Smoking Cessation

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Smoking Cessation

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NCCN Guidelines Panel Disclosures

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### NCCN Smoking Cessation Panel Members

### Summary of Guidelines Updates

### General Principles of the Smoking Cessation Guidelines (Intro)

### Initial Evaluation and Assessment of Patient Smoking (SC-1)

### Current Smokers and Those Who Have Smoked Within Last 30 Days (SC-2)

### Former Smokers and Recent Quitters (>30 Days Since Last Smoked) (SC-3)

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### Principles of Smoking Cessation and Cancer Surgery (SC-D)

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Updates in Version 2.2019 of the NCCN Guidelines for Smoking Cessation from Version 1.2018 include:

MS-1
• The Discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 1.2019 of the NCCN Guidelines for Smoking Cessation from Version 1.2018 include:

INTRO
• Clinical recommendations
  ▶ First bullet, first subbullet modified: "...nicotine replacement therapy (NRT) or and varenicline."
  ▶ Fourth bullet modified: "...including surgery, radiation therapy, systemic therapy, and end-of-life care."
  ▶ Last bullet added: Despite emerging evidence, there is still insufficient evidence to recommend 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. Thus, patients should be counseled toward the use of evidence-based smoking cessation methods.
  ▶ Nasal spray added to the list of short-acting NRT options in footnote a.

SC-1
• Changed "<" to "more than."
• Footnote b modified: "...discontinue the use of all combustible tobacco products..."

SC-2
• Moved the assessment of patient readiness to quit from the last bullet of the first column to the next column, under "engage patients in a personalized motivational dialog about smoking cessation."
• Management, ready to quit within 4 weeks or has quit within prior 30 days: added "For those still smoking" before the last two sub-bullets.
• Footnote i: changed "physician" to "provider."
• Footnote j modified: "Making an immediate quit attempt is recommended, but smoking reduction with pharmacotherapy and counseling may be considered..."

SC-3
• Heading modified: Evaluation of Relapse Risk
• Evaluation
  ▶ First line modified: Evaluate and document patient Risk factors for smoking relapse
  ▶ Sixth bullet modified: Currently using smoking cessation pharmacotherapy or other nicotine delivery mechanisms
  ▶ Last bullet added: Low self-confidence in ability to quit/maintain abstinence
• Re-evaluation after management, modified: "...in person or by phone/telehealth" (changed throughout the Guidelines)
• Footnote m modified: "Providers should discuss risk of relapse and smoking slips and provide guidance and support to encourage continued smoking cessation attempts. While NRT may be used long-term to help former smokers maintain abstinence, methods other than NRT may be considered so as not to reintroduce the former smoker to nicotine."

SC-4
• Assessment modified: "Assess smoking status and toxicity of pharmacotherapy periodically, in-person or by phone/telehealth at a minimum..." (Also on SC-5)
• Footnote s added: Combination NRT or varenicline are the preferred pharmacotherapy options. However, bupropion or combination bupropion/NRT may be appropriate for select patients (eg, those with symptoms of depression or fatigue, or those who cannot tolerate NRT or varenicline).

SC-5
• Added to heading: Relapse or Persistent Smoking
• Added to second column: Assess motivation to quit.
• This page was significantly revised and simplified.
Updates in Version 1.2019 of the NCCN Guidelines for Smoking Cessation from Version 1.2018 include:

**SC-A**
- Fourth bullet modified: For patients using alternative approaches, including electronic cigarettes, continue to provide support during quit attempts.
- Under ENDS
  - Second bullet added: The use of ENDS is sometimes referred to as vaping or juuling.
  - Third bullet modified: Despite emerging evidence, there is still insufficient evidence to recommend e-cigarette use in smoking cessation, alone or in combination with evidence-based smoking cessation methods. Insufficient evidence also exists in regard to the safety and efficacy of e-cigarette use in patients with cancer. For patients who choose to use e-cigarettes despite recommendations to use evidence-based pharmacotherapies, encourage abstinence and behavioral counseling.
- Fourth bullet added: The most effective use of ENDS is unknown, particularly when considering factors such as real world use and the addition of behavior therapy. Efficacy of ENDS use in patients with cancer is also unknown. Thus, patients should be counseled toward the use of evidence-based smoking cessation methods.
- Fifth bullet added: Educate patients on the unknown risks of using electronic cigarettes in lieu of evidence-based methods. Continue to provide support during any quit attempts.
- References have been moved from the footnotes to the Discussion section.

**SC-B**

**SC-D (continued)**
- Added to second sub-bullet: There are concerns that some surgeons do not allow patients to use NRT peri- or post-operatively. While some data from animal studies has suggested an association between nicotine and decreased wound healing, no such studies exist in humans. NRT typically provides less nicotine than cigarettes, and nearly doubles the chance of smoking abstinence.
- Last bullet modified: Although quitting smoking reduces surgical risk, access to cancer surgery should not be restricted solely on the basis of continued smoking for smokers.

**SC-E (1 of 2)**
- Second bullet modified: Through behavior therapy, smokers are provided with problem-solving skills, learn coping skills and receive support and encouragement.
- Fourth bullet modified: Symptoms typically peak between 48-72 hours after quitting, and last about 2-3 weeks before subsiding.

**SC-E (2 of 2)**
- First bullet, added: "...within 3 weeks of cessation (within 1 week preferred-as a majority of smokers relapse within this timeframe)."

**SC-F (1 of 2)**
- Table has been updated to reflect the changes on SC-4/5.
- Pharmacotherapy options have been preference stratified.
- "Bupropion (sustained release)" has been changed to "bupropion".

**SC-F (2 of 2)**
- Varenicline, standard dose, added: If severe renal impairment, maximum dose = 0.5 mg, twice daily
- Bupropion, standard dose
  - Included doses for sustained and extended release.
- Last bullet modified: Adjust dose or frequency for renal or hepatic insufficiency.
- Footnote f modified: See drug labels and full prescribing information for varenicline, bupropion, and NRT products. Black box warnings may have been recently updated, refer to the National Institutes of Health website at https://dailymed.nlm.nih.gov/dailymed.
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, primary cancer 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. 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) or varenicline.
  ‣ Behavior therapy with multiple counseling sessions is most effective, and 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 and can be managed. 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 an integral part of oncology treatment and continued throughout the entire oncology care continuum, including surgery, radiation therapy, systemic therapy, and 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.

• Despite emerging evidence, there is still insufficient evidence to recommend 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. Thus, patients should be counseled toward the use of evidence-based smoking cessation methods.

