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A review of the effects of tobacco smoking on cancer treatment: smoking cessation intervention should be integrated into the cancer care continuum

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Literature Review

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Abstract

Background: The adverse health effects associated with smoking tobacco have been well investigated, and its detrimental effects on cancer treatment outcomes, efficacy and quality of life (QOL) for cancer patients have also been well documented. Tobacco smoke contains many thousands of chemicals, including a plethora of carcinogens, and the exposure of human cells to these carcinogens, and their metabolic activation, is the main mechanism by which smoking-related cancer is initiated.

Materials and Methods: This paper reports on a narrative review of recent studies in the field of effects of tobacco smoking on cancer treatment, including the effects of carcinogens in smoke on carcinogenesis, cell mutations and the immune system. The health effects of smokeless tobacco, effects of tobacco smoking on cancer treatment, and its impact on surgery, radiation therapy and chemotherapy are reported. The potential risks of second primary cancers or recurrence from tobacco use, the effects of second-hand smoking and cancer treatment, the impact of smoking on the QOL after cancer treatment and the need to integrate smoking cessation programs into the cancer care continuum are also reported.

Conclusions: Tobacco use has a direct impact on cellular function by inhibiting apoptosis, stimulating proliferation and decreasing the efficacy of cancer treatment; therefore, quitting its use has the potential to improve treatment response rates and survival, as well as reduces the risk of developing second cancers and potentially improves the QOL after treatment. Smoking cessation is one of the most important interventions to prevent cancer and is also essential after the diagnosis of cancer to improve clinical outcomes. Due to the numerous benefits of smoking cessation, it should become a critical component of the cancer care continuum in all oncology programs – from prevention of cancer through diagnosis, treatment, survivorship and palliative care. Evidence-based smoking cessation intervention should be sustainably integrated into any comprehensive cancer program, and the information should be targeted to the specific benefits of cessation in cancer patients.

Introduction

The adverse health effects associated with tobacco smoking have been well investigated over the past few decades[1–25]; however, it is estimated that approximately 4·6 million Canadians are still considered active smokers and nearly 45,000 die from tobacco-related disease each year.[1] In recent years, the detrimental effects of tobacco smoking on the outcomes of cancer treatment, treatment efficacy and the quality of life (QOL) of cancer patients have also been investigated.[26–74] The World Health Organisation (WHO) and the International Agency for Research on Cancer (IARC)[3] have published an authoritative series on carcinogenic risks to humans on the basis of an extensive evaluation of the international literature and concluded that tobacco smoking increases the risk of all histologic types of lung cancer. Moreover, tobacco use was determined to be causally associated with oral cavity cancers (lip, tongue, floor of mouth, buccal mucosa, upper and lower gum, retromolar trigone and hard palate), laryngeal cancers, oropharyngeal cancers, hypopharyngeal cancers, sinonasal cancers, nasopharyngeal cancers, oesophageal cancers and an increased risk of leukaemia. Furthermore, they also determined that tobacco smoking is a risk factor for developing cancers of the stomach and pancreas, transitional cell carcinoma of the bladder, ureter and renal pelvis, and cancers of the uterine cervix and kidney.[3] An increased susceptibility to pulmonary complications due to tobacco smoking has been reported to be due to the impairment of mucus transport and pulmonary

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macrophage function, increased bronchial reactivity, reduction of the closing capacity of the lung, and increased arterial carbon monoxide levels due to continued tobacco smoking.[6]

