MI (see section on *Motivational Interviewing* below) as elements of the treatment plan.[159,194] Optimally, behavior therapy plans should take into account a patient's nicotine dependence levels, previous quit attempts, and cessation aids utilized. In doing so, patients can be equipped with tailored strategies to cope with nicotine withdrawal symptoms, environmental smoking triggers, and stressful situations. For instance, the addition of a cognitive behavior therapy program designed to improve stress management improved cessation rates over controls receiving standard smoking cessation therapy.[247]

Providers should prepare patients for nicotine withdrawal symptoms and cravings, which typically peak at several days to 2 weeks post-cessation before gradually subsiding.[248-250]

A number of modalities can be employed to deliver behavior therapy to patients. Counseling can take place in a variety of settings such as in person, remotely by telephone,[45] or through web-based interventions.[251] Effective in-person counseling can occur as an individual session or in the group therapy setting.[252,253] Additionally, print materials[254] and mobile telephone "apps"[255-257] can be used to deliver behavior therapy. However, providers should be aware that media-based behavioral interventions, particularly those using mobile telephones, may vary in the degree to which they comply with clinical practice guidelines.[258]

A recent study investigated preferences for the provision of smoking cessation information among Canadian patients with cancer. Patients most often preferred print materials (45%), followed by telephone support (39%), speaking with a clinician (29%), website-based information (15%), and support groups (11%). Younger patients (≤45 years) were more likely to prefer cessation advice via telephone, while older patients preferred print materials.[259] Selection of a particular modality or modalities should be guided by patient preference, medical history, and resource availability.

For patients who are unable to quit, referral to a smoking cessation clinic is encouraged when available. If specialized resources are limited, effective behavior counseling can still be provided. For instance, brief counseling by providers has been shown to generate a small but important increase in quit rates.[41-43] Additionally, quitlines can provide essential behavioral support in the absence of in-person counseling resources.[45] For instance, the addition of combination NRT to quitline counseling improved cessation outcomes.[260]

Tailoring Behavior Therapy for Patients with Cancer

As resources allow, specialized treatment centers should provide tailored smoking cessation therapy programs that address the unique needs of patients with cancer, or refer to external resources (eg, quitlines) that provide such specialized services. For patients in active cancer treatment, behavior therapy can be provided during scheduled oncology visits to obviate the need for additional appointments. Beneficial services might include individual and group therapy focusing on the challenges specific to cancer treatment and survival, which would ideally be provided by clinicians experienced in working with patients with cancer. A recent study suggested age-based differences in preferences for smoking cessation resources.[259]

The prevalence of mental disorders or serious emotional issues in patients with cancer is high, with several large studies reporting rates between 30% and 40%.[261-263] The high rates of anxiety, depression, and stress can present a significant challenge for patients with cancer who attempt to quit smoking in the face of these common smoking/relapse triggers. Patients with cancer, particularly those experiencing psychiatric comorbidity, may benefit significantly from behavior therapy programs tailored to manage cancer-related issues that predispose patients to relapse. Referral to specialized smoking cessation programs may be necessary so that these patients have access to staff trained to treat comorbid substance dependence and mental health disorders.

Motivational Enhancement

All cancer patients and survivors should be encouraged to quit. Strategies to enhance motivation to quit are beneficial for all patients, including those who are currently ambivalent or unwilling to quit. Motivational interviewing is one evidence-based approach to foster motivation to quit in which a clinician offers empathy as the patient explores ambivalence regarding quitting smoking. Clinicians reflect, validate, and summarize patient concerns and help patients identify discrepancies between smoking and core values/goals (eg, health, parenting) and support patient confidence regarding quitting.[29,158,159]

A 2015 Cochrane database review of 28 studies examined the efficacy of MI for smoking cessation, revealing a modest but significant increase in chance of quitting with MI versus brief advice or usual care.[264] MI by a primary care physician appeared to be somewhat more successful than that administered by counselors, although both were effective. Notably, one-time short MI sessions of less than 20 minutes had demonstrated efficacy.[264] A recent systematic review summarized the evidence to support MI for behavioral change, including smoking cessation, in patients with cancer.[265]

In order to promote willingness to quit smoking, the US Preventive Services Task Force (USPSTF) recommends a model of MI that employs the “5 R’s” of the personal Relevance of quitting; personal Risks of continuing smoking; personal Rewards of quitting; identifying Roadblocks to quitting; and Repeating the message at every contact.[194] This model encourages that motivational information be relevant to the individual patient, and that clinicians and patients work together to identify personalized risks of smoking and potential rewards of cessation. By having the patient identify perceived roadblocks to quitting, providers can suggest tailored treatments to address patient-reported concerns. Finally, this model recommends repetition of MI at each patient visit, coupled with reminders that repeated quit attempts may be necessary to achieve long-term cessation.

Alternative Treatment Approaches

The panel has reviewed the available evidence for alternative smoking cessation treatment approaches. Continue to provide motivational and

behavioral support to all patients during quit attempts, regardless of what smoking cessation methods are being used, including e-cigarettes. Particular attention has been paid to the discussion of e-cigarettes for smoking cessation given increasing popularity and widespread use. Limited data are available on the safety and efficacy of these approaches, specifically for patients with cancer; data have been drawn primarily from studies in the general population.

The panel has found insufficient evidence to support the use of alternative therapies alone or in combination with standard smoking cessation methods, and use of alternative therapies is not recommended. The guidelines recommend that patients use evidence-based cessation methods to avoid any delay in achieving smoking abstinence. Smoking slips and relapse are common, and prior unsuccessful quit attempts with conventional therapies do not justify the use of unproven alternative cessation methods. When discussing alternative therapies, providers should counsel patients on potential interactions with evidence-based cessation methods and/or cancer treatments.

Electronic Cigarettes/Electronic Nicotine Delivery Systems

The popularity of electronic cigarettes, “e-cigarettes,” and their various derivatives is a recent phenomenon, and, as such, the available literature is new and relatively limited, particularly within specific subpopulations such as patients with cancer. Electronic nicotine delivery systems (ENDS) are not FDA-approved smoking cessation devices. At the present time, the panel does not recommend use of e-cigarettes, and instead known effective methods for smoking cessation should be offered. Below, we discuss the current data and expert opinions on e-cigarettes for smoking cessation.

Several health care organizations have released similar policy statements concerning ENDS, highlighting the urgent need for research on the safety of these devices and efficacy as a cessation aid. The American Heart Association, AACR, and ASCO recognize the potential for ENDS to alter existing smoking behaviors, as well as the lack of definitive data regarding associated benefits and harms.[266,267] Experts in the field generally acknowledge that ENDS may offer an attractive approach for smoking reduction and/or cessation in certain populations. However, these policy statements also highlight the unknown potential for ENDS to affect nicotine addiction, combustible tobacco product use, and renormalization of smoking behaviors. In the September 2015 Final Recommendation Summary, the USPSTF concluded “that the current evidence is insufficient to recommend ENDS for tobacco cessation. The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety”.[268] Currently, provider education and training on e-cigarette use may be inadequate, and clinicians have reported low confidence in their ability to provide patient counseling on this matter.[269]

One study examined e-cigarette use in 1074 patients with cancer who enrolled in a tobacco treatment program at a comprehensive cancer center.[270] The study revealed a marked increase in e-cigarette use from 10.6% to 38.5% between 2012 and 2013. E-cigarette users, most often patients with thoracic or head and neck cancers, were more nicotine dependent and had greater numbers of prior quit attempts. At follow-up (6–12 months after intake), e-cigarette users were no more likely to have quit than non-users (OR, 1.0; 95% CI, 0.5–1.7), calling into question the potential benefits of e-cigarettes as a cessation agent for patients with cancer. In a cross-sectional analysis of cancer survivors in the United States (n = 2695 excluding non-melanoma skin cancers), e-cigarette use was highest among current cigarettes smokers, compared

with former or never cigarette smokers.[271] Collectively, these studies highlight the importance of addressing e-cigarette usage by patients with cancer and cancer survivors.