\(^a\)Combination NRT = Nicotine patch + short-acting NRT (ie, lozenge, gum, inhaler, nasal spray).

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

INITIAL EVALUATION

Assess current cigarette smoking status of all patients with cancer:
• Have you ever smoked cigarettes?
• Do you currently smoke cigarettes or have you smoked in the last 30 days?

STATUS

- Current smoker and/or those who have smoked within the last 30 days
- Former smoker or recently quit (more than 30 days–1 year since patient last smoked)
- Long-term former smoker (more than 1 year since last smoked)
- Never smoked

See Assessment of Current Smokers (SC-2)
See Assessment of Former Smokers (SC-3)
Encourage patient to remain smoke-free and not to use any combustible products

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

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.

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).

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

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CURRENT SMOKERS AND THOSE WHO HAVE SMOKED WITHIN LAST 30 DAYS

EVALUATION
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? (ie, within 5 minutes. See Discussion)
  ◦ 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^ (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)
• Smoking status of individuals within household

MANAGEMENT

Ready to quit within 4 weeks or has quit within prior 30 days

Engage patients in a personalized motivational dialog about smoking cessation
• Review risks of smoking and benefits of quitting (See SC-B)
• Provide patient education resources (See SC-C)
• Assess patient readiness to quit

Not ready to quit within 4 weeks

• Assess and address barriers and concerns of patient.
• Consider smoking reduction with a goal of setting a quit date in the near future
  • Encourage immediate initiation of pharmacotherapy for targeted reduction of cigarettes per day

Begin smoking cessation treatment (See SC-4)

Reassess readiness to quit at each visit

For lung cancer screening recommendations, see NCCN Guidelines for Lung Cancer Screening.

^ 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.

k 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. While NRT may be used long-term to help former smokers maintain abstinence, methods other than NRT may be considered so as not to reintroduce the former smoker to nicotine. See Principles of Behavioral Strategies (SC-E).

n See Principles of Smoking Cessation Pharmacotherapy (SC-F).
## FORMER SMOKERS AND RECENT QUITTERS (More than 30 Days Since Last Smoked)

### EVALUATION OF RELAPSE RISK

- **Risk factors for smoking relapse:**
  - Frequent/intense cravings
  - Elevated anxiety/stress/depression
  - Current or prior history of mental illness
  - Living/working with smokers
  - Time since quitting (<1 year)
  - Currently using smoking cessation pharmacotherapy or other nicotine delivery mechanisms
  - Drug/alcohol use or abuse (i.e., marijuana, opioids, stimulants)
  - Low self-confidence in ability to quit/maintain abstinence

### MANAGEMENT

| ≥1 risk factors/high risk for relapse | Behavior therapy, including counseling on relapse risk factors and prevention and Consider pharmacotherapy as clinically indicated to maintain abstinence | Reevaluate smoking status and risk of relapse at each visit or more often as indicated, in person or by phone/telehealth |
| 0 risk factors/low risk for relapse | Reinforce success and importance of remaining abstinent | Reevaluate smoking status and risk of relapse at each visit |

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**m**Providers should discuss risk of relapse and smoking slips and provide guidance and support to encourage continued smoking cessation attempts. While NRT may be used long-term to help former smokers maintain abstinence, methods other than NRT may be considered so as not to reintroduce the former smoker to nicotine. 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.

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GENERAL APPROACH TO SMOKING CESSATION FOR PATIENTS WITH CANCER AND SURVIVORS

PRIMARY THERAPY

Combination NRT\(^{a}\) + behavior therapy x 12 wk\(^{i}\) (category 1) (For standard dose, see SC-F, 2 of 2)\(^{u}\)

Varenicline\(^{v}\) + behavior therapy x 12 wk\(^{j}\) (category 1) (For standard dose, see SC-F, 2 of 2)\(^{u}\)

ASSESSMENT/FOLLOW-UP

Assess smoking status and toxicity of pharmacotherapy in-person or by phone/telehealth at a minimum:\(^{w,x}\)

- Within 3 wks after cessation (within 1 wk preferred) and
- At 12 wks

Smoke free

Relapse or still smoking\(^{j}\)

If relapse, re-initiate primary therapy with either combination NRT or varenicline

See Therapy For Relapse/Persistent Smoking (SC-5)

\(^{a}\) Combination NRT = Nicotine patch + short-acting NRT (ie, lozenge, gum, inhaler, nasal spray).

\(^{i}\) Making an immediate quit attempt is recommended but smoking reduction with pharmacotherapy and counseling may be considered with a goal of cessation at a future quit date (ie, 1–3 mo).

\(^{v}\) See Principles of Smoking Cessation Pharmacotherapy (SC-F).

\(^{j}\) See Principles of Behavioral Strategies (SC-E).

\(^{q}\) 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).

\(^{t}\) The use of marijuana, or other substances associated with smoking relapse, is discouraged for those attempting to quit smoking.

\(^{s}\) Combination NRT or varenicline are the preferred pharmacotherapy options. However, bupropion or combination bupropion/NRT may be appropriate for select patients (eg, those with symptoms of depression or fatigue, or those who cannot tolerate NRT or varenicline).

\(^{u}\) Patient assistance programs may be available.

\(^{w}\) Nausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy.

\(^{x}\) Nicotine withdrawal symptoms typically peak within 2 weeks of quitting. Encourage continued therapy through brief slips.

\(^{y}\) Adjust behavior therapy frequency as needed, and adjust pharmacotherapy dose for undesirable side effects or if high risk of relapse is suspected.

\(^{†}\) 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).

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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

#### Relapse or Persistent Smoking

<table>
<thead>
<tr>
<th>Assess:</th>
<th>Continue/resume primary therapy and provide additional behavior therapy or switch to alternate primary therapy not previously used (combination NRT or varenicline) and provide additional behavior therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>W, X, Z</td>
<td>After switching therapy or making dose adjustments, reassess smoking status and therapy toxicity periodically, in-person or by phone/telehealth at a minimum: Within 3 wks and Following 12 wks of therapy.</td>
</tr>
<tr>
<td>Smoke free</td>
<td></td>
</tr>
</tbody>
</table>

#### Relapse

- Behavior therapy
- Varenicline
- Combination NRT
- Combination NRT + bupropion
- Bupropion

### Efficacy Data

- Efficacy data are lacking for the use of e-cigarettes and alternative therapies (eg, hypnosis, acupuncture, nutritional supplements).