Tobacco is a known addictive consumer product that has been reported to be associated with several health problems and the leading cause of preventable mortality worldwide.[2] Most tobacco products are made from *Nicotiana tabacum*,[4] and over 7,000 chemical compounds have been identified in tobacco leaf, some of which are released through smoking or ingestion. The WHO and the IARC have evaluated several of these chemical compounds and generated sufficient evidence of carcinogenicity in either laboratory animals or humans.[4] These carcinogenic substances included N-nitrosamines, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, numerous polycyclic aromatic hydrocarbons (e.g., benzo[a]pyrene), radioactive polonium and benzene.[4] Several studies[26–70] that have established a link between the use of tobacco products and some human cancers have shown the association to result from the combination of nicotine content in tobacco, the tar by-product, carbon monoxide and the presence of thousands of chemicals, some of which are currently known to be carcinogenic.[5] Nicotine in tobacco smoke is the second most abundant chemical constituent and known to be highly addictive and toxic, but it is not carcinogenic. However, its mutagenic and tumour-promoting activities may result from its ability to damage the genome, disrupt cellular metabolic processes and facilitate growth and spread of transformed cells. Nicotine addiction will result in a continued use of tobacco products, leading to repeated and prolonged exposure to the many carcinogens contained in tobacco smoke.[5] Tobacco tar (considered to pose the biggest health risk) is the chemical substance made when tobacco is burned, and it contains most of the cancer-causing and other harmful chemicals found in tobacco smoke.[5] When tobacco smoke is inhaled, the tar can form a sticky layer on the inside of the lungs and damage them, leading to lung cancer, emphysema or other lung problems. Cigarettes and other smoked tobacco products may produce different amounts of tar, depending on how they are produced.

This narrative literature review covers the effects of tobacco smoking on cancer treatment and the need to integrate evidence-based smoking cessation interventions into the cancer therapy trajectory. The effects of carcinogens in tobacco smoke on carcinogenesis, cell mutation and the immune system are examined. Other topics discussed include the health effects of smokeless tobacco, the effect of tobacco smoking on cancer treatment, and its impact on cancer surgery, radiation therapy and chemotherapy. The review also covers tobacco smoking and the risk of second primary cancers or recurrence, the effects of second-hand smoking and cancer treatment, impact of smoking on the QOL of patients after cancer diagnosis and treatment. Furthermore, the need to integrate smoking cessation intervention into oncology programs to help improve treatment outcomes, decrease symptom burden after treatment, limit the likelihood of treatment interruptions, and increase the QOL following treatment is also emphasised.

Effects of Carcinogens in Tobacco Smoke and Cancers

The cancers encompass a wide variety of diseases that share a common characteristic of unregulated cell growth; however, carcinogenesis or the development of cancer is a multistage process.[8] For cells to escape normal growth regulation mechanisms, there must be both enabling of oncogenes (genes that stimulate cell division) and switching off of tumour suppressor genes (genes that prevent cell division), so that the affected cells are constantly stimulated to divide without any control to regulate mitosis.[8] Cells with damaged DNA are usually eliminated through apoptosis; however, aberrant cells may escape normal growth control and acquire mutations that may alter apoptosis and thereby allow the development of cancer.[8] Tobacco-related carcinogenesis, therefore, requires multiple genetic changes within the context of long-term or repeated exposure to genotoxic products in tobacco.[8]

Tobacco smoke and carcinogenesis

Tobacco smoke contains many thousands of chemicals, including a plethora of carcinogens, and the exposure of human tissues and organs to these carcinogens, and their metabolic activation, is the main mechanism by which smoking-related cancers are initiated.[9] Most of these carcinogens require metabolic activation to become intermediate agents, generally electrophiles, which react with nucleophilic sites in the DNA to form DNA adducts.[9] Over the past two decades, the systemic nature of exposure to carcinogens inhaled from tobacco smoke has become evident from the widespread formation of DNA and protein adducts in human tissues and the detection of tobacco-related carcinogens and their metabolites in various bodily fluids. Phillips[10] reported that there is a significant association between smoking status and bulky DNA adduct levels, which are the highest in current smokers; however, in former smokers, the levels decline with years of abstinence from smoking. He further indicated that DNA adducts formed by benzo[a]pyrene were detected more frequently in the colonic mucosa of smokers and at higher concentrations than in non-smokers. Phillips[10] further reported that, if DNA adducts escape cellular repair mechanisms, these could persist and may lead to miscoding, resulting in a mutation. Although there is no single mechanism of tobacco-related carcinogenesis, the availability of a large variety of tobacco products containing thousands of chemicals and how they are consumed influence the release of various carcinogens into the biological system of the smoker, leading to a link between tobacco use and cancer induction.[10] When carcinogens from tobacco products enter the body (directly through either inhalation or ingestion – smokeless tobacco) these are absorbed into the circulatory system. Many of these compounds are then converted into reactive electrophilic metabolites by oxidative (phase I) enzymes, to allow the attachment of a conjugate by inactivating (phase II) enzymes, so that the substrate becomes more hydrophilic and can easily be excreted from the cell.[10] However, the substrates produced in phase I have a higher potential to damage DNA compared with the precursor chemicals; thus, carcinogens in tobacco may get metabolically activated by phase I enzymes.[10]