High-quality data on e-cigarette use for smoking cessation, including head-to-head comparisons of e-cigarettes with evidence-based therapies, are extremely limited. In the largest RCT to date, 657 individuals were randomized to receive nicotine e-cigarettes, placebo e-cigarettes, or nicotine patch. Abstinence rates were unexpectedly low across all groups, with no statistically significant differences in biochemically verified smoking abstinence between treatment groups at 6 months.[272] Systematic reviews have summarized the data from the general population to determine the potential efficacy of e-cigarettes as a smoking cessation aid. Conclusions have varied, likely due to the limited overall pool of data and heterogeneous study measures.

Recent data suggest a detrimental impact of e-cigarette use on smoking cessation. In a comprehensive meta-analysis of 20 controlled studies (2 trials, 15 cohort studies, and 3 cross-sectional studies), individuals using e-cigarettes were 28% less likely to achieve smoking cessation (OR, 0.72; 95% CI, 0.57–0.91).[273] Sensitivity analyses revealed no impact of quit intention and other study variables. Similarly, e-cigarette use did not decrease cigarette smoking in a cross-sectional study in 106 patients with head and neck cancers seeking to quit. Non-users of e-cigarettes had a significantly greater rate of cessation compared with e-cigarette users (72% vs. 39%; P =.0057).[274]

However, some earlier studies suggested a potential benefit of e-cigarettes for smoking cessation. In one meta-analysis, findings suggested that more individuals reduced cigarette consumption with nicotine e-cigarette vs. placebo (RR, 1.31; 95% CI, 1.02–1.68), and one study suggested that nicotine e-cigarettes improved reduction over nicotine patch (RR, 1.41; 95% CI, 1.20–1.670).[275] Across all 13 studies examined, no serious adverse events were reported.[275] Similarly, a 2015 systematic review and meta-analysis of data from 1242 participants suggested that nicotine-containing e-cigarettes were more effective cessation aids than non-nicotine–containing e-cigarettes (RR, 2.29; 95% CI, 1.05–4.97).[276] E-cigarette use over a minimum of 6 months was associated with an 18% reported smoking cessation rate (effect size, 0.20; 95% CI, 0.11–0.28), and e-cigarette use was also associated with smoking reduction.[276] A large cross-sectional study of 5863 adults in the United Kingdom assessed the “real-world effectiveness” of e-cigarettes for smoking cessation compared to NRT and unaided quitting, revealing that e-cigarette users were more likely to report abstinence compared with the other cohorts (e-cigarettes vs. NRT: OR, 2.23; 95% CI, 1.70–2.93; e-cigarettes vs. no aid OR 1.38; 95% CI, 1.08–1.76).[277] These observations persisted when adjusting for measures of nicotine dependence across the cohorts.

Other Alternative Approaches

Very limited data exist to support exercise-based interventions; small study size, inadequate controls, and insufficient exercise intensity limit the ability to make conclusions based on the existing evidence.[278] Sufficient efficacy data are also lacking to support the use of alternative therapies such as acupuncture, hypnosis, and nutritional supplements. A 2014 systematic review of the data on acupuncture, acupressure, and laser therapy revealed no consistent, bias-free evidence to support these methods for smoking cessation, although pooled evidence was suggestive of possible short-term benefits.[279] Acupuncture was less effective than NRT and there was no evidence to support electrostimulation for smoking cessation. Similarly, systematic reviews of the data on hypnosis for smoking cessation revealed inadequate high-quality evidence to support this approach.[280,281] Claims of efficacy

data for hypnosis from several studies were not substantiated by the review of RCT data. Controlled studies are needed to provide higher quality evidence on these interventions both in the general population and among patients with cancer.

References

1. Smoking & Tobacco Use: Fast Facts. In: Office on Smoking and Health NCfCDPaHP ed. Atlanta: Centers for Disease Control and Prevention; 2017. Available at: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm.

2. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services 2014. Available at: http://www.surgeongeneral.gov/library/reports/50-years-of-progress/.

3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25559415.

4. Cancer and tobacco use. CDC Vital Signs. Altanta: Centers for Disease Control and Prevention; 2016. Available at: https://www.cdc.gov/vitalsigns/pdf/2016-11-vitalsigns.pdf.

5. Lortet-Tieulent J, Goding Sauer A, Siegel RL, et al. State-level cancer mortality attributable to cigarette smoking in the United States. JAMA Intern Med 2016;176:1792-1798. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27775761.

6. Tseng TS, Lin HY, Moody-Thomas S, et al. Who tended to continue smoking after cancer diagnosis: the national health and nutrition examination survey 1999-2008. BMC Public Health 2012;12:784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22974404.

7. Park ER, Japuntich SJ, Rigotti NA, et al. A snapshot of smokers after lung and colorectal cancer diagnosis. Cancer 2012;118:3153-3164. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22271645.

8. Underwood JM, Townsend JS, Tai E, et al. Persistent cigarette smoking and other tobacco use after a tobacco-related cancer diagnosis. J Cancer Surviv 2012;6:333-344. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22706885.

9. Westmaas JL, Newton CC, Stevens VL, et al. Does a recent cancer diagnosis predict smoking cessation? An analysis from a large prospective US cohort. J Clin Oncol 2015;33:1647-1652. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25897151.

10. Westmaas JL, Alcaraz KI, Berg CJ, Stein KD. Prevalence and correlates of smoking and cessation-related behavior among survivors of ten cancers: findings from a nationwide survey nine years after diagnosis. Cancer Epidemiol Biomarkers Prev 2014;23:1783-1792. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25100826.

11. Mayer DK, Carlson J. Smoking patterns in cancer survivors. Nicotine Tob Res 2011;13:34-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21097514.

12. Toll BA, Brandon TH, Gritz ER, et al. Assessing tobacco use by cancer patients and facilitating cessation: an American Association for Cancer Research policy statement. Clin Cancer Res 2013;19:1941-1948. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23570694.

13. Hanna N, Mulshine J, Wollins DS, et al. Tobacco cessation and control a decade later: American society of clinical oncology policy statement update. J Clin Oncol 2013;31:3147-3157. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23897958.

14. Goldstein AO, Ripley-Moffitt CE, Pathman DE, Patsakham KM. Tobacco use treatment at the U.S. National Cancer Institute's designated Cancer Centers. Nicotine Tob Res 2013;15:52-58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22499079.

15. Barzilai DA, Goodwin MA, Zyzanski SJ, Stange KC. Does health habit counseling affect patient satisfaction? Prev Med 2001;33:595-599. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11716655.

16. Conroy MB, Majchrzak NE, Regan S, et al. The association between patient-reported receipt of tobacco intervention at a primary care visit and smokers' satisfaction with their health care. Nicotine Tob Res 2005;7 Suppl 1:S29-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16036267.

17. Weaver KE, Danhauer SC, Tooze JA, et al. Smoking cessation counseling beliefs and behaviors of outpatient oncology providers. Oncologist 2012;17:455-462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22334454.

18. Warren GW, Marshall JR, Cummings KM, et al. Addressing tobacco use in patients with cancer: a survey of American Society of Clinical Oncology members. J Oncol Pract 2013;9:258-262. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23943904.

19. Warren GW, Marshall JR, Cummings KM, et al. Practice patterns and perceptions of thoracic oncology providers on tobacco use and cessation in cancer patients. J Thorac Oncol 2013;8:543-548. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23529191.

20. Warren GW, Dibaj S, Hutson A, et al. Identifying targeted strategies to improve smoking cessation support for cancer patients. J Thorac Oncol 2015;10:1532-1537. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26317914.

21. Gritz ER, Dresler C, Sarna L. Smoking, the missing drug interaction in clinical trials: ignoring the obvious. Cancer Epidemiol Biomarkers Prev 2005;14:2287-2293. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16214906.

22. Peters EN, Torres E, Toll BA, et al. Tobacco assessment in actively accruing National Cancer Institute Cooperative Group Program Clinical Trials. J Clin Oncol 2012;30:2869-2875. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22689794.

23. McAfee T, Babb S, McNabb S, Fiore MC. Helping smokers quit--opportunities created by the Affordable Care Act. N Engl J Med 2015;372:5-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25409263.