### Additional Therapy/Follow-up

- Extend duration of pharmacotherapy as clinically indicated (ie, >6 mo)
- Assess smoking status:
  - At end of therapy
  - 6 & 12 mo after therapy

### Toxicity Monitoring

- Nicotine withdrawal symptoms typically peak within 2 weeks of quitting. Encourage continued therapy through brief slips.
- Adjust behavior therapy frequency as needed, and adjust pharmacotherapy dose for undesirable side effects or if high risk of relapse is suspected.
- Decision to continue or switch therapy should be based on prior cessation success, patient preference, toxicity, and/or a change in clinical status (eg, upcoming surgery).

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n See Principles of Smoking Cessation Pharmacotherapy (SC-F).
p See Principles of Behavioral Strategies (SC-E).
q Efficacy data are lacking for the use of e-cigarettes and alternative therapies (eg, hypnosis, acupuncture, nutritional supplements).

r The use of marijuana, or other substances associated with smoking relapse, is discouraged for those attempting to quit smoking.

s Combination NRT or varenicline are the preferred pharmacotherapy options. However, bupropion or combination bupropion/NRT may be appropriate for select patients (eg, those with symptoms of depression or fatigue, or those who cannot tolerate NRT or varenicline).

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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, 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.
- The use of ENDS is sometimes referred to as vaping or juuling.
- Despite emerging evidence, there is still insufficient evidence to recommend e-cigarette use in smoking cessation, alone or in combination with evidence-based smoking cessation methods. Insufficient evidence also exists in regard to the safety and efficacy of e-cigarette use in patients with cancer. For patients who choose to use e-cigarettes despite recommendations to use evidence-based pharmacotherapies, encourage abstinence and behavioral counseling.
  - The American Heart Association, American Cancer Society, 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. However, ENDS are not recommended by these associations because of the insufficient data on efficacy and safety.
  - According to the US Preventive 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.”
- The most effective use of ENDS is unknown, particularly when considering factors such as real-world use and the addition of behavior therapy. Efficacy of ENDS use in patients with cancer is also unknown. Thus, patients should be counseled toward the use of evidence-based smoking cessation methods.
- Educate patients on the unknown risks of using electronic cigarettes in lieu of evidence-based methods. Continue to provide support during any quit attempts.

#### Other Alternative Methods

- There is currently insufficient evidence to support the use of alternative methods (eg, hypnosis, acupuncture, nutritional supplements) when used alone or in combination with standard smoking cessation methods.
- 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.

See Discussion for References
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. 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.\(^7-9\)
  - Patients who receive RT and continue to smoke may also have an increased risk of developing second primary cancer.\(^10-13\)
- 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).\(^14-16\)
  - Smoking may impair wound healing following surgery for cancer.\(^17,18\)
  - Increased infection rates, cardiovascular and pulmonary complications, and longer postoperative hospital stays are more commonly observed in patients who smoke.\(^19\)
  - Postoperative mortality rates are higher among patients who smoke.\(^20\)

**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.\(^21-25\)
- There is insufficient evidence that NRT increases the risk of myocardial infarction or cardiovascular disease.\(^26\)

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.

References
SMOKING-ASSOCIATED RISKS FOR PATIENTS WITH CANCER

REFERENCES


### SMOKING CESSATION RESOURCES FOR PATIENTS AND HEALTH PROVIDERS

#### Cancer-Related Resources for Patients

<table>
<thead>
<tr>
<th>Organization</th>
<th>Website/Contact Info</th>
<th>Guides for Quitting/Additional Resources</th>
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</table>
| American Cancer Society (ACS) | • Website: [https://www.cancer.org/healthy/stay-away-from-tobacco.html](https://www.cancer.org/healthy/stay-away-from-tobacco.html)  
| American Lung Association | • Website: [http://www.lung.org/stop-smoking/](http://www.lung.org/stop-smoking/)  
| Smokefree.gov | • Website: [https://www.smokefree.gov/](https://www.smokefree.gov/)  
• NCI Quitline: 1.877.448.7848  
• Springboard Beyond Cancer: [https://survivorship.cancer.gov/](https://survivorship.cancer.gov/)  
• SmokeFree Text Messaging Programs (available for adults, teens, moms, Veterans, español): [https://smokefree.gov/smokefree-text-messaging-programs](https://smokefree.gov/smokefree-text-messaging-programs)  

#### General Resources For Patients

<table>
<thead>
<tr>
<th>Organization</th>
<th>Website</th>
<th>Quitline/Online Support</th>
</tr>
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<tbody>
<tr>
<td>American Heart Association</td>
<td><a href="https://healthyforgood.heart.org/">https://healthyforgood.heart.org/</a></td>
<td></td>
</tr>
<tr>
<td>American Indian Commercial Tobacco Program</td>
<td><a href="https://americanindian.quitlogix.org">https://americanindian.quitlogix.org</a></td>
<td>1.855.372.0037</td>
</tr>
</tbody>
</table>
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](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/](http://www.becomeanex.org/) | ExCommunity: [https://excommunity.becomeanex.org](https://excommunity.becomeanex.org) |

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**Note:** 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.

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**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.

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## SMOKING CESSTATION RESOURCES FOR PATIENTS AND HEALTH CARE PROVIDERS

### Cancer-Related Resources for Health Professionals

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<tr>
<th>Organization</th>
<th>Guidelines and Resources</th>
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### General Resources for Health professionals

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<thead>
<tr>
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<th>Website/Resource</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Academy of Family Physicians (AAFP)</td>
<td>Ask and Act Smoking Cessation Program: <a href="http://www.aafp.org/about/initiatives/ask-act.html">http://www.aafp.org/about/initiatives/ask-act.html</a></td>
</tr>
</tbody>
</table>
| Association for the Treatment of Tobacco Use and Dependence (ATTUD)/Council for Tobacco Treatment Training Programs (CTTTP) | • [http://www.attud.org/](http://www.attud.org/)  
• Accredited training programs: [http://ctttp.org/accredited-programs/](http://ctttp.org/accredited-programs/) |
| National Behavioral Health Network | [https://www.bhthechange.org/](https://www.bhthechange.org/) |
| RxForChange: Clinician-Assisted Tobacco Cessation | [http://rxforchange.ucsf.edu/](http://rxforchange.ucsf.edu/) |

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.
Smokers who need surgery should be treated with evidence-based smoking cessation therapy, including pharmacotherapy and behavior therapy, in order to improve surgical outcomes and long-term cessation rates. There is substantial evidence that smoking cessation with either counseling or pharmacotherapy alone is less effective than the combination of the two.