The complexity of the mixture of carcinogens in tobacco smoke shows that different carcinogens may be responsible for different types of damage in different individuals, in addition to the random component of carcinogenesis.[8] According to Kuper et al.,[8] carcinogens must be metabolically activated to exert their deleterious effects; however, this process is also counteracted by ongoing detoxification of carcinogens in the body. Therefore, the balance between the activation and detoxification partly determines the individual's susceptibility to the carcinogenic effects of tobacco use. They, furthermore, reported in animal studies that the application of tobacco smoke condensate to the skin induced skin cancer in mice and rabbits, and intrapulmonary injection of smoke condensate induced lung cancer in rats, while whole smoke and its particulate phase triggered malignant respiratory tract tumours in hamsters and rats.[8] It has been demonstrated that some tobacco-specific nitrosamines (i.e., N-nitrosonornicotine) that are present

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in smokeless tobacco are potent carcinogens and have produced carcinomas of the upper digestive tract, nasal cavity and the respiratory tract in experimental animals.[4,11] Benzo[a]pyrene, which is a polycyclic aromatic hydrocarbon, can also induce lung tumours upon local administration or inhalation.[11] Peppone et al.[67] have indicated that tobacco smoke can induce cell division in colorectal adenocarcinomas, increase tumour growth factors and reduce apoptosis in colon cells. In a recent study, Hecht[7] reviewed the detection of urinary carcinogen metabolites as biomarkers for investigating the relationship between tobacco smoking and carcinogenesis in humans. Although nicotine is not a tumour initiator in carcinogenesis, its metabolites promote tumour growth through mechanisms such as increased proliferation, angiogenesis (development of new blood vessels), epithelial-to-mesenchymal cell transition and the simulation of autocrine pathways associated with tumour growth.[55,56]

Tobacco smoke and cell mutations

Exposure to tobacco products such as extracts of moist oral snuff can produce mutations, sister chromatid exchange (i.e., identical copies [chromatids] formed by DNA replication of a chromosome, with both copies joined together by a common centromere), and chromosomal aberrations in a variety of experimental models.[10] In addition, tobacco smoke contains free radicals that can induce oxidative damage of DNA in humans and cause mutations that could trigger the activation of an oncogene or the deactivation of a p53 tumour suppressor gene.[10,11] According to Gibbons et al.,[11] the p53 gene is a key regulator of the cell cycle; the authors observed that mutations of the p53 gene are more common in lung and oral cancer patients who are smokers.

Tobacco smoke and the immune system

Sopori and Kozak[12] have demonstrated in both human and experimental models that tobacco smoking could result in the impairment of immune system functioning, thereby increasing the risk of some cancers. They observed that smokers have higher rates of infection, lower serum levels of most immunoglobulin classes, and lower antibody titres when infected.[12,13] In an animal model study, it was observed that exposure to tobacco smoke resulted in the suppression of primary antibody response as well as an increased susceptibility to infections.[12,13] Tobacco smoke and/or nicotine has the potential to influence the hypothalamo-pituitary-adrenal axis by stimulating the release of catecholamines and adrenocorticotropic hormone, or modulating cytokine production and thus changing the Th1/Th2 (Type 1:Type 2 helper cells) ratio, or reducing the responsiveness of T cells (a lymphocyte of a type produced by the thymus gland that actively participates in the immune response).[12,13]

Effects of Tobacco Smoking on Cancer Treatment

A growing number of studies[26–74] have described the effects of ongoing tobacco smoking on cancer treatment, and outcomes including both short-term and long-term effects have shown that patients with cancer who are active smokers at the time of diagnosis have poorer prognosis compared with non-smokers. According to Gritz et al.,[30] active tobacco use after cancer diagnosis poses unique risks to patients by compromising the effectiveness of the treatment, increasing the risk of treatment-related complications, increasing physical symptoms, reducing overall survival, decreasing disease-free survival, reducing the QOL, increasing disease recurrence and increasing the risk of second primary cancers. In another study, Gritz et al.[31] reported that continued use of tobacco is a serious concern for patients at all stages of the disease and treatment, including survivors of cancer and those with advanced disease stages, as tobacco use has a direct impact on cellular function by inhibiting apoptosis, stimulating proliferation and decreasing the efficacy of treatment. Smoking cessation following the diagnosis of cancer has the potential to improve treatment response rates and survival, as well as reduces the risk of developing a second cancer.[32,33] It has also been reported that the effects of tobacco smoking on cancer treatment decline with time since cessation.[34]