24. Eng L, Alton D, Che J, et al. Awareness among patients with cancer of the harms of continued smoking [abstract]. Journal of Clinical Oncology 2017;35:179-179. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.5_suppl.179.

25. Malarcher A, Dube S, L. S, et al. Quitting Smoking Among Adults - United States, 2001-2010. Morbidity and Mortality Weekly Report. Vol. 60: Centers for Disease Control and Prevention; 2011:1513-1519. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6044a2.htm#tab1.

26. Twyman L, Bonevski B, Paul C, Bryant J. Perceived barriers to smoking cessation in selected vulnerable groups: a systematic review of the qualitative and quantitative literature. BMJ Open 2014;4:e006414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25534212.

27. Ramaswamy AT, Toll BA, Chagpar AB, Judson BL. Smoking, cessation, and cessation counseling in patients with cancer: A population-based analysis. Cancer 2016;122:1247-1253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26881851.

28. Chapple A, Ziebland S, McPherson A. Stigma, shame, and blame experienced by patients with lung cancer: qualitative study. BMJ 2004;328:1470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15194599.

29. Schnoll RA, Malstrom M, James C, et al. Correlates of tobacco use among smokers and recent quitters diagnosed with cancer. Patient Educ Couns 2002;46:137-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11867244.

30. Morgan G, Schnoll RA, Alfano CM, et al. National cancer institute conference on treating tobacco dependence at cancer centers. J Oncol Pract 2011;7:178-182. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21886500.

31. Mazza R, Lina M, Boffi R, et al. Taking care of smoker cancer patients: a review and some recommendations. Ann Oncol 2010;21:1404-1409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20089563.

32. Aigner CJ, Cinciripini PM, Anderson KO, et al. The association of pain with smoking and quit attempts in an electronic diary study of cancer patients trying to quit. Nicotine Tob Res 2016;18:1449-1455. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26038362.

33. Eng L, Qiu X, Su J, et al. The role of second-hand smoke exposure on smoking cessation in non-tobacco-related cancers. Cancer 2015;121:2655-2663. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25877384.

34. Martinez E, Tatum KL, Weber DM, et al. Issues related to implementing a smoking cessation clinical trial for cancer patients. Cancer Causes Control 2009;20:97-104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18758971.

35. Diaz DB, Brandon TH, Sutton SK, et al. Smoking relapse-prevention intervention for cancer patients: Study design and baseline data from the surviving SmokeFree randomized controlled trial. Contemp Clin Trials 2016;50:84-89. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27468664.

36. Park ER, Ostroff JS, Perez GK, et al. Integrating tobacco treatment into cancer care: Study protocol for a randomized controlled comparative effectiveness trial. Contemp Clin Trials 2016;50:54-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27444428.

37. U.S. National Library of Medicine. Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html. Accessed May 2015.

38. Carroll AJ, Veluz-Wilkins AK, Blazekovic S, et al. Cancer-related disease factors and smoking cessation treatment: Analysis of an ongoing clinical trial. Psychooncology 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28636795.

39. Gritz ER, Fingeret MC, Vidrine DJ, et al. Successes and failures of the teachable moment: smoking cessation in cancer patients. Cancer 2006;106:17-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16311986.

40. Tang MW, Oakley R, Dale C, et al. A surgeon led smoking cessation intervention in a head and neck cancer centre. BMC Health Serv Res 2014;14:636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25527115.

41. Stead LF, Buitrago D, Preciado N, et al. Physician advice for smoking cessation. Cochrane Database Syst Rev 2013;5:CD000165. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23728631.

42. Coleman T. ABC of smoking cessation. Use of simple advice and behavioural support. BMJ 2004;328:397-399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14962878.

43. Aveyard P, Begh R, Parsons A, West R. Brief opportunistic smoking cessation interventions: a systematic review and meta-analysis to compare advice to quit and offer of assistance. Addiction 2012;107:1066-1073. Available at:

44. Lee SM, Landry J, Jones PM, et al. The effectiveness of a perioperative smoking cessation program: a randomized clinical trial. Anesth Analg 2013;117:605-613. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23868890.

45. Stead LF, Hartmann-Boyce J, Perera R, Lancaster T. Telephone counselling for smoking cessation. Cochrane Database Syst Rev 2013;8:CD002850. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23934971.

46. Lichtenstein E, Zhu SH, Tedeschi GJ. Smoking cessation quitlines: an underrecognized intervention success story. Am Psychol

2010;65:252-261. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20455619.

47. Sobus SL, Warren GW. The biologic effects of cigarette smoke on cancer cells. Cancer 2014;120:3617-3626. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25043526.

48. Rink M, Zabor EC, Furberg H, et al. Impact of smoking and smoking cessation on outcomes in bladder cancer patients treated with radical cystectomy. Eur Urol 2013;64:456-464. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23206854.

49. Ehdaie B, Furberg H, Zabor EC, et al. Impact of smoking status at diagnosis on disease recurrence and death in upper tract urothelial carcinoma. BJU Int 2013;111:589-595. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22642265.

50. Cumberbatch MG, Rota M, Catto JW, La Vecchia C. The role of tobacco smoke in bladder and kidney carcinogenesis: a comparison of exposures and meta-analysis of incidence and mortality risks. Eur Urol 2015;70:458-466. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26149669.

51. Cumberbatch MG, Rota M, Catto JW, La Vecchia C. The Role of Tobacco Smoke in Bladder and Kidney Carcinogenesis: A Comparison of Exposures and Meta-analysis of Incidence and Mortality Risks. Eur Urol 2016;70:458-466. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26149669.

52. Braithwaite D, Izano M, Moore DH, et al. Smoking and survival after breast cancer diagnosis: a prospective observational study and systematic review. Breast Cancer Res Treat 2012;136:521-533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23053660.

53. Boone SD, Baumgartner KB, Baumgartner RN, et al. Active and passive cigarette smoking and mortality among Hispanic and non-Hispanic white women diagnosed with invasive breast cancer. Ann Epidemiol 2015;25:824-831. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26387598.

54. Passarelli MN, Newcomb PA, Hampton JM, et al. Cigarette smoking before and after breast cancer diagnosis: Mortality from breast cancer and smoking-related diseases. J Clin Oncol 2016;34:1315-1322. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26811527.

55. Waggoner SE, Darcy KM, Fuhrman B, et al. Association between cigarette smoking and prognosis in locally advanced cervical carcinoma treated with chemoradiation: a Gynecologic Oncology Group study. Gynecol Oncol 2006;103:853-858. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16815535.

56. Gillison ML, Zhang Q, Jordan R, et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. J Clin Oncol 2012;30:2102-2111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22565003.

57. Walter V, Jansen L, Hoffmeister M, Brenner H. Smoking and survival of colorectal cancer patients: systematic review and meta-analysis. Ann Oncol 2014;25:1517-1525. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24692581.

58. Walter V, Jansen L, Hoffmeister M, et al. Smoking and survival of colorectal cancer patients: population-based study from Germany. Int J Cancer 2015;137:1433-1445. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25758762.

59. Sharp L, McDevitt J, Brown C, Comber H. Smoking at diagnosis significantly decreases 5-year cancer-specific survival in a population-based cohort of 18 166 colon cancer patients. Aliment Pharmacol Ther 2017;45:788-800. Available at:

60. Modesitt SC, Huang B, Shelton BJ, Wyatt S. Endometrial cancer in Kentucky: the impact of age, smoking status, and rural residence. Gynecol Oncol 2006;103:300-306. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16631234.

61. Kountourakis P, Correa AM, Hofstetter WL, et al. Combined modality therapy of cT2N0M0 esophageal cancer: the University of Texas M. D. Anderson Cancer Center experience. Cancer 2011;117:925-930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20960497.

62. Zheng Y, Cao X, Wen J, et al. Smoking affects treatment outcome in patients with resected esophageal squamous cell carcinoma who received chemotherapy. PLoS One 2015;10:e0123246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25874561.

63. Platek AJ, Jayaprakash V, Merzianu M, et al. Smoking cessation is associated with improved survival in oropharynx cancer treated by chemoradiation. Laryngoscope 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27346612.