For primary therapy and follow-up recommendations, see SC-4. Preoperative pharmacotherapy options depend on urgency of surgery, within one week or more than one week. Options include:

- If <7 days to surgery, combination NRT preferred (category 1) or varenicline, because guidelines for quitting with NRT includes a quit date within 24 hours, while varenicline is typically 7 days. However, in some clinical situations the quit date for varenicline may be sooner.
- If ≥7 days to surgery, either combination NRT (category 1) or varenicline (category 1).

There is no clear evidence that NRT degrades the wound healing benefits of smoking cessation. NRT offers benefits over continued smoking. There are concerns that some surgeons do not allow patients to use NRT peri- or post-operatively. While some data from animal studies has suggested an association between nicotine and decreased wound healing, no such studies exist in humans. NRT typically provides less nicotine than cigarettes, and nearly doubles the chance of smoking abstinence.1

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). Quitting smoking reduces these complications. There is no evidence that quitting smoking shortly before surgery increases the risks of any complications.

Patients should be encouraged to quit smoking as soon as possible before surgery, regardless of how short the time to surgery is.

Longer periods of smoking cessation confer better surgical outcomes but should not delay appropriate timing for cancer resection.

There is insufficient evidence to support delaying a quit attempt at any time prior to surgery.

Although quitting smoking reduces surgical risk, access to cancer surgery should not be restricted solely on the basis of continued smoking.

PRINCIPLES OF BEHAVIORAL STRATEGIES

- 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 learn coping skills and receive support and education. Behavior therapy, tailored to the patient’s nicotine dependence and previous quit attempts, provides strategies for:\(^1-3\)
  - Coping with nicotine withdrawal symptoms and cravings (Note: Symptoms typically peak between 48-72 hours after quitting, and last about 2-3 weeks before subsiding.)
  - 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.\(^3-5\)
  - 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.\(^3\)

- In smokers with cancer, there is a high incidence of depression, anxiety, and stress, all of which are common causes of relapse. Providers should routinely assess for these symptoms among smokers throughout treatment for tobacco dependence. 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.

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.
Behavior Therapy/Counseling Recommendations:

• Four or more sessions during each 12-week course of pharmacotherapy. The first session is recommended within 3 weeks of cessation (within 1 week preferred as a majority of smokers relapse in this timeframe⁶).
  - 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.³

• Individual or group therapy, in-person and/or by phone/telehealth, 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.

References

**PRINCIPLES OF SMOKING CESSATION PHARMACOTHERAPY**

- 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 6 months or longer to promote continued cessation while attempting to avoid longer periods of time if possible. Varenicline can be used up to 1 year for continued abstinence.
- Follow-up is recommended (in-person or by phone/telehealth) 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-week intervals), and after completion of therapy, is recommended.
- Nicotine withdrawal symptoms typically peak within 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.

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
<th>Useful in Certain Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Therapy Options</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Combination NRT: Nicotine patch + short-acting NRT (lozenge/gum/inhaler/nasal spray) or • Varenicline(^a,b)</td>
<td>• None</td>
<td>• Bupropion(^b) ± NRT (for patients with depression or fatigue, or those who cannot tolerate NRT or varenicline)</td>
</tr>
<tr>
<td>*<em>Subsequent Therapy Options</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Consider continuing or resuming the initial pharmacotherapy (combination NRT or varenicline) or • Switch to alternate preferred primary therapy option not previously used (combination NRT or varenicline)</td>
<td>• Combination NRT + bupropion(^b) • Bupropion(^b)</td>
<td></td>
</tr>
</tbody>
</table>

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

\(^a\)Nausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy.

\(^b\)Bupropion should be avoided for patients with brain metastases due to seizure risk. Varenicline should be used with caution for those with 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**

- 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.  
- A 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.

<table>
<thead>
<tr>
<th>Combination NRT (preferred)</th>
<th>Standard Dose</th>
<th>Duration</th>
<th>Adverse Effects and Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Begin with 21 mg patch + short-acting NRT&lt;sup&gt;d&lt;/sup&gt;</td>
<td>12 wks&lt;sup&gt;e&lt;/sup&gt;</td>
<td>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 underdose when using combination NRT. Nicotine overdose is rare, but possible and usually short-lived.</td>
</tr>
<tr>
<td></td>
<td>If 21 mg patch is not effective, consider using more than one patch to increase the dose to 35 or 42 mg</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Short-acting NRT every 2 h (while awake), or more often as needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varenicline (preferred)</td>
<td>Initiate dosing 1–2 wks prior to quitting</td>
<td>12 wks&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Nausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy.</td>
</tr>
<tr>
<td></td>
<td>Days 1–3: 0.5 mg orally, once daily</td>
<td></td>
<td>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 for patients without a previous history, and discontinue use if these signs occur. Use with caution for patients with seizure risk.</td>
</tr>
<tr>
<td></td>
<td>Days 4–7: 0.5 mg orally, twice daily</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Day 8 to end of treatment: 1 mg orally, twice daily, if tolerated</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>If severe renal impairment, maximum dose = 0.5 mg, twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion ± NRT</td>
<td>Initiate dosing 1–2 wks prior to quitting</td>
<td>7–12 wks&lt;sup&gt;e&lt;/sup&gt;</td>
<td>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 for patients 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.</td>
</tr>
<tr>
<td></td>
<td>Days 1–3: 150 mg orally, once daily</td>
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<td></td>
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<tr>
<td></td>
<td>Day 4–end of treatment:</td>
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<tr>
<td></td>
<td>Sustained release: 150 mg orally, twice daily, if tolerated; or</td>
<td></td>
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<tr>
<td></td>
<td>Extended release: 300 mg, once daily, if tolerated</td>
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<tr>
<td></td>
<td>Maximum 300 mg per day</td>
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<tr>
<td></td>
<td>Adjust dose or frequency for renal or hepatic insufficiency</td>
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</tbody>
</table>

<sup>c</sup> Dose adjustments may be considered if clinically indicated.  
<sup>d</sup> Gradually decrease dose over 10 weeks or more. Dose reduction may not be appropriate for patients with limited life expectancy.  
<sup>e</sup> Therapy may be extended to promote continued cessation (ie, 6 mo–1 y).  
<sup>f</sup> See drug labels and full prescribing information for varenicline, bupropion, and NRT products. Black box warnings may have been recently updated.  
**Discussion**