Impact of tobacco smoking on cancer surgery

Tobacco smoking has been shown to negatively impact the outcomes of surgical procedures in general, including increased postoperative complications, reduced QOL (e.g., dyspnoea, fatigue, pain), increased length of hospital stay and increased mortality.[36–38] Therefore, cancer patients who smoke at the time of diagnosis and continue to smoke while undergoing any form of surgical procedure for their treatment are prone to these same negative impacts as a result of their continued tobacco use. Myles et al.[39] have indicated that nicotine is a potent vasoconstrictor and can induce wound ischemia by impeding blood flow, therefore contributing to an increased risk of infection and complications after surgery. They further reported that tobacco smokers undergoing ambulatory surgery have a higher rate of perioperative complications and are more likely to suffer from respiratory complications in the operating room and in the post-anaesthesia care unit due mainly to coughing, laryngospasm, bronchospasm, apnoea and breath-holding. Tobacco contains many toxic substances that are known to impair wound healing and increase surgical site infections, which are more likely to be prevalent with continued tobacco use because of increased levels of carbon monoxide circulation in the bloodstream.[40] According to Schmidt-Hansen et al.,[38] the presence of carbon monoxide in the bloodstream reduces oxygen transport, and cyanide inhibits mitochondrial oxidative metabolism, which are the major contributing factors to tissue ischemia, wound breakdown and infection.

Sorensen[41] conducted a study that aimed to identify the effects of tobacco smoking on postoperative healing and to determine the impact of perioperative smoking cessation intervention on general, thoracic, orthopaedic, plastic and reconstructive surgeries. Healing outcomes were classified into short-term (necrosis of wound and tissue flaps, healing delay and dehiscence of wounds and sutured tissue, surgical site infections and non-specified wound complications) and long-term (hernias and lack of fistula or bone healing).[41] It was observed that short-term healing complications, including necrosis of wounds and tissue flaps, fistulas caused by necrotic suture or mesh erosion, healing delay and dehiscence of wounds and tissue, were more frequent among smokers, and the assessment of their surgical sites showed significantly more infections. For patients who had breast surgery and breast reconstructive surgery (including post-mastectomy reconstruction), the study showed that wound necrosis was four times higher among the smokers. The study also showed a high incidence of necrotic complications after lung cancer surgery and pelvic organ prolapse repair.[41] For the long-term healing complications, the study observed hernia to be more frequent and a significantly higher incidence of lack of fistula and bone healing among smokers.[41]

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An assessment of long-term outcomes after spinal surgery found failed bone union to be more frequent, and unhealed sternocutaneous fistula and anal fistula were more frequent among smokers. The study concluded that postoperative healing complications occur significantly more often in smokers compared with non-smokers and in former smokers compared with those who never smoked; however, perioperative smoking cessation intervention reduces the risk of surgical site infections.[41]

Other studies[26–31,42,43] have also supported the negative consequences of tobacco use during surgical treatment of cancers. For example, smokers can develop severe pulmonary complications following surgery, and hence many surgeons insist that patients should stop smoking for at least 2 weeks before surgery, whereas others recommend a minimum of 2 months of abstinence from smoking if timing permits.[31] Major pulmonary complications resulting in increased death rates have been reported in patients following pneumonectomy who continued to smoke up to 1 month before surgery compared with those who quit smoking preprocedure.[42] Gritz et al.[31] have reported that wound healing is compromised when smoking as a result of the vasoconstrictive actions of nicotine, an effect that has been shown in breast reconstruction after mastectomy and in other forms of surgery for smoking-related tumours. A prospective study was conducted by Lassig et al.[43] to evaluate the healing in head-and-neck surgical wounds via cytokines and clinical outcomes, as well as cutaneous perfusion by SPY (Novadaq, Technologies Inc, Bonita Springs, FL) angiography in patients undergoing surgery. They studied the association between biomarkers and tobacco exposure, as well as cutaneous perfusion by smoking status, and demonstrated alterations in epidermal growth factor and soluble FMS-like tyrosine kinase-1 at the level of local wound, suggesting modifications in the inflammatory phase of wound healing in current and former smokers.[43] Furthermore, the study showed diminished cutaneous perfusion in a group of smokers undergoing surgery.