64. Hoff CM, Grau C, Overgaard J. Effect of smoking on oxygen delivery and outcome in patients treated with radiotherapy for head and neck squamous cell carcinoma--a prospective study. Radiother Oncol 2012;103:38-44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22385797.

65. Sharp L, McDevitt J, Carsin AE, et al. Smoking at diagnosis is an independent prognostic factor for cancer-specific survival in head and neck cancer: findings from a large, population-based study. Cancer Epidemiol Biomarkers Prev 2014;23:2579-2590. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25128401.

66. Choi SH, Terrell JE, Bradford CR, et al. Does Quitting Smoking Make a Difference Among Newly Diagnosed Head and Neck Cancer Patients? Nicotine Tob Res 2016;18:2216-2224. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27613928.

67. Ehdaie B, Furberg H, Zabor EC, et al. Comprehensive assessment of the impact of cigarette smoking on survival of clear cell kidney cancer. J Urol 2014;191:597-602. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24018238.

68. Keizman D, Gottfried M, Ish-Shalom M, et al. Active smoking may negatively affect response rate, progression-free survival, and overall survival of patients with metastatic renal cell carcinoma treated with sunitinib. Oncologist 2014;19:51-60. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24309979.

69. Fajkovic H, Shariat SF, Klatte T, et al. Impact of smoking status on survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. World J Urol 2016;34:1411-1419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26879416.

70. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. BMJ 2010;340:b5569. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20093278.

71. Tao L, Wang R, Gao YT, Yuan JM. Impact of postdiagnosis smoking on long-term survival of cancer patients: the Shanghai cohort study. Cancer Epidemiol Biomarkers Prev 2013;22:2404-2411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24319070.

72. Warren GW, Kasza KA, Reid ME, et al. Smoking at diagnosis and survival in cancer patients. Int J Cancer 2013;132:401-410. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22539012.

73. Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P. Smoking and lung cancer survival: the role of comorbidity and treatment. Chest 2004;125:27-37. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14718417.

74. Kelemen LE, Warren GW, Koziak JM, et al. Smoking may modify the association between neoadjuvant chemotherapy and survival from ovarian cancer. Gynecol Oncol 2016;140:124-130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26549109.

75. Lin Y, Yagyu K, Ueda J, et al. Active and passive smoking and risk of death from pancreatic cancer: findings from the Japan Collaborative

Cohort Study. Pancreatology 2013;13:279-284. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23719601.

76. Yuan C, Morales-Oyarvide V, Babic A, et al. Cigarette Smoking and Pancreatic Cancer Survival [abstract]. Journal of Clinical Oncology 2017;35:1822-1828. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2016.71.2026.

77. Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. JAMA 2011;305:2548-2555. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21693743.

78. Chelghoum Y, Danaila C, Belhabri A, et al. Influence of cigarette smoking on the presentation and course of acute myeloid leukemia. Ann Oncol 2002;13:1621-1627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12377652.

79. Ramamoorthy S, Luo L, Luo E, Carethers JM. Tobacco smoking and risk of recurrence for squamous cell cancer of the anus. Cancer Detect Prev 2008;32:116-120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18639388.

80. Wyszynski A, Tanyos SA, Rees JR, et al. Body mass and smoking are modifiable risk factors for recurrent bladder cancer. Cancer 2014;120:408-414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24122218.

81. Ogihara K, Kikuchi E, Yuge K, et al. Refraining from smoking for 15 years or more reduced the risk of tumor recurrence in non-muscle invasive bladder cancer patients. Ann Surg Oncol 2016;23:1752-1759. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26671037.

82. Bishop JD, Killelea BK, Chagpar AB, et al. Smoking and breast cancer recurrence after breast conservation therapy. Int J Breast Cancer 2014;2014:327081. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24693439.

83. Han MA, Kim YW, Choi IJ, et al. Association of smoking history with cancer recurrence and survival in stage III-IV male gastric cancer patients. Cancer Epidemiol Biomarkers Prev 2013;22:1805-1812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23904463.

84. Joshu CE, Mondul AM, Meinhold CL, et al. Cigarette smoking and prostate cancer recurrence after prostatectomy. J Natl Cancer Inst 2011;103:835-838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21498781.

85. Moreira DM, Aronson WJ, Terris MK, et al. Cigarette smoking is associated with an increased risk of biochemical disease recurrence, metastasis, castration-resistant prostate cancer, and mortality after radical prostatectomy: results from the SEARCH database. Cancer 2014;120:197-204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24127391.

86. Rieken M, Shariat SF, Kluth LA, et al. Association of cigarette smoking and smoking cessation with biochemical recurrence of prostate cancer in patients treated with radical prostatectomy. Eur Urol 2015;68:949-956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26050111.

87. Boyle JM, Tandberg DJ, Chino JP, et al. Smoking history predicts for increased risk of second primary lung cancer: a comprehensive analysis. Cancer 2015;121:598-604. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25283893.

88. Shiels MS, Gibson T, Sampson J, et al. Cigarette smoking prior to first cancer and risk of second smoking-associated cancers among survivors of bladder, kidney, head and neck, and stage I lung cancers. J Clin Oncol 2014;32:3989-3995. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25385740.

89. Ford MB, Sigurdson AJ, Petrulis ES, et al. Effects of smoking and radiotherapy on lung carcinoma in breast carcinoma survivors. Cancer 2003;98:1457-1464. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14508833.

90. van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. J Natl Cancer Inst 1995;87:1530-1537. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7563187.

91. Balduyck B, Sardari Nia P, Cogen A, et al. The effect of smoking cessation on quality of life after lung cancer surgery. Eur J Cardiothorac Surg 2011;40:1432-1437; discussion 1437-1438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21498082.

92. Erhunmwunsee L, Onaitis MW. Smoking cessation and the success of lung cancer surgery. Curr Oncol Rep 2009;11:269-274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19508831.

93. Mason DP, Subramanian S, Nowicki ER, et al. Impact of smoking cessation before resection of lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database study. Ann Thorac Surg 2009;88:362-370; discussion 370-361. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19632374.

94. Gajdos C, Hawn MT, Campagna EJ, et al. Adverse effects of smoking on postoperative outcomes in cancer patients. Ann Surg Oncol 2012;19:1430-1438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22065194.

95. Sharma A, Deeb AP, Iannuzzi JC, et al. Tobacco smoking and postoperative outcomes after colorectal surgery. Ann Surg 2013;258:296-300. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23059503.

96. Ehlers SL, Gastineau DA, Patten CA, et al. The impact of smoking on outcomes among patients undergoing hematopoietic SCT for the treatment of acute leukemia. Bone Marrow Transplant 2011;46:285-290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20479707.

97. Chang DW, Reece GP, Wang B, et al. Effect of smoking on complications in patients undergoing free TRAM flap breast reconstruction. Plast Reconstr Surg 2000;105:2374-2380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10845289.

98. Spear SL, Ducic I, Cuoco F, Hannan C. The effect of smoking on flap and donor-site complications in pedicled TRAM breast reconstruction. Plast Reconstr Surg 2005;116:1873-1880. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16327598.

99. Marin VP, Pytynia KB, Langstein HN, et al. Serum cotinine concentration and wound complications in head and neck reconstruction. Plast Reconstr Surg 2008;121:451-457. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18300961.

100. Chen AM, Chen LM, Vaughan A, et al. Tobacco smoking during radiation therapy for head-and-neck cancer is associated with unfavorable outcome. Int J Radiat Oncol Biol Phys 2011;79:414-419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20399030.

101. Browman GP, Wong G, Hodson I, et al. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Engl J Med 1993;328:159-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8417381.

102. Zevallos JP, Mallen MJ, Lam CY, et al. Complications of radiotherapy in laryngopharyngeal cancer: effects of a prospective smoking cessation program. Cancer 2009;115:4636-4644. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19569250.

103. Egestad H, Emaus N. Changes in health related quality of life in women and men undergoing radiation treatment for head and neck cancer and the impact of smoking status in the radiation treatment period. Eur J Oncol Nurs 2014;18:339-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24877857.

