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TOBACCO & CANCER TREATMENT OUTCOMES

- *Tobacco use by cancer patients is linked to increased risks of adverse cancer treatment outcomes, including overall mortality, cancer-specific mortality and second primary cancers, in addition to the well established risks of tobacco-related health problems.*
- *Tobacco use can lead to poorer cancer treatment outcomes by increasing the aggressiveness of cancer, altering drug disposition and increasing treatment-related complications and tobacco-related comorbidities.*
- *Quitting tobacco use has the potential to improve cancer treatment outcomes among current tobacco users.*
- *Even after a diagnosis of cancer, a substantial proportion of tobacco users continue to use, or relapse after attempting to quit, which is due in large part to the addictiveness of tobacco.*
- *Cancer care providers should actively support tobacco-using patients to quit or seek assistance from tobacco cessation services.*
- *Cancer care providers should advocate that the establishments and buildings in which cancer patients work and live become and remain smoke-free.*

Tobacco use

Worldwide, more than 1.1 billion people smoke tobacco and at least 367 million people use smokeless tobacco (World Health Organization, 2018a). Tobacco smoking is known to cause adverse health effects, including cardiovascular and respiratory diseases and cancer (United States Department of Health and Human Services, 2010), and was responsible for approximately 11.5% of total deaths in 2015 (GBD, 2015).

Cancer burden

Cancer has imposed considerable human suffering and economic cost worldwide (Stewart & Wild, 2014; World Health Organization, 2017a). Over 14 million people were diagnosed with cancer in 2012 (Ferlay et al., 2013) and approximately 9 million people died of cancer in 2016 (World Health Organization, 2018b). An estimated 22% of cancer-deaths are attributable to tobacco use (World Health Organization, 2012).

While significant improvements in survival rates have been achieved for cancers such as colon, rectal and breast in high-income settings, survival rates remain poor for certain cancer types (e.g. cancers of the liver and lung) as well as in regions where access to optimum diagnostic and treatment services is limited (Allemani et al., 2015).

Tobacco definitions

Smoked tobacco: any product made entirely or partly of leaf tobacco that is intended to be lit and the produced smoke inhaled. Examples include manufactured cigarettes, roll-your-own cigarettes, water pipes (e.g. hookah, shisha), cigars, kreteks and bidis.

Smokeless tobacco: any product that consists of cut, ground, powdered or leaf tobacco that is intended to be placed, loose or in sachets, in the oral or nasal cavity. Examples include snuff, chewing tobacco, gutka and mishri.

Second-hand smoke (SHS): the combination of "mainstream" smoke (the smoke emerging from the mouth end of a cigarette during smoking) that is exhaled by the smoker, and "side-stream" smoke emitted into the environment from lit cigarettes and other tobacco products (International Agency for Research on Cancer, 2012). The terms "passive smoking", "involuntary smoking" and "environmental tobacco smoke" are also often used to describe exposure to SHS.

The problem: tobacco use by cancer patients

A substantial proportion of tobacco users continue tobacco use, or relapse, even after a diagnosis of cancer. A systematic review of 16 longitudinal studies on tobacco use after a diagnosis of lung or head and neck cancer found that on average 42.2% (range 25.6–57.3%) of patients who were

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smoking at diagnosis continued to smoke after diagnosis (Burris et al., 2015). Persistent smoking appears also to be common in patients with a cancer for which there is limited evidence for carcinogenicity of tobacco smoking (International Agency for Research on Cancer, 2012); for example, a prospective cohort study of breast cancer patients in Sweden showed that only about 10% of 206 preoperative smokers were abstinent from smoking during the first postoperative year (Persson et al., 2016).

Tobacco users with cancer have greater risks, not only of the well known tobacco-related health problems, such as cardiovascular and respiratory diseases and further cancers, but also unfavourable cancer treatment outcomes (Florou et al., 2014; United States Department of Health and Human Services, 2014). The 2014 United States Surgeon General's report (United States Department of Health and Human Services, 2014), which represents the largest evaluation of scientific evidence about the effects of smoking on cancer treatment outcomes, concluded that the evidence is sufficient to infer a causal relationship between cigarette smoking and adverse health outcomes, including all-cause mortality, cancer-specific mortality and further primary tobacco-related cancers. As lifespan increases and cancer survival rates improve, the problem of continued tobacco use among cancer patients and survivors becomes ever more important.