Impact of tobacco smoking on radiation therapy

The presence of oxygen in tumours has a significant impact on the outcome of radiation therapy. Several studies[32,44–47] have demonstrated that well-oxygenated tumours respond significantly better to radiotherapy by a factor of 2·5–3 than hypoxic (a condition in which the body or a region of the body is deprived of adequate oxygen supply at the tissue level) tumours, and the increased radio response is known as the oxygen enhancement ratio. The oxygen effect is most commonly explained by the oxygen fixation hypothesis, which postulates that radical-induced DNA damage can be permanently 'fixed' by molecular oxygen, rendering the DNA damage irreparable.[47] Therefore, radiation therapy will give better outcomes for patients who quit smoking before the onset of their treatment since smoking will deprive the body of the much-needed oxygen.[48] Radiation therapy is more effective at killing cells that lie close to capillaries because those cells will be more oxygenated; however, the presence of harmful chemicals in tobacco smoke could impair the blood's ability to carry oxygenated blood to tissues, thereby rendering radiation therapy less effective in patients who continue to smoke during treatment.[48]

Szeszko et al.[75] compared the incidence of Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) grade III and higher acute mucositis in patients with head-and-neck cancer who continued to smoke during radiotherapy with those who quit smoking and concluded that smoking during radiotherapy is not related to acute mucosal toxicity. However, several recent studies[33,49,54,76–78] have reported definitive associations between history of tobacco use and poorer survival or increased risk of death and considered smoking history as an important risk factor for radiotherapy-induced oral mucosal reactions in head-and-neck cancer patients. Tao et al.[76] investigated the risk factors associated with acute oral mucosal reaction during radiotherapy of head-and-neck squamous cell carcinoma and reported smoking as an important risk factor for acute oral mucosal reaction. They indicated that during tobacco combustion, the release of phenols, aldehydes and other chemicals may invade the oral mucosa and reduce the level of epidermal growth factor in the saliva, thereby reducing cell proliferation and inhibiting healing of mucosal injury. Thus, smokers are more likely to have severe radiation-induced oral mucosal reactions during radiotherapy. Browman et al.[49] reported that head-and-neck cancer patients who are active smokers during radiation therapy experienced reduced treatment efficacy, increased toxicity and side effects, have a much lower treatment response rate and a lower 2-year survival. The study found that patients who are recent quitters were similar to those who are long-term quitters in terms of survival at 18 months, an indication that it is never too late to quit smoking in order to relish the benefits of radiation therapy. A clinical investigation[33] was conducted to evaluate the effect of continued tobacco smoking among patients undergoing radiation therapy for head-and-neck cancers and compared the clinical outcomes among active smokers and quitters. It was found that 55% of patients who had quit smoking prior to treatment were still alive 5 years later, compared with 23% of those who continued to smoke.[33] Those patients who continued to smoke also experienced increased risk of side effects, including oral mucositis, loss of taste, xerostomia, weight loss, fatigue, pneumonitis, bone and soft tissue damage and damaged voice quality.[33] Jethwa and Khariwala[54] studied tobacco-related carcinogenesis in head-and-neck squamous cell carcinoma (HNSCC) patients and demonstrated the negative effects on a variety of treatment-related outcomes among smokers. Chen et al.[33] conducted a matched control study of patients undergoing radiation therapy for HNSCC and evaluated the effects of smoking on treatment outcomes. They observed that patients who remain active smokers throughout radiation treatment demonstrated significantly lower 5-year overall survival (23% vs. 55%), locoregional control (58% vs. 69%) and disease-free survival (42% vs. 65%).[33]