104. Eifel PJ, Jhingran A, Bodurka DC, et al. Correlation of smoking history and other patient characteristics with major complications of pelvic radiation therapy for cervical cancer. J Clin Oncol 2002;20:3651-3657. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12202666.

105. Kucera H, Enzelsberger H, Eppel W, Weghaupt K. The influence of nicotine abuse and diabetes mellitus on the results of primary irradiation in the treatment of carcinoma of the cervix. Cancer 1987;60:1-4. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3581022.

106. Rades D, Setter C, Schild SE, Dunst J. Effect of smoking during radiotherapy, respiratory insufficiency, and hemoglobin levels on outcome in patients irradiated for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;71:1134-1142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18258387.

107. Alsadius D, Hedelin M, Johansson KA, et al. Tobacco smoking and long-lasting symptoms from the bowel and the anal-sphincter region after radiotherapy for prostate cancer. Radiother Oncol 2011;101:495-501. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21737169.

108. Steinberger E, Kollmeier M, McBride S, et al. Cigarette smoking during external beam radiation therapy for prostate cancer is associated with an increased risk of prostate cancer-specific mortality and treatment-related toxicity. BJU Int 2015;116:596-603. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25345838.

109. Pickles T, Liu M, Berthelet E, et al. The effect of smoking on outcome following external radiation for localized prostate cancer. J Urol 2004;171:1543-1546. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15017216.

110. Hooning MJ, Botma A, Aleman BM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst 2007;99:365-375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17341728.

111. Tyc VL, Hudson MM, Hinds P, et al. Tobacco use among pediatric cancer patients: recommendations for developing clinical smoking interventions. J Clin Oncol 1997;15:2194-2204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9196131.

112. Tobacco Use During Cancer Treatment. American Society for Clinical Oncology; 2012. Available at: http://www.cancer.net/navigating-cancer-care/prevention-and-healthy-living/tobacco-use/tobacco-use-during-cancer-treatment. Accessed September 23, 2015.

113. Geng Y, Savage SM, Razani-Boroujerdi S, Sopori ML. Effects of nicotine on the immune response. II. Chronic nicotine treatment induces T cell anergy. J Immunol 1996;156:2384-2390. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8786295.

114. Kalra R, Singh SP, Savage SM, et al. Effects of cigarette smoke on immune response: chronic exposure to cigarette smoke impairs antigen-mediated signaling in T cells and depletes IP3-sensitive Ca(2+) stores. J Pharmacol Exp Ther 2000;293:166-171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10734166.

115. Geng Y, Savage SM, Johnson LJ, et al. Effects of nicotine on the immune response. I. Chronic exposure to nicotine impairs antigen receptor-mediated signal transduction in lymphocytes. Toxicol Appl Pharmacol 1995;135:268-278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8545837.

116. Singh SP, Kalra R, Puttfarcken P, et al. Acute and chronic nicotine exposures modulate the immune system through different pathways. Toxicol Appl Pharmacol 2000;164:65-72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10739745.

117. Birrell MA, Wong S, Catley MC, Belvisi MG. Impact of tobacco-smoke on key signaling pathways in the innate immune response in lung macrophages. J Cell Physiol 2008;214:27-37. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17541958.

118. Mehta H, Nazzal K, Sadikot RT. Cigarette smoking and innate immunity. Inflamm Res 2008;57:497-503. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19109742.

119. Kimura T, Shibata Y, Yamauchi K, et al. Oxidized phospholipid, 1-palmitoyl-2-(9'-oxo-nonanoyl)-glycerophosphocholine (PON-GPC),

produced in the lung due to cigarette smoking, impairs immune function in macrophages. Lung 2012;190:169-182. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21986851.

120. Ferson M, Edwards A, Lind A, et al. Low natural killer-cell activity and immunoglobulin levels associated with smoking in human subjects. Int J Cancer 1979;23:603-609. Available at: http://www.ncbi.nlm.nih.gov/pubmed/457307.

121. Tollerud DJ, Clark JW, Brown LM, et al. Association of cigarette smoking with decreased numbers of circulating natural killer cells. Am Rev Respir Dis 1989;139:194-198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2912340.

122. Arcavi L, Benowitz NL. Cigarette smoking and infection. Arch Intern Med 2004;164:2206-2216. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15534156.

123. Nishioka T, Luo LY, Shen L, et al. Nicotine increases the resistance of lung cancer cells to cisplatin through enhancing Bcl-2 stability. Br J Cancer 2014;110:1785-1792. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24548862.

124. Zhang J, Kamdar O, Le W, et al. Nicotine induces resistance to chemotherapy by modulating mitochondrial signaling in lung cancer. Am J Respir Cell Mol Biol 2009;40:135-146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18676776.

125. Zhao J, Xin M, Wang T, et al. Nicotine enhances the antiapoptotic function of Mcl-1 through phosphorylation. Mol Cancer Res 2009;7:1954-1961. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19903766.

126. Shen T, Le W, Yee A, et al. Nicotine induces resistance to chemotherapy in nasal epithelial cancer. Am J Rhinol Allergy 2010;24:e73-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20338106.

127. Trevino JG, Pillai S, Kunigal S, et al. Nicotine induces inhibitor of differentiation-1 in a Src-dependent pathway promoting metastasis and chemoresistance in pancreatic adenocarcinoma. Neoplasia 2012;14:1102-1114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23308043.

128. Li H, Shi Q. Drugs and diseases interacting with cigarette smoking in US prescription drug labelling. Clin Pharmacokinet 2015;54:493-501. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25701380.

129. O'Malley M, King AN, Conte M, et al. Effects of cigarette smoking on metabolism and effectiveness of systemic therapy for lung cancer. J Thorac Oncol 2014;9:917-926. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24926542.

130. Hamilton M, Wolf JL, Rusk J, et al. Effects of smoking on the pharmacokinetics of erlotinib. Clin Cancer Res 2006;12:2166-2171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16609030.

131. van der Bol JM, Mathijssen RH, Loos WJ, et al. Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropenia. J Clin Oncol 2007;25:2719-2726. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17563393.

132. Darwish M, Bond M, Hellriegel E, et al. Pharmacokinetic and pharmacodynamic profile of bendamustine and its metabolites. Cancer Chemother Pharmacol 2015;75:1143-1154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25829094.

133. Prescribing Information: Treanda (bendamustine hydrochloride). Teva Pharmaceuticals; Available at: http://www.treandahcp.com/pdf/TREANDA_final_PI.pdf. Accessed July 15, 2016.

134. de Graan AJ, Loos WJ, Friberg LE, et al. Influence of smoking on the pharmacokinetics and toxicity profiles of taxane therapy. Clin Cancer Res 2012;18:4425-4432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22645049.

135. Peppone LJ, Mustian KM, Morrow GR, et al. The effect of cigarette smoking on cancer treatment-related side effects. Oncologist 2011;16:1784-1792. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22135122.

136. Danson SJ, Rowland C, Rowe R, et al. The relationship between smoking and quality of life in advanced lung cancer patients: a prospective longitudinal study. Support Care Cancer 2016;24:1507-1516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26364190.

137. Ditre JW, Gonzalez BD, Simmons VN, et al. Associations between pain and current smoking status among cancer patients. Pain 2011;152:60-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21168758.

138. Gonzalez A, Japuntich S, Keating NL, et al. Pain experiences among a population-based cohort of current, former, and never regular smokers with lung and colorectal cancer. Cancer 2014;120:3554-3561. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25043285.

139. Logan HL, Fillingim RB, Bartoshuk LM, et al. Smoking status and pain level among head and neck cancer patients. J Pain 2010;11:528-534. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20015696.

140. Novy DM, Lam C, Gritz ER, et al. Distinguishing features of cancer patients who smoke: pain, symptom burden, and risk for opioid misuse. J Pain 2012;13:1058-1067. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23010143.

141. The Health Benefits of Smoking Cessation: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services 1990. Available at: http://profiles.nlm.nih.gov/NN/B/B/C/T/.

142. Sitas F, Weber MF, Egger S, et al. Smoking cessation after cancer. J Clin Oncol 2014;32:3593-3595. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25267760.