Although tobacco users with cancer may be well aware of such tobacco-related health risks, cessation of tobacco use remains challenging because of the addictiveness of the products. Therefore, it is important for both smokers diagnosed with cancer and the health-care providers treating them to know whether, and to what extent, continuation or cessation of tobacco use after a diagnosis of cancer might affect the patient's cancer treatment outcomes. This knowledge may influence the level of support that patients may seek, or their health-care providers organize, to help cancer sufferers quit.

Pathways: how continued tobacco use worsens cancer treatment outcomes

There are several lines of evidence explaining the mechanisms of inference between tobacco use by cancer patients and poorer cancer treatment outcomes. The suggested mechanisms include the effects of tobacco on biological characteristics of cancer cells, drug disposition, treatment-related complications and tobacco-related comorbidities.

Altered cancer biology Tobacco smoke and nicotine can increase the aggressiveness of cancer by promoting cell proliferation, migration, invasion, metastasis and angiogenesis; by inhibiting apoptosis of cancer cells; or by modulating tumour-associated immune responses (Sobus & Warren, 2014; Warren & Singh, 2013). Such effects can reduce the effectiveness of cancer treatment (Condoluci et al., 2016; Sanner & Grimsrud, 2015; Warren, Sobus & Gritz, 2014). An in vivo study showed that mice that were treated with nicotine during radiation or chemoradiation therapy had greater tumour regrowth compared with mice treated with only radiation or chemoradiation (Warren et al., 2012). Similarly, another in vivo study examining chemotherapy suggested that exposure to nicotine during cancer treatment may be an important determinant of cancer treatment outcome (Banerjee, Al-Wadei & Schuller, 2013).

Altered drug metabolism Tobacco smoke can also alter drug disposition by multiple mechanisms; for example, polycyclic aromatic hydrocarbons (PAHs) affect the transcriptional and epigenetic regulation of cytochrome P450 (CYP) enzymes, which are responsible for metabolizing toxic substances and consequently accelerate the clearance of certain systemic therapies (O'Malley et al., 2014; Petros et al., 2012). A study of 1047 lung cancer patients indicated that clearance of erlotinib, which is primarily metabolized by CYP enzymes, is faster in current smokers than in former or never smokers (Lu et al., 2006). This faster clearance of anticancer drugs and the resulting reduced systemic exposure could lead to suboptimal treatment efficacy.

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Increased treatment-related complications The 2014 United States Surgeon General's report stated that the majority of studies showed a statistically significant positive association between current smoking and treatment-related toxicity in cancer patients. There is also evidence suggesting that smoking cessation may reduce cancer-treatment-related complications (e.g. pulmonary or wound-healing complications) (Bjarnason et al., 2009; Jung et al., 2015; Kuri et al., 2005; United States Department of Health and Human Services, 2014; Zaman et al., 2012; Zevallos et al., 2009). Having serious treatment-related complications may delay or preclude cancer treatment (Hendren et al., 2010; Merkow et al., 2013; Merkow et al., 2014) and lead to a suboptimal therapeutic outcome (Tevis et al., 2013).

Increased tobacco-related comorbidity As in the general population, patients with cancer who smoke have an increased risk of developing tobacco-related comorbidities including second primary cancer (United States Department of Health and Human Services, 2014). For instance, older women with breast cancer who continued smoking after diagnosis had a higher risk of respiratory cancer compared with those who quit smoking after diagnosis (Passarelli et al., 2016). Furthermore, having a comorbidity has been associated with an increased risk of breast-cancer-specific mortality in older women with breast cancer, which may be due to an interruption or reduction of treatment (Patnaik et al., 2011). It is also important to note that cardiovascular disease and secondary cancer for which tobacco use is a major risk factor are common causes of death among patients with prostate cancer and breast cancer (Bittner et al., 2008; Passarelli et al., 2016; Patnaik et al., 2011).

Continuation or cessation of tobacco use and cancer treatment outcomes

The following section summarizes representative studies that focused on the association between continuation or cessation of tobacco use following a cancer diagnosis and cancer treatment outcomes (see methods section).