<table>
<thead>
<tr>
<th>NCCN Categories of Evidence and Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category 1:</strong> Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.</td>
</tr>
<tr>
<td><strong>Category 2A:</strong> Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.</td>
</tr>
<tr>
<td><strong>Category 2B:</strong> Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.</td>
</tr>
<tr>
<td><strong>Category 3:</strong> Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.</td>
</tr>
</tbody>
</table>

**All recommendations are category 2A unless otherwise indicated.**

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**NCCN Categories of Preference**

**Preferred intervention:** Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability

**Other recommended intervention:** Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes

**Useful in certain circumstances:** Other interventions that may be used for selected patient populations (defined with recommendation)

**All recommendations are considered appropriate**

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Overview

Nearly 40 million adults in the United States currently smoke cigarettes, accounting for approximately 14% of the adult population in 2017—15.8% of males and 12.2% of females.\(^1\) Cigarette smoking results in more than 480,000 premature deaths yearly, and 1 in every 5 deaths are smoking-related.\(^2\) Tobacco smoking has been implicated in causing cancers of the 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.\(^3\)

In the United States, declining premature mortality has been attributed to smoking cessation.\(^6\) 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 tobacco products (eg, cigars, hookah) 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.\(^7\) 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.\(^8\)

Smoking often persists beyond cancer treatment and well into survivorship. In a population-based study using the Behavioral Risk Factor
Survival 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.\(^9\) 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.\(^10\) One study revealed smoking prevalence to be highest among survivors of bladder, lung, and ovarian cancers.\(^11\) Other studies have found high prevalence of continued smoking in survivors of cervical cancers.\(^12\)

**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.”\(^13\)

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.\(^14\)

More than 80% of oncology care-providing hospitals offer smoking cessation programs, with nationally designated cancer centers being more likely to offer programs owned by the hospital or health system.\(^15\) 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.\(^16\) 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.\(^13\) Several studies have linked increased patient satisfaction to the delivery of smoking cessation advice or intervention.\(^17,18\) 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.\(^19-22\) However, smoking assessment rates were weaker outside of the academic/university setting (ie, for those practicing in a hospital-based, nonacademic, or private setting).\(^22\) Regardless of work setting, only 30% to 44% of respondents reported discussing specific interventions or providing subsequent follow-up. Moreover, the majority of respondents reported inadequate training and/or a lack of confidence in ability to provide effective smoking cessation counseling and intervention.\(^19-22\) A dearth of smoking assessment and documentation has also been demonstrated in oncology trials.\(^23,24\)
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.25

**Smoking Cessation in Oncology Patients**

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 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.

Smoking cessation in this patient population presents a number of challenges. Patients may have limited awareness about the harms associated with continued smoking upon a diagnosis of cancer. A survey assessed knowledge of the harms of continued smoking in 985 current or former smokers with a cancer diagnosis.26 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.

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.27 Importantly, patients and providers in the oncology setting face additional life challenges that can amplify the magnitude of these barriers. However, pain, desire to maintain personal control, 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.28-34 An ongoing trial examined whether cancer-related disease factors adversely affected engagement with smoking cessation treatment with varenicline and behavior counseling.35 Disease factors such as tumor site, cancer treatment, and time since diagnosis were not associated with medication adherence, counseling adherence, or abstinence rates. Although health-related quality of life (HRQOL) was predictive of medication adherence, abstinence rates were not impacted.35

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.36 Surveys of oncology providers have identified common themes among barriers to smoking cessation for patients with cancer. In a large survey, medical and radiation oncologists reported a preference for smoking cessation interventions to be managed by other members of the health care team.37 Inadequate provider training, lack of time, and perceived patient harm/benefit are often cited by oncology providers as barriers to successful intervention.20,38 Providers have also cited patient-related factors such as inability to quit, lack of motivation, or resistance to treatment.19,20 Several groups have described interventions to improve referral to smoking cessation services for patients with cancer by successfully integrating smoking cessation treatment into the cancer care plan.39,40

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. Ongoing randomized controlled trials (RCTs) are examining smoking cessation interventions designed specifically 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, using the following search terms: (smoking[Title] OR tobacco[Title]) AND (cessation[Title]) 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.

The search results were narrowed by selecting studies in humans published in English and their potential relevance was examined. 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 at [www.NCCN.org](http://www.NCCN.org).

**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 tobacco products, including cigars, hookah, 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, primary cancer recurrence, and secondary cancers. Importantly, a diagnosis of cancer may present a teachable moment and valuable opportunity for providers to encourage smoking cessation. 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 treatment 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. Quitlines may be used as an adjunct, especially in lower-resource settings.

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 and can be managed. 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.

Smoking cessation interventions should be offered as an integral part of oncology treatment and continued throughout the oncology care continuum, including surgery, radiation therapy (RT), systemic therapy, and end-of-life care. Emphasis on patient preferences and values is important when considering the best approach to fostering smoking cessation in that setting.

Despite emerging evidence, there is still insufficient evidence to recommend the use of e-cigarettes in smoking cessation, alone or in combination with evidence-based smoking cessation methods. Evidence regarding the safety and efficacy of e-cigarette use in patients with cancer is also lacking. Thus, patients should be counseled toward the use of evidence-based smoking cessation methods. For full discussion, see the section on Electronic Cigarettes/Electronic Nicotine Delivery Systems.

**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). These data have been corroborated by clinical studies. Per the Surgeon General’s Report, *The Health Consequences of Smoking—50 Years of Progress*, 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 HRQOL, 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, breast, cervix, colon/rectum, endometrium, esophagus, head and neck, kidney, lung, ovary, pancreas, and prostate, as well as hematologic malignancies and brain metastases.

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. Additionally, over half of the reviewed studies found at least a 50% increase in risk of death. 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. 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).

**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. 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.

Disease sites with data linking current patient smoking to increased risk of recurrence include the anus, bladder, breast, lung, stomach, and prostate.

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. Additionally, data also suggest that smoking interacts synergistically with RT to elevate the risk of second primary cancers.

**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. 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. The adverse effects of smoking on postoperative outcomes were 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 from 2002 through 2008.\textsuperscript{101} 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). 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.