143. Johnston-Early A, Cohen MH, Minna JD, et al. Smoking abstinence and small cell lung cancer survival. An association. JAMA 1980;244:2175-2179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6252357.

144. Khuri FR, Kim ES, Lee JJ, et al. The impact of smoking status, disease stage, and index tumor site on second primary tumor incidence and tumor recurrence in the head and neck retinoid chemoprevention trial. Cancer Epidemiol Biomarkers Prev 2001;10:823-829. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11489748.

145. Roach MC, Rehman S, DeWees TA, et al. It's never too late: Smoking cessation after stereotactic body radiation therapy for non-small cell lung carcinoma improves overall survival. Pract Radiat Oncol 2016;6:12-18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26598909.

146. Fleshner N, Garland J, Moadel A, et al. Influence of smoking status on the disease-related outcomes of patients with tobacco-associated superficial transitional cell carcinoma of the bladder. Cancer 1999;86:2337-2345. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10590376.

147. Tabuchi T, Goto A, Ito Y, et al. Smoking at the time of diagnosis and mortality in cancer patients: What benefit does the quitter gain? Int J Cancer 2017;140:1789-1795. Available at:

148. Dobson Amato KA, Hyland A, Reed R, et al. Tobacco cessation may improve lung cancer patient survival. J Thorac Oncol 2015;10:1014-1019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26102442.

149. Richardson GE, Tucker MA, Venzon DJ, et al. Smoking cessation after successful treatment of small-cell lung cancer is associated with fewer smoking-related second primary cancers. Ann Intern Med 1993;119:383-390. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8393311.

150. Garces YI, Schroeder DR, Nirelli LM, et al. Second primary tumors following tobacco dependence treatments among head and neck cancer patients. Am J Clin Oncol 2007;30:531-539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17921716.

151. Amri R, Bordeianou LG, Sylla P, Berger DL. Does active smoking induce hematogenous metastatic spread in colon cancer? Am J Surg 2015;210:930-932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26251219.

152. Kuri M, Nakagawa M, Tanaka H, et al. Determination of the duration of preoperative smoking cessation to improve wound healing after head and neck surgery. Anesthesiology 2005;102:892-896. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15851873.

153. Baser S, Shannon VR, Eapen GA, et al. Smoking cessation after diagnosis of lung cancer is associated with a beneficial effect on performance status. Chest 2006;130:1784-1790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17166997.

154. Garces YI, Hays JT. Tobacco dependence: why should an oncologist care? J Clin Oncol 2003;21:1884-1886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12721267.

155. Land SR, Toll BA, Moinpour CM, et al. Research priorities, measures, and recommendations for assessment of tobacco use in clinical cancer research. Clin Cancer Res 2016;22:1907-1913. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26888828.

156. Warren GW, Marshall JR, Cummings KM, et al. Automated tobacco assessment and cessation support for cancer patients. Cancer 2014;120:562-569. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24496870.

157. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 1991;86:1119-1127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1932883.

158. Miller WR, Rollnick S. Motivational Interviewing: Preparing People for Change (ed 3). New York, NY: The Guilford Press; 2012.

159. Rollnick S, Miller WR, Butler CC. Motivational Interviewing in Health Care: Helping Patients Change Behavior (ed 1). New York, NY: The Guilford Press; 2007.

160. Lindson-Hawley N, Aveyard P, Hughes JR. Reduction versus abrupt cessation in smokers who want to quit. Cochrane Database Syst Rev 2012;11:CD008033. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23152252.

161. Lindson-Hawley N, Aveyard P, Hughes JR. Gradual reduction vs abrupt cessation as a smoking cessation strategy in smokers who want to quit. JAMA 2013;310:91-92. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23821093.

162. Ostroff JS, Burkhalter JE, Cinciripini PM, et al. Randomized trial of a presurgical scheduled reduced smoking intervention for patients newly diagnosed with cancer. Health Psychol 2014;33:737-747. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23895203.

163. Ehlers SL, Bronars CA, Patten CA, et al. Accuracy of self-reported tobacco use status among hematopoietic SCT patients. Bone Marrow Transplant 2014;49:961-965. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24732958.

164. Hald J, Overgaard J, Grau C. Evaluation of objective measures of smoking status--a prospective clinical study in a group of head and neck cancer patients treated with radiotherapy. Acta Oncol 2003;42:154-159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12801134.

165. Warren GW, Arnold SM, Valentino JP, et al. Accuracy of self-reported tobacco assessments in a head and neck cancer treatment population. Radiother Oncol 2012;103:45-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22119370.

166. Jung KH, Kim SM, Choi MG, et al. Preoperative smoking cessation can reduce postoperative complications in gastric cancer surgery. Gastric Cancer 2015;18:683-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25139298.

167. Yoshida N, Baba Y, Hiyoshi Y, et al. Duration of smoking cessation and postoperative morbidity after esophagectomy for esophageal cancer: How long should patients stop smoking before surgery? World J Surg 2016;40:142-147. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26330238.

168. Lugg ST, Tikka T, Agostini PJ, et al. Smoking and timing of cessation on postoperative pulmonary complications after curative-intent lung cancer surgery. J Cardiothorac Surg 2017;12:52. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28629433.

169. Theadom A, Cropley M. Effects of preoperative smoking cessation on the incidence and risk of intraoperative and postoperative complications in adult smokers: a systematic review. Tob Control 2006;15:352-358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16998168.

170. Thomsen T, Villebro N, Moller AM. Interventions for preoperative smoking cessation. Cochrane Database Syst Rev 2014;3:CD002294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24671929.

171. Wong J, Abrishami A, Yang Y, et al. A perioperative smoking cessation intervention with varenicline: a double-blind, randomized, placebo-controlled trial. Anesthesiology 2012;117:755-764. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22890119.

172. Moller AM, Villebro N, Pedersen T, Tonnesen H. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. Lancet 2002;359:114-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11809253.

173. Lindstrom D, Sadr Azodi O, Wladis A, et al. Effects of a perioperative smoking cessation intervention on postoperative complications: a randomized trial. Ann Surg 2008;248:739-745. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18948800.

174. Sorensen LT. Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. Ann Surg 2012;255:1069-1079. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22566015.

175. Sorensen LT, Karlsmark T, Gottrup F. Abstinence from smoking reduces incisional wound infection: a randomized controlled trial. Ann Surg 2003;238:1-5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12832959.

176. Sorensen LT, Jorgensen LN, Zillmer R, et al. Transdermal nicotine patch enhances type I collagen synthesis in abstinent smokers. Wound Repair Regen 2006;14:247-251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16808802.

177. Bottorff JL, Seaton CL, Viney N, et al. The Stop Smoking Before Surgery Program: impact on awareness of smoking-related perioperative complications and smoking behavior in Northern Canadian communities. J Prim Care Community Health 2016;7:16-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26385995.

178. Cropley M, Theadom A, Pravettoni G, Webb G. The effectiveness of smoking cessation interventions prior to surgery: a systematic review. Nicotine Tob Res 2008;10:407-412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18324557.

179. Kotz D, Brown J, West R. 'Real-world' effectiveness of smoking cessation treatments: a population study. Addiction 2014;109:491-499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24372901.

180. Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev 2012;10:CD008286. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23076944.

181. Stead LF, Lancaster T. Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation. Cochrane Database Syst Rev 2012;12:CD009670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23235680.

182. Ferguson SG, Shiffman S, Gitchell JG. Nicotine replacement therapies: patient safety and persistence. Patient Relat Outcome Meas 2011;2:111-117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22915971.

183. Leyro TM, Hall SM, Hickman N, et al. Clinical management of tobacco dependence in inpatient psychiatry: provider practices and patient utilization. Psychiatr Serv 2013;64:1161-1165. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24185538.

184. Shiffman S. Use of more nicotine lozenges leads to better success in quitting smoking. Addiction 2007;102:809-814. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17493108.

185. Hughes JR. Dependence potential and abuse liability of nicotine replacement therapies. Biomed Pharmacother 1989;43:11-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2659095.

186. Moore TJ, Furberg CD, Glenmullen J, et al. Suicidal behavior and depression in smoking cessation treatments. PLoS One 2011;6:e27016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22073240.