Smoked tobacco and cancer treatment outcomes

All-cause mortality A meta-analysis showed an increased risk of all-cause mortality associated with continued smoking after a diagnosis of early stage non-small cell lung cancer (hazard ratio (HR) 2.94; 95% confidence interval (CI) 1.15–7.54) or early stage small cell lung cancer (HR 1.86; 95% CI 1.33–2.59) compared with quitting smoking around the time of diagnosis (Parsons et al., 2010). These results are in line with the findings of later studies (Dobson Amato et al., 2015; Koshiaris et al., 2017; Roach et al., 2016; Tao et al., 2013); quitting tobacco use after a diagnosis of lung cancer has been associated with a median 9–11-month improvement in overall survival (Dobson Amato et al., 2015; Koshiaris et al., 2017). Similar results have been found for other cancers, such as head and neck, colorectal and bladder cancers (Choi et al., 2016; Tao et al., 2013; van Imhoff et al., 2015).

Cancer-specific mortality, recurrence Systematic reviews found greater risks of recurrent non-small cell lung cancer (HR 1.86; 95% CI 1.01–3.41) and recurrent small cell lung cancer (HR 1.26; 95% CI 1.06–1.50) (Parsons et al., 2010) and higher rates of head and neck cancer recurrence (risk difference: range 23–30%) (van Imhoff et al., 2015) in patients who continued to smoke after diagnosis compared with those who quit smoking after diagnosis. A recent review of studies related to smoking cessation for bladder cancer outcomes also concluded that smoking cessation even after diagnosis may improve treatment outcomes while acknowledging that the evidence is relatively weak (Soria et al., 2018).

Adverse effects of continued tobacco use on cancer treatment outcomes have also been observed in patients with a cancer type for which there is limited evidence for carcinogenicity of tobacco smoking (International Agency for Research on Cancer, 2012). A subset analysis of a population-based prospective observational study showed that smoking cessation after a diagnosis of breast cancer is associated with lower breast-cancer-specific mortality compared with continued smoking,

although the results did not reach statistical significance (HR 0.67; 95% CI 0.38–1.19) (Passarelli et al., 2016).

Quality of life Studies have suggested that patients with cancer who continue to smoke reported worse health-related quality of life than former smokers and that cessation of smoking around the time of diagnosis could improve quality of life and symptoms (Bloom et al., 2015; Chen et al., 2012; Ong et al., 2016). For instance, Bloom et al. found that smokers diagnosed with lung or head and neck cancer who remained abstinent from smoking during the year after surgical cancer treatment reported lower levels of depressive symptoms than those who resumed smoking (Bloom et al., 2015).

Smokeless tobacco and cancer treatment outcomes

No study was identified relating to continuation or cessation of smokeless tobacco use by cancer patients in relation to cancer treatment outcomes (see methods section). Provided that smokeless tobacco contains compounds found in smoked tobacco, such as nicotine and PAHs (International Agency for Research on Cancer, 2012), the risks associated with continued use of smokeless tobacco or the benefits associated with cessation of such use in relation to cancer treatment outcomes should be investigated.

Second-hand smoke and cancer treatment outcomes

No study was identified relating to the impact of post-diagnosis exposure to SHS on cancer treatment outcomes (see methods section). While the concentrations of compounds in SHS are lower than those in mainstream smoke because of the rapid dilution and dispersion of SHS into the environment (International Agency for Research on Cancer, 2004), non-smokers exposed to SHS have an elevated level of biomarkers of nicotine (International Agency for Research on Cancer, 2004; Okoli et al., 2007) and PAHs (Suwan-ampai et al., 2009). Given that these compounds can alter cancer biology and/or drug disposition (O'Malley et al., 2014; Sobus & Warren, 2014), the impact of SHS on cancer treatment outcomes should also be investigated.

Conclusions and future research

Although the body of evidence that specifically addresses risks related to continued smoking as opposed to smoking cessation following a cancer diagnosis is relatively small, the existing data support the conclusion that continued smoking negatively affects cancer treatment outcomes including survival, recurrence and quality of life and that, by quitting smoking, patients with cancer have the potential to improve their cancer treatment outcomes (United States Department of Health and Human Services, 2014) in addition to other unfavourable outcomes such as decreased circulation and lung function and tobacco-related diseases (World Health Organization, 2017b). Our views are consistent with the conclusion of the 2014 United States Surgeon General's report that further action for tobacco cessation is needed to reduce an avoidable burden of morbidity and premature mortality in the at-risk population of patients with cancer. Addressing tobacco use in patients diagnosed with cancer should be an important part of cancer care.