Similar findings have been reported by other groups for patients who had surgery for lung cancer, bladder cancer, and in patients with leukemia undergoing hematopoietic stem cell transplantation.\textsuperscript{102-107} 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 more than 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.\textsuperscript{108} 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 or head and neck cancers, smoking was associated with significantly higher risk of flap complications and delayed healing,\textsuperscript{109-112} and evidence suggested that complication risk may be reduced by preoperative smoking cessation.\textsuperscript{109,112}

\textbf{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. Patients who receive RT and continue to smoke may also have an increased risk of developing second primary cancer. Smoking amplified the risk of second primary cancer associated with RT for initial breast, lung, or cervical cancers.\textsuperscript{113-116} In patients with head and neck cancer receiving RT, current smokers had poorer rates of locoregional control.\textsuperscript{72,117} 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.\textsuperscript{118} 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.\textsuperscript{119} 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.\textsuperscript{120} Among 3489 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.\textsuperscript{121} 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.\textsuperscript{122} Smoking during RT for non-small-cell lung cancer was associated with significantly decreased locoregional control.\textsuperscript{123} 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.\textsuperscript{124-126} Concurrent smoking and RT increased the risk of cardiovascular disease in 4414 10-year survivors of breast cancer.\textsuperscript{127}

**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.\textsuperscript{23} 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.\textsuperscript{128} 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.\textsuperscript{128,129}

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.\textsuperscript{23,128} Preclinical and clinical studies suggest that smoking and nicotine exposure can be detrimental to the function of both the adaptive\textsuperscript{130-133} and innate immune system.\textsuperscript{134-138} Similarly, cigarette smoking may increase the incidence of infection, particularly for smoking-related infectious diseases such as pneumonia and influenza.\textsuperscript{139}

Preclinical studies also suggest a potential link between nicotine exposure from smoking and the development of chemoresistance,\textsuperscript{140-144} 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.\textsuperscript{145} 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.\textsuperscript{146,147} Similarly, smoking increases the clearance time of irinotecan, potentially lessening systemic exposure.\textsuperscript{146,148} 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.\textsuperscript{146} Bendamustine metabolism is also likely to be impacted by smoking, resulting in decreased drug plasma concentration and increased concentration of its active metabolites.\textsuperscript{149,150} 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.\textsuperscript{151}

**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 afterward. Additional studies suggest that current smokers with cancer may experience more severe or frequent pain than nonsmoking counterparts.

**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 (e.g., 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. 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. 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 retrospective cohorts of patients with lung or head and neck cancers, but similar patterns have been observed for colorectal, bladder, and kidney cancers, as well as various other disease sites.

Retrospective studies have estimated a roughly 25% reduction in risk of mortality between smokers and former smokers diagnosed with NSCLC and bladder cancers.

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. 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%).

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. 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 (i.e., 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). 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%). 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 a
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. 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.

Cessation at or near cancer diagnosis appears to reduce treatment-related complications compared to patients who continued smoking. In patients undergoing lung cancer resection, studies suggest that preoperative cessation mitigates the risk of pulmonary complications and in-hospital mortality. In one study, 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. A larger retrospective study comparing preoperative cessation intervals of increasing lengths suggested that longer periods of preoperative cessation may be more effective than shorter periods for reducing risk of postoperative complications, although cessation for any amount of time prior to surgery significantly reduced risk. 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.

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. Additionally, patients with cancer who quit smoking benefited from lower rates of smoking-related cardiovascular and pulmonary disease.

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. 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. 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.

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). 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
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. 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 (more than 30 days to 1 year prior), and former smokers (more than 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. Smoking status of individuals within the patient’s household should also be noted. 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 (ie, within 5 minutes), 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. However, the panel has opted to recommend a more streamlined assessment for use in the oncology setting.

To best tailor treatment, providers should also gather information regarding the patient’s history of quit attempts and why they were or were not 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 reasons for why these aids were unsuccessful—such as medication side effects, continued cravings, or inefficacy—are important pieces of information.

Providers are encouraged to engage patients in a personalized 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. For a summary of
the methods and data on MI for smoking cessation, see the Principles of Behavior Therapy section below.

Patient readiness to quit should be assessed jointly with the patient and provider. 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 pharmacotherapy and counseling with the goal of cessation in the near future. The panel encourages immediate initiation of pharmacotherapy and counseling 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. 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. At each visit, providers should reassess readiness to quit and engage in motivational dialog as indicated.

Assessing Former Smokers/Recent Quitters

Providers should evaluate and document the risk of relapse for patients with more than 30 days’ abstinence. The panel suggests the following characteristics to identify patients at high risk for relapse: frequent/intense cravings; elevated anxiety, stress, or depression; current or prior history of mental illness; cohabitating or working with smokers; quitting within the past year; use of ongoing smoking cessation pharmacotherapy or other nicotine delivery mechanisms; drug/alcohol use or abuse; and/or low self-confidence in ability to quit/maintain abstinence. 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. While NRT may be used long-term to help former smokers maintain abstinence, methods other than NRT may be considered to avoid reintroducing nicotine to 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 via phone/telehealth. 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 might underestimate the rate of active smoking among patients with cancer, as is evidenced by research comparing self-reported and objective measures. 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 the section on Smoking-Related Effects on Treatment Efficacy, Side Effects, and Outcomes in this Discussion. Preoperative pharmacotherapy options for patients within 1 week of surgery include combination NRT (preferred; category 1) or varenicline. NRT is listed as preferred in this setting because guidelines for its use include a quit date within 24 hours, while varenicline quit dates are typically 7 days from initiation of therapy. However, in some clinical situations, varenicline has been used with an earlier quit date. If there is a week or more until scheduled surgery, combination NRT or varenicline are both category 1 recommendations.

The panel recognizes that some surgeons do not allow perioperative NRT use in their patients. This practice may be due to findings in animal studies regarding an association between nicotine and decreased wound healing. However, no similar data in humans exist, and NRT typically provides a lower overall dose of nicotine compared with cigarettes, while nearly doubling the chance of achieving smoking abstinence.\textsuperscript{187} NRT at the normal doses has not been shown to negatively affect acute wound healing,\textsuperscript{188-190} and offers benefits over continued smoking.