187. Thomas KH, Martin RM, Davies NM, et al. Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. BMJ 2013;347:f5704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24124105.

188. Thomas KH, Martin RM, Knipe DW, et al. Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis. BMJ 2015;350:h1109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25767129.

189. Hollands GJ, McDermott MS, Lindson-Hawley N, et al. Interventions to increase adherence to medications for tobacco dependence. Cochrane Database Syst Rev 2015;2:CD009164. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25914910.

190. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013;5:CD009329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23728690.

191. Smith SS, McCarthy DE, Japuntich SJ, et al. Comparative effectiveness of 5 smoking cessation pharmacotherapies in primary care clinics. Arch Intern Med 2009;169:2148-2155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20008701.

192. Cahill K, Stevens S, Lancaster T. Pharmacological treatments for smoking cessation. JAMA 2014;311:193-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24399558.

193. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2012;11:CD000146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23152200.

194. Fiore MC, Jaen CR, Baker TB, al. e. Treating Tobacco Use and Dependence: 2008 Update. In: Panel TUaDG ed. A Public Health Service-Sponsored Clinical Practice Guideline. Rockville, MD; 2008. Available at: http://www.ncbi.nlm.nih.gov/books/NBK63952/.

195. Benowitz NL, Jacob P, 3rd, Fong I, Gupta S. Nicotine metabolic profile in man: comparison of cigarette smoking and transdermal nicotine. J Pharmacol Exp Ther 1994;268:296-303. Available at:

196. Benowitz NL, Porchet H, Sheiner L, Jacob P, 3rd. Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. Clin Pharmacol Ther 1988;44:23-28. Available at:

197. Benowitz NL, Jacob P, 3rd, Savanapridi C. Determinants of nicotine intake while chewing nicotine polacrilex gum. Clin Pharmacol Ther 1987;41:467-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3829583.

198. Mills EJ, Thorlund K, Eapen S, et al. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. Circulation 2014;129:28-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24323793.

199. Kimmel SE, Berlin JA, Miles C, et al. Risk of acute first myocardial infarction and use of nicotine patches in a general population. J Am Coll Cardiol 2001;37:1297-1302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11300438.

200. Hubbard R, Lewis S, Smith C, et al. Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death. Tob Control 2005;14:416-421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16319366.

201. Meine TJ, Patel MR, Washam JB, et al. Safety and effectiveness of transdermal nicotine patch in smokers admitted with acute coronary syndromes. Am J Cardiol 2005;95:976-978. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15820167.

202. Warren GW, Singh AK. Nicotine and lung cancer. J Carcinog 2013;12:1. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23599683.

203. Martinez-Garcia E, Irigoyen M, Gonzalez-Moreno O, et al. Repetitive nicotine exposure leads to a more malignant and metastasis-prone phenotype of SCLC: a molecular insight into the importance of quitting smoking during treatment. Toxicol Sci 2010;116:467-476. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20457658.

204. Maier CR, Hollander MC, Hobbs EA, et al. Nicotine does not enhance tumorigenesis in mutant K-ras-driven mouse models of lung cancer. Cancer Prev Res (Phila) 2011;4:1743-1751. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22027685.

205. Murphy SE, von Weymarn LB, Schutten MM, et al. Chronic nicotine consumption does not influence 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis. Cancer Prev Res (Phila) 2011;4:1752-1760. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22027684.

206. Stepanov I, Carmella SG, Briggs A, et al. Presence of the carcinogen N'-nitrosonornicotine in the urine of some users of oral nicotine replacement therapy products. Cancer Res 2009;69:8236-8240. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19843845.

207. Murray RP, Connett JE, Zapawa LM. Does nicotine replacement therapy cause cancer? Evidence from the Lung Health Study. Nicotine Tob Res 2009;11:1076-1082. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19571249.

208. Shields PG. Long-term nicotine replacement therapy: cancer risk in context. Cancer Prev Res (Phila) 2011;4:1719-1723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22052338.

209. Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. J Med Chem 2005;48:3474-3477. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15887955.

210. Mills EJ, Wu P, Lockhart I, et al. Comparisons of high-dose and combination nicotine replacement therapy, varenicline, and bupropion for smoking cessation: a systematic review and multiple treatment meta-analysis. Ann Med 2012;44:588-597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22860882.

211. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev 2012;4:CD006103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22513936.

212. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers

with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet 2016;387:2507-2520. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27116918.

213. Price S, Hitsman B, Veluz-Wilkins A, et al. The use of varenicline to treat nicotine dependence among patients with cancer. Psycho-Oncology 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27218657.

214. Ebbert JO, Hughes JR, West RJ, et al. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. JAMA 2015;313:687-694. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25688780.

215. Tonstad S, Tonnesen P, Hajek P, et al. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA 2006;296:64-71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16820548.

216. Hajek P, McRobbie H, Myers Smith K, et al. Increasing varenicline dose in smokers who do not respond to the standard dosage: a randomized clinical trial. JAMA Intern Med 2015;175:266-271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25545858.

217. Gonzales D, Hajek P, Pliamm L, et al. Retreatment with varenicline for smoking cessation in smokers who have previously taken varenicline: a randomized, placebo-controlled trial. Clin Pharmacol Ther 2014;96:390-396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24911368.

218. Lerman C, Schnoll RA, Hawk LW, Jr., et al. Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial. Lancet Respir Med 2015;3:131-138. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25588294.

219. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006;296:56-63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16820547.

220. Williams KE, Reeves KR, Billing CB, Jr., et al. A double-blind study evaluating the long-term safety of varenicline for smoking cessation. Curr Med Res Opin 2007;23:793-801. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17407636.

221. Anthenelli RM, Morris C, Ramey TS, et al. Effects of varenicline on smoking cessation in adults with stably treated current or past major depression: a randomized trial. Ann Intern Med 2013;159:390-400. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24042367.

222. Prochaska JJ, Hilton JF. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis. BMJ 2012;344:e2856. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22563098.

223. Svanstrom H, Pasternak B, Hviid A. Use of varenicline for smoking cessation and risk of serious cardiovascular events: nationwide cohort study. BMJ 2012;345:e7176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23138033.

224. Sharma A, Thakar S, Lavie CJ, et al. Cardiovascular adverse events associated with smoking-cessation pharmacotherapies. Curr Cardiol Rep 2015;17:554. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25410148.

225. Chelladurai Y, Singh S. Varenicline and cardiovascular adverse events: a perspective review. Ther Adv Drug Saf 2014;5:167-172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25083271.

226. Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. CMAJ 2011;183:1359-1366. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21727225.

227. Kotz D, Viechtbauer W, Simpson C, et al. Cardiovascular and neuropsychiatric risks of varenicline: a retrospective cohort study. Lancet Respir Med 2015;3:761-768. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26355008.

228. FDA updates label for stop smoking drug Chantix (varenicline) to include potential alcohol interaction, rare risk of seizures, and studies of side effects on mood, behavior, or thinking. FDA Drug Safety Communication. Silver Spring, MD: U.S. Food and Drug Administration; 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm436494.htm.

229. Serafini A, Crespel A, Velizara R, Gelisse P. Varenicline-induced grand mal seizure. Epileptic Disord 2010;12:338. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21287775.

230. Stapleton J, West R, Hajek P, et al. Randomized trial of nicotine replacement therapy (NRT), bupropion and NRT plus bupropion for smoking cessation: effectiveness in clinical practice. Addiction 2013;108:2193-2201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23859696.

231. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 1999;340:685-691. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10053177.

232. Evins AE, Cather C, Culhane MA, et al. A 12-week double-blind, placebo-controlled study of bupropion sr added to high-dose dual nicotine replacement therapy for smoking cessation or reduction in schizophrenia. J Clin Psychopharmacol 2007;27:380-386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17632223.

233. Hughes JR, Stead LF, Hartmann-Boyce J, et al. Antidepressants for smoking cessation. Cochrane Database Syst Rev 2014;1:CD000031. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24402784.

234. van der Meer RM, Willemsen MC, Smit F, Cuijpers P. Smoking cessation interventions for smokers with current or past depression. Cochrane Database Syst Rev 2013;8:CD006102. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23963776.