Tobacco smoking during radiation therapy also increases the risks of complications associated with the treatment. In a study of women who underwent pelvic radiation therapy for stage I or II carcinoma of the cervix, it was observed that smoking one or more packs of cigarettes per day was a strong predictor of small bowel complications.[52] It was also reported that smoking history is a major risk factor for radiation pneumonitis after radiotherapy for lung cancer.[53] Zevallos et al.[50] observed that laryngopharyngeal cancer patients who smoke, compared with their counterparts who had quit smoking prior to starting radiation therapy, had a higher risk of increased scar tissue development and difficulty with food intake, leading to increased hospitalisations and the need for feeding tubes. A randomised phase III trial of radiotherapy in oropharyngeal cancer patients demonstrated that the risk of cancer progression increases directly as a function of tobacco exposure at diagnosis and during therapy.[51] Ford et al.[35] reported that the risk of second primary tumours is significantly increased in patients who smoke, and this elevated risk applies to malignancies that are both directly or indirectly related to smoking. They

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indicated that patients undergoing radiation therapy for breast cancer are at increased risk of lung secondary primary tumours if they smoke.[35]

Impact of tobacco smoking on chemotherapy

Numerous studies[26–28,32,53–60] have demonstrated that tobacco smoking or tobacco exposure can impact the metabolism of systemic chemotherapy drugs. Petros et al.[32] and Monson et al.[53] have demonstrated that nicotine in tobacco smoke has the potential to affect systemic therapies through various mechanisms and pathways such as increasing the number of drug-binding proteins such as alpha-1-acid glycoprotein, altering the level of some cytochrome P (CYP)-450 enzymes responsible for drug metabolism and altering the level of uridine diphosphate glucuronyltransferase isoenzyme. Catassi et al.[56] investigated the multiple roles of nicotine on cell proliferation and inhibition of apoptosis and its implications on lung carcinogenesis and observed that nicotine impairs the therapeutic effects of chemotherapy. They reported that nicotine and its metabolites can activate nicotinic acetylcholine receptors and beta-adrenergic receptors in both cancerous and non-cancerous tissue, promoting a more aggressive tumour phenotype that may be less responsive to treatment.[56] According to Catassi et al.,[56] nicotine can induce resistance to chemotherapy-induced apoptosis by modulating mitochondrial signalling, which can reduce the effectiveness of cancer treatments because many cancer therapeutic agents induce apoptosis via the mitochondrial death pathway.

Tobacco smoke is known to contain several constituents that can interact with drug-metabolising enzymes and affect systemic treatment outcomes. Cataldo et al.[57] have reported that polycyclic aromatic hydrocarbons and products of incomplete combustion commonly found among carcinogens in tobacco smoke are potent inducers of hepatic enzymes. Many chemotherapy drugs are substrates for hepatic CYP-1A2, and their metabolism can be induced in smokers, resulting in a clinically significant decrease in pharmacologic effects such as reduced blood levels and therapeutic effectiveness; thus, smokers may require higher doses of drugs that are CYP-1A2 substrates.[57]

Although the effects of tobacco smoking on chemotherapy have been explored the least, probably due to a failure to assess or record smoking status and dose during treatment, there are some potential sequelae of smoking, which include exacerbation of drug toxicity and side effects and further impairment of the immune function.[58] Dresler and Gritz[59] have reported that nicotine can alter the basal metabolic rate (thus smokers have increased energy expenditures) that might exacerbate cancer-related cachexia via the induction of hepatic enzymes, and could also increase the metabolism of many pharmaceutical agents, thus potentially decreasing their efficacy. The modulation of several physiologic processes involved in drug disposition has been associated with long-term exposure to tobacco smoke. The most common of these processes are the effects of smoking on CYP-450-mediated metabolism, glucuronidation and protein binding.[32] Perturbation in the pharmacokinetics of anti-cancer drugs by the chemicals in tobacco could result in clinically significant consequences, as these drugs are among the most toxic but potentially beneficial pharmaceuticals prescribed for cancer patients. Xu et al.[60] have investigated the effects that nicotine has in inhibiting apoptosis induced by cisplatin (commonly used to treat advanced oral cancers) in human oral cancer cell lines (Tca8113). The cells were stimulated with nicotine in the presence or absence of cisplatin, and apoptosis was assayed. The authors observed that nicotine inhibited apoptosis induced by cisplatin; survivin played a role in the inhibitory effect of nicotine on apoptosis; the depletion of survivin reduced the protective effect of nicotine against cisplatin-induced apoptosis; and Akt (a physiological survivin kinase) is activated by nicotine.[60] The treatment of Tca8113 cells with phosphatidylinositol 3-kinase inhibitor LY294002 blocked nicotine-induced survivin expression and enhanced cell apoptosis.[60] The studies suggested that exposure to nicotine has negative impacts on the apoptotic potential of chemotherapeutic drugs, and that survivin plays a key role in the anti-apoptotic effect of nicotine.[60]