Preoperative smoking cessation has been shown to reduce post-operative complications. In randomized trials of smoking cessation or reduction interventions, postoperative complications from orthopedic surgery were significantly decreased in patients who quit compared with smoking controls.\textsuperscript{191,192} Study findings also support the benefits of preoperative smoking cessation in patients with cancer, which has been shown to reduce postoperative morbidity in patients undergoing surgery for various cancer types.\textsuperscript{104,105,107,193,194} The optimal timeframe for cessation to achieve full benefit is not yet clear, but longer periods of time may be more effective for reducing postoperative complications.\textsuperscript{104,105}

Smokers who need surgery should be treated with evidence-based smoking cessation therapy, including pharmacotherapy and behavior therapy, in order to improve surgical outcomes and long-term cessation rates.\textsuperscript{191,192,195,196} For patients with planned cancer surgery, cessation should occur as soon as possible before surgery, regardless of how soon surgery will be occurring. There is no evidence to support a harmful effect of a quit attempt at any point in time before surgery. Although longer periods of preoperative smoking cessation may confer better surgical outcomes,\textsuperscript{104,105,194,197} the panel emphasizes that patient smoking should not delay appropriate timing for cancer resection, and access to cancer surgery should not be restricted solely on the basis of continued smoking.\textsuperscript{198}

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.\textsuperscript{197} Providing surgery-specific resources and advice for smoking cessation may facilitate smoking reduction or cessation in patients undergoing elective (non-cancer) surgery.\textsuperscript{199,200}
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.\(^{201-203}\)

Preferred primary therapy options in these guidelines are 1) combination NRT (category 1); or 2) varenicline (category 1). The combination NRT approach includes the use of a nicotine patch plus a short-acting NRT for comfort, such as nicotine gum, lozenge, inhaler, or nasal spray. Patients commonly underdose when using combination NRT.\(^{204-206}\) Patients should be advised that nicotine overdose is rare but possible, and usually short-lived. Regarding varenicline, providers should 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, bupropion should be avoided in patients with brain metastases due to increased seizure risk. Use varenicline with caution in patients with 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. While combination NRT or varenicline are preferred primary pharmacotherapy options, bupropion or combination bupropion/NRT may be appropriate for select patients (eg, those with symptoms of depression or fatigue, or for NRT/varenicline intolerance). See the section below on Treatment for Relapse or Persistent Smoking 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 in person or by phone/telehealth at a minimum of: within 3 weeks after cessation (within 1 week preferred), and 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 48 to 72 hours after quitting and last about 2 to 3 weeks 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.\(^{207}\) 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 or telehealth. 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/telehealth. 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/telehealth. Motivational strategies should be employed to promote continued abstinence. Duration
of pharmacotherapy can be extended beyond 6 months if clinically indicated. Varenicline can be used up to 1 year for continued abstinence. Patients who experience smoking relapse can be considered for second-line therapy.

**Treatment for Relapse or Persistent Smoking**

For patients who continue to smoke or experience relapse, assess primary therapy effectiveness and medical adherence. The panel recommends one of two options in this setting. The first option is to continue or resume primary therapy and provide additional behavior therapy. The second option is switching to the alternate preferred option (combination NRT or varenicline [both category 1]). These regimens should always be paired with additional behavior therapy. In most circumstances, both preferred primary therapy approaches (combination NRT and varenicline) should be tried before proceeding to any of the subsequent pharmacotherapy options. However, bupropion or combination bupropion/NRT may be appropriate in earlier treatment settings for select patients (eg, those with symptoms of depression or fatigue, or those intolerant to NRT or varenicline). The decision to continue or switch therapy should be based on prior cessation success, patient preference, toxicity, and/or a change in clinical status (eg, upcoming surgery).

Subsequent options for pharmacotherapy include combination NRT with bupropion, or bupropion alone. 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.

Follow-up is recommended preferably within 1 week of 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, but recent large-scale analyses of the data support the safety of these regimens. 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.\textsuperscript{207,213}

Below, data from various clinical trials are discussed. Included in this discussion are findings from a Cochrane network meta-analysis that included data on pharmacologic interventions across 267 individual studies in 101,804 participants.\textsuperscript{214} 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, paired with behavior therapy.\textsuperscript{215} 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.\textsuperscript{195,214,216,217} 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).\textsuperscript{214} Data show that all forms of NRT are superior to placebo,\textsuperscript{218} but smokers using combination NRT were almost three times as likely to succeed (OR, 2.73; 95% CI, 2.07–3.65).\textsuperscript{214} 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).\textsuperscript{214,219}

The success of NRT appears to be bolstered by 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.\textsuperscript{201}

**Safety**

The safety of combination NRT for use in humans has been demonstrated and benefits are considered to outweigh potential risks.\textsuperscript{220} Importantly, providers should be aware that blood nicotine levels from NRT, including combination NRT, are significantly less than that from smoking cigarettes.\textsuperscript{221-223} In fact, patients commonly underdose when using combination NRT,\textsuperscript{204-206} 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.\textsuperscript{224,225} 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.\textsuperscript{218,219,225,226} Data from large case series have not shown elevated risk with the use of NRT in patients with acute coronary syndromes.\textsuperscript{227,228}

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.\textsuperscript{229} Some *in vitro* data suggested that nicotine
increased the malignant potential of small cell lung cancer cells\textsuperscript{230}; induced chemoresistance in models using lung cancer cells\textsuperscript{140-142} and nasal epithelial cells\textsuperscript{143}; and promoted chemoresistance and metastasis in pancreatic cancer cell and mouse models.\textsuperscript{144} However, other studies suggested no effects of physiological levels of nicotine exposure on tumorigenesis in mouse lung cancer models.\textsuperscript{231,232} Moreover, there is insufficient evidence that NRT causes cancer in humans.\textsuperscript{231-235} 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.\textsuperscript{234}

**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.\textsuperscript{236}

Systematic reviews/meta-analyses have identified varenicline as the most effective single pharmacotherapy option for smoking cessation.\textsuperscript{214,237,238} However, medication adherence is an important factor in cessation success.\textsuperscript{207} 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).\textsuperscript{214} 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).\textsuperscript{214} 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.\textsuperscript{214}

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).\textsuperscript{239} 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.\textsuperscript{240}

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.\textsuperscript{241} 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.\textsuperscript{242} Additionally, another RCT showed that varenicline was effective and well tolerated for retreating patients who had previously received this agent (n = 498).\textsuperscript{243}

Several studies have also suggested that varenicline dose increases beyond the standard 2 mg/d may boost treatment efficacy in patients who had a low or no response to standard dosing.\textsuperscript{244-246} 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.\textsuperscript{244} However, dose increases did exacerbate adverse effects such as nausea and vomiting for some individuals.\textsuperscript{244,246}
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.\textsuperscript{247,248}

Concerns regarding neuropsychiatric adverse effects of varenicline have been extensively investigated in smokers with comorbid mental illness.\textsuperscript{214} Despite reviews of case reports that raised concern,\textsuperscript{210} 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.\textsuperscript{212} Another trial showed that varenicline increased smoking cessation rates without exacerbating anxiety and depression symptoms in adults with stably treated current or past depression.\textsuperscript{249} 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.\textsuperscript{239}

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.\textsuperscript{214,224,250,251} However, the cardiovascular safety of varenicline has remained a topic of interest and concern.\textsuperscript{252-254}

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 (ie, depression, self-harm) events compared with NRT.\textsuperscript{255} 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 can be a concern in certain individuals receiving varenicline therapy.\textsuperscript{256,257} In patients with brain metastases who have a history or elevated risk of seizure, varenicline should be used with caution.