235. Hays JT, Hurt RD, Rigotti NA, et al. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. a randomized, controlled trial. Ann Intern Med 2001;135:423-433. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11560455.

236. Englisch S, Morgen K, Meyer-Lindenberg A, Zink M. Risks and benefits of bupropion treatment in schizophrenia: a systematic review of the current literature. Clin Neuropharmacol 2013;36:203-215. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24201231.

237. Koegelenberg CF, Noor F, Bateman ED, et al. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. JAMA 2014;312:155-161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25005652.

238. Ramon JM, Morchon S, Baena A, Masuet-Aumatell C. Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. BMC Med 2014;12:172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25296623.

239. Hajek P, Smith KM, Dhanji AR, McRobbie H. Is a combination of varenicline and nicotine patch more effective in helping smokers quit than varenicline alone? A randomised controlled trial. BMC Med 2013;11:140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23718718.

240. Rose JE, Behm FM. Combination treatment with varenicline and bupropion in an adaptive smoking cessation paradigm. Am J Psychiatry 2014;171:1199-1205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24934962.

241. Ebbert JO, Hatsukami DK, Croghan IT, et al. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. JAMA 2014;311:155-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24399554.

242. Aveyard P, Johnson C, Fillingham S, et al. Nortriptyline plus nicotine replacement versus placebo plus nicotine replacement for smoking cessation: pragmatic randomised controlled trial. BMJ 2008;336:1223-1227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18441375.

243. Klemp I, Steffenssen M, Bakholdt V, et al. Counseling is effective for smoking cessation in head and neck cancer patients - a systematic review and meta-analysis. J Oral Maxillofac Surg 2016;74:1687-1694. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26973223.

244. Hall SM, Humfleet GL, Munoz RF, et al. Using extended cognitive behavioral treatment and medication to treat dependent smokers. Am J Public Health 2011;101:2349-2356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21653904.

245. Hall SM, Humfleet GL, Munoz RF, et al. Extended treatment of older cigarette smokers. Addiction 2009;104:1043-1052. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19392908.

246. Killen JD, Fortmann SP, Schatzberg AF, et al. Extended cognitive behavior therapy for cigarette smoking cessation. Addiction 2008;103:1381-1390. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18855829.

247. Yalcin BM, Unal M, Pirdal H, Karahan TF. Effects of an anger management and stress control program on smoking cessation: a randomized controlled trial. J Am Board Fam Med 2014;27:645-660. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25201934.

248. Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. Nicotine Tob Res 2007;9:315-327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17365764.

249. McLaughlin I, Dani JA, De Biasi M. Nicotine withdrawal. Curr Top Behav Neurosci 2015;24:99-123. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25638335.

250. Shiffman S, Patten C, Gwaltney C, et al. Natural history of nicotine withdrawal. Addiction 2006;101:1822-1832. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17156182.

251. Civljak M, Stead LF, Hartmann-Boyce J, et al. Internet-based interventions for smoking cessation. Cochrane Database Syst Rev 2013;7:CD007078. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23839868.

252. Stead LF, Lancaster T. Group behaviour therapy programmes for smoking cessation. Cochrane Database Syst Rev 2005:CD001007. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15846610.

253. Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation. Cochrane Database Syst Rev 2005:CD001292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15846616.

254. Hartmann-Boyce J, Lancaster T, Stead LF. Print-based self-help interventions for smoking cessation. Cochrane Database Syst Rev 2014;6:CD001118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24888233.

255. Whittaker R, McRobbie H, Bullen C, et al. Mobile phone-based interventions for smoking cessation. Cochrane Database Syst Rev 2012;11:CD006611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23152238.

256. Free C, Knight R, Robertson S, et al. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. Lancet 2011;378:49-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21722952.

257. Abroms LC, Boal AL, Simmens SJ, et al. A randomized trial of Text2Quit: a text messaging program for smoking cessation. Am J Prev

Med 2014;47:242-250. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24913220.

258. Abroms LC, Padmanabhan N, Thaweethai L, Phillips T. iPhone apps for smoking cessation: a content analysis. Am J Prev Med 2011;40:279-285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21335258.

259. Sampson L, Papadakos J, Milne V, et al. Preferences for the provision of smoking cessation education among cancer patients. J Cancer Educ 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27075196.

260. Smith SS, Keller PA, Kobinsky KH, et al. Enhancing tobacco quitline effectiveness: identifying a superior pharmacotherapy adjuvant. Nicotine Tob Res 2013;15:718-728. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22992296.

261. Mehnert A, Kuhnt S, Brahler E, et al. Twelve-month prevalence of mental disorders in cancer patients across major tumor entities [abstract]. ASCO Meeting Abstracts 2015;33:9552. Available at: http://meeting.ascopubs.org/cgi/content/abstract/33/15_suppl/9552.

262. Singer S, Das-Munshi J, Brahler E. Prevalence of mental health conditions in cancer patients in acute care--a meta-analysis. Ann Oncol 2010;21:925-930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19887467.

263. Mehnert A, Brahler E, Faller H, et al. Four-week prevalence of mental disorders in patients with cancer across major tumor entities. J Clin Oncol 2014;32:3540-3546. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25287821.

264. Lindson-Hawley N, Thompson TP, Begh R. Motivational interviewing for smoking cessation. Cochrane Database Syst Rev 2015;3:CD006936. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25726920.

265. Spencer JC, Wheeler SB. A systematic review of Motivational Interviewing interventions in cancer patients and survivors. Patient Educ Couns 2016;99:1099-1105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26879805.

266. Brandon TH, Goniewicz ML, Hanna NH, et al. Electronic nicotine delivery systems: a policy statement from the American Association forCancer Research and theAmerican Society of Clinical Oncology. J Clin Oncol 2015;33:952-963. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25572671.

267. Bhatnagar A, Whitsel LP, Ribisl KM, et al. Electronic cigarettes: a policy statement from the American Heart Association. Circulation 2014;130:1418-1436. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25156991.

268. Final Recommendation Summary: Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions. U.S. Preventative Services Task Force; 2015. Available at: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1?ds=1&s=tobacco. Accessed July 15, 2016.

269. Sherratt FC, Newson L, Field JK. Electronic cigarettes: a survey of perceived patient use and attitudes among members of the British thoracic oncology group. Respir Res 2016;17:55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27184050.

270. Borderud SP, Li Y, Burkhalter JE, et al. Electronic cigarette use among patients with cancer: characteristics of electronic cigarette users and their smoking cessation outcomes. Cancer 2014;120:3527-3535. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25252116.

271. Salloum RG, Getz KR, Tan AS, et al. Use of electronic cigarettes among cancer survivors in the U.S. Am J Prev Med 2016;51:762-766. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27242079.

272. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet 2013;382:1629-1637. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24029165.

273. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. Lancet Respir Med 2016;4:116-128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26776875.

274. McQueen N, Partington EJ, Harrington KF, et al. Smoking cessation and electronic cigarette use among head and neck cancer patients. Otolaryngol Head Neck Surg 2016;154:73-79. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26519457.

275. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. Cochrane Database Syst Rev 2014;12:CD010216. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25515689.

276. Rahman MA, Hann N, Wilson A, et al. E-cigarettes and smoking cessation: evidence from a systematic review and meta-analysis. PLoS One 2015;10:e0122544. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25822251.

277. Brown J, Beard E, Kotz D, et al. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. Addiction 2014;109:1531-1540. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24846453.

278. Ussher MH, Taylor AH, Faulkner GE. Exercise interventions for smoking cessation. Cochrane Database Syst Rev 2014;8:CD002295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25170798.

279. White AR, Rampes H, Liu JP, et al. Acupuncture and related interventions for smoking cessation. Cochrane Database Syst Rev 2014;1:CD000009. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24459016.

280. Abbot NC, Stead LF, White AR, et al. Hypnotherapy for smoking cessation. Cochrane Database Syst Rev 2000:CD001008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10796583.

281. Barnes J, Dong CY, McRobbie H, et al. Hypnotherapy for smoking cessation. Cochrane Database Syst Rev 2010:CD001008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20927723.