Consistent with recommendations by Gritz et al. (2014) and Land et al. (2016), WHO and the International Agency for Research on Cancer encourage further research efforts in the following areas: the effects of different forms of tobacco (smoked tobacco, smokeless tobacco and SHS) or nicotine use, and of reduction or cessation, on cancer treatment and its outcomes, including cancers that are not considered to be caused by tobacco; the effects of tobacco on the biology of cancer and its response to cancer treatment; and the optimal methods to achieve cessation of tobacco use in patients with cancer in order to maximize the benefits of their cancer treatment. In order to facilitate research, incorporation of a structured tobacco assessment into routine clinical practice and clinical trials is recommended (Gritz et al., 2014; Land et al., 2016).

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Population-level action

Despite the importance of tobacco cessation support, surveys of oncology providers revealed that less than half (39–42%) actively treat tobacco use or refer patients to tobacco cessation services (Warren et al., 2013; Warren et al., 2015). The major barriers to providing tobacco cessation support are a lack of education or experience in providing tobacco cessation interventions and a lack of available resources for referrals (Warren et al., 2015).

As recommended by the WHO Framework Convention on Tobacco Control (WHO FCTC) guidelines and several professional organizations, brief advice should be incorporated into all health-care systems (World Health Organization, 2003), including oncology clinics, so that all cancer patients who smoke can be identified and offered smoking cessation support. In order to establish a basic infrastructure to provide tobacco cessation services to all cancer patients who use tobacco, sustainable funding should be identified and allocated to dedicated tobacco cessation services (e.g. quitlines, affordable and high-quality treatment for tobacco dependence) as well as tobacco treatment training programmes for health-care providers (World Health Organization, 2003).

In addition, the WHO FCTC guidelines recommend evidence-based tobacco control measures such as implementation and enforcement of smoke-free legislation to protect all people from smoke in workplaces and public places, including health-care facilities; mass-media anti-tobacco campaigns and labelling of tobacco products to raise the public's awareness of the adverse health effects of tobacco use; and increases in taxes on tobacco products (World Health Organization, 2003).

Individual-level action

To assess and address tobacco use and dependence in all cancer patients, cancer care providers should use the "5 A's" treatment model (Fiore et al., 2008; Simmons et al., 2012; World Health Organization, 2014), and also seek specialized tobacco cessation resources. Furthermore, health-care providers should educate family members and caregivers of cancer patients about the importance of eliminating exposure to SHS because such exposure significantly increases the risk of relapse to smoking (Eng et al., 2015).

Information for health professionals can be obtained from several sources. Examples include:

- Treating tobacco use and dependence: 2008 update
- NCCN clinical practice guidelines in oncology: smoking cessation
- ASCO tobacco toolkit
- Rx for Change: clinician-assisted tobacco cessation

Information for patients can be obtained from sources such as:

- smokefree.gov
- The Global Quitline Network https://globalqlnetwork.wordpress.com/quitlines-around-the-world/

The "5 A's" treatment model

Ask about tobacco use: identify and document the tobacco use status of every patient at every visit.

Advise to quit: in a clear, strong and personalized manner, urge every tobacco user to quit.

Assess willingness to make a quit attempt: ask two questions: (1) Would you like to be a non-tobacco user? and (2) Do you think you have a chance of quitting successfully?

Assist in quit attempt: help the patient develop a quit plan including setting a quit date, provide practical counselling, provide intratreatment social support, provide supplementary materials including information on quitlines, and recommend the use of approved medication, if needed.

Arrange follow-up: arrange a follow-up contact* with the patient, or refer the patient to specialist support if needed.

**The first contact is recommended within the first week after the quit date and the second contact is recommended within one month after the quit date.*

Methods

WHO and the International Agency for Research on Cancer systematically searched for articles in English before November 2017 on the associations between continued tobacco use or cessation of such use following cancer diagnosis and cancer treatment outcomes in three databases: PubMed, Web of Science and the Cochrane Library. The search prioritized systematic reviews and original studies published after the most recent systematic reviews. The authors highlighted representative studies to provide a concise summary of the current knowledge; thus, not every available study was cited. Any funding by or links to the tobacco industry were checked for identified articles because such studies would be considered non-independent as per Article 5.3 of the WHO FCTC.

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