Subsequent Therapy Options
Recommended subsequent therapy options in these guidelines include combination NRT with bupropion or bupropion alone. 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.\textsuperscript{258} 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.\(^{29}\) 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.\(^{260}\) A 2014 meta-analysis of 12 trials examining this combination revealed a nonsignificant trend in improved cessation with the addition of NRT to bupropion.\(^{261}\)

**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 acetylcholine receptors. A 2014 Cochrane review of 44 trials examined bupropion efficacy, revealing an RR of 1.62 (95% CI, 1.49–1.76).\(^{261}\) 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).\(^{239}\) 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.\(^{258,262}\) Additionally, longer duration of bupropion treatment may help to prevent relapse in those who have successfully quit.\(^{263}\)

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.\(^{261}\) 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 with varenicline.\(^{210}\) 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.\(^{214,264}\) In the EAGLES trial, no significant increase in neuropsychiatric events was observed for bupropion relative to nicotine patch or placebo.\(^{239}\)

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.\(^{214,224,261}\)

**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.\(^{265}\) No significant differences were noted for side effect incidence between varenicline/NRT and varenicline/placebo with the exception of skin
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). However, as an adjunct to NRT, clear-cut benefits were not observed. 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).

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.

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. A 2012 systematic review of 41 studies provided support for the efficacy of this approach. 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. 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).

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. The evidence supports a measurable dose-response effect of behavior therapy with more numerous and/or longer sessions delivering improved outcomes.

The panel recommends that the first counseling session occur within 3 weeks of cessation, but preferably within 1 week as a majority of smokers relapse during this period. 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. Importantly, if intensive therapy is not feasible, brief counseling should still be given. Studies have demonstrated a small but significant benefit of brief counseling lasting only a few minutes.

The most successful behavior therapy strategies employ practical counseling in which patients learn coping skills and receive support and education. 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.

Providers should prepare patients for nicotine withdrawal symptoms and cravings, which typically peak 48 to 72 hours after quitting and last about 2 to 3 weeks before gradually subsiding.

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 phone or telehealth, or through web-based interventions. Effective in-person counseling can occur as an individual session or in the group therapy setting. Additionally, print materials and mobile telephone “apps” can be used to deliver behavior therapy. However, providers should be aware that media-based behavioral interventions, particularly those using mobile telephones, might vary in the degree to which they comply with clinical practice guidelines.

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. 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. Additionally, quitlines can provide essential behavioral support in the absence of in-person counseling resources. For instance, the addition of combination NRT to quitline counseling improved cessation outcomes.

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. Interventions initiated during hospital stays have also been successful. Intensive behavioral interventions provided during hospitalization, with at least a month of subsequent follow-up upon discharge, increased smoking cessation rates. 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.

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%. 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. Providers should routinely assess for these symptoms among smokers throughout treatment for tobacco dependence. 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. MI 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.

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. 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. A recent systematic review summarized the evidence to support MI for behavioral change, including smoking cessation, in patients with cancer.

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. 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. 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 recommend 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 relapses 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, also known as e-cigs, vaping, or juuling, 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. 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, American Cancer Society, 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. 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.” An update to this recommendation is currently in progress.

For background information, an overview of safety and efficacy, and public health concerns surrounding e-cigarette use, see reviews by Drope et al and Glantz and Bareham.

Efficacy in the General Population

In the first head-to-head comparison, an RCT (n = 886) compared e-cigarettes to NRT (combination NRT allowed), paired with at least 4 weeks of behavioral support. Abstinence rates at 1 year were 18% and 9.9% for e-cigarettes and NRT, respectively (RR, 1.83; 95% CI, 1.30–2.58; P < .001). However, prolonged e-cigarette use extended beyond the initial treatment period, particularly among abstainers, with unclear health implications. In a real-world setting, smokers who reported dual use of e-cigarettes were more likely to report abstinence at 6 months, but this pattern was no longer present at 12 or 18 months.

Initiation of e-cigarette use may lead to long-term use and the continued use of both e-cigarettes and cigarettes. Although individuals using e-cigarettes alone or NRT alone had lower levels of toxins than those using...
In 2016, several systematic reviews and meta-analyses reported somewhat divergent findings. A meta-analysis of 20 controlled studies (2 trials, 15 cohort studies, and 3 cross-sectional studies) by Kalkhoran and Glantz (2016) calculated that individuals using e-cigarettes were 28% less likely to achieve smoking cessation (OR, 0.72; 95% CI, 0.57–0.91). Two additional meta-analyses concluded that, based on low- or very-low-quality evidence, e-cigarettes may be helpful for smoking reduction and possibly cessation for some smokers.

A large cross-sectional survey 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 self-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).

**Studies in Patients with Cancer**

One study examined e-cigarette use in 1074 patients with cancer who enrolled in a tobacco treatment program at a comprehensive cancer center. 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. Collectively, these studies highlight the importance of addressing e-cigarette usage by patients with cancer and cancer survivors.

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). Another cross-sectional study surveyed 121 patients with cancer who were currently using e-cigarettes. Eighty-one percent of e-cigarette users reported smoking cessation and their motivation for initiating e-cigarette use, but 51% also reported dual use of combustible cigarettes with e-cigarettes. Additionally, more than 70% reported that they had not discussed their e-cigarette use with their oncology care providers. Patients surveyed also expressed a preference for e-cigarettes over NRT.

**NCCN Recommendations**

Despite emerging evidence, the current body of evidence is insufficient to recommend e-cigarette use in smoking cessation, alone or in combination with evidence-based methods. Insufficient evidence also exists concerning the safety and efficacy of e-cigarette use in patients with cancer. Additionally, it is not yet clear how factors such as real world use or the addition of behavior therapy may influence the efficacy and safety of e-cigarettes.

The panel recommends that providers educate patients on the unknown risks of using e-cigarettes in lieu of evidence-based methods. Continue to provide support during any quit attempts. For patients who choose to use e-cigarettes despite recommendations to use evidence-based methods, encourage abstinence and behavioral counseling.
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.\textsuperscript{318} 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.\textsuperscript{319} 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.\textsuperscript{320,321} 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.
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