Smoking and Risk of Second Primary Cancers or Recurrence

Tucker et al.[61] have investigated the risk of second primary cancers related to smoking and treatment of small-cell lung cancer patients. They reported an increase in the risk of second cancers (mostly non–small-cell cancers of the lung) by 3·5-fold among smokers compared with the general population. This translated into 327 excess cancers per 10,000 person-years among those patients who had a smoking history (i.e., who were ex-smokers, recent quitters or current smokers).[61] Furthermore, the risk of a second lung cancer increased in current smokers who received chest radiation, while the risk of second lung cancers was lower for patients who are non-smokers.[61] Chen et al.[62] conducted a study on how the impact of smoking cessation might reduce tumour recurrence in non-muscle invasive bladder cancers and demonstrated that active smokers had a 2·2-fold risk of bladder cancer recurrence compared with those who quit. Their findings further showed that the risk of recurrence might significantly reduce in patients who cease smoking even after the diagnosis of bladder cancer.[62] Do et al.[63] also investigated the correlation between smoking-related second primary tumour development and tobacco smoking habits after diagnosis and definitive treatment in head-and-neck cancer patients. They observed that patients who continue to smoke after a successful treatment of their malignancies have a substantially higher risk of developing smoking-related second primary tumours.[63] Their results demonstrated that smoking cessation subsequent to a diagnosis has potential benefits with regard to risk reduction for secondary primary tumours and that continued smoking is associated with a threefold increase in the risk.[63]

Effects of Second-Hand Smoking and Cancer Treatment

Exposure to second-hand smoke has been identified as a risk factor for various cancers associated with the respiratory system, especially lung cancers.[64] Asomaning et al.[65] have reported that people who are exposed to second-hand smoke have a higher risk of lung cancer compared with active smokers, especially in subjects exposed to tobacco smoke before the age of 25. Tobacco smoke particles that accumulate in the lungs through the respiratory system can lead to sister chromosome exchange, DNA oxidative damage and an increase in the number of p53 mutations in lung cancers.[64,65] Janerich et al.[66] have investigated lung cancer and exposure to tobacco smoke in the household and observed an increased risk in the spouses of smokers. In this case–control study of patients with lung cancer, the authors observed the highest risk in those who were exposed to household smoke during childhood and adolescence years.[66] Household exposure to ≥25 smoker-years

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during childhood and adolescence doubled the risk for lung cancer.[66] A causal link between parental smoking and childhood cancers has also been established.[68,69,70] Recent studies have shown that children born of parents who smoke (father, mother or both, including the preconception period and pregnancy) are at a significantly higher risk of hepatoblastoma, a rare embryonic cancer.[68,69]

Impact of Smoking on Survivorship and QOL after Cancer Treatment

The impact of continued smoking on survivorship and QOL after cancer treatment is very concerning. Parsons et al.[71] described a systematic review on the influence of smoking cessation on the prognosis of early-stage lung cancer and reported that people who continue to smoke after a diagnosis almost double their risk of dying and that smoking cessation after diagnosis improved prognostic outcomes and potentially improved their QOL. Mayne et al.[72] observed that the risk of death is potentially associated with smoking status at diagnosis and increases with increasing tobacco use as measured in pack-years or years of smoking for patients with early-stage HNSCC. Sharp et al.,[77] in a large population-based study, investigated whether smoking at diagnosis is an independent prognostic factor for cancer-specific survival in head-and-neck cancer and found that head-and-neck cancer patients who smoked at diagnosis had a significantly increased rate of death from smoking. Smith et al.[78] investigated the effects of continued smoking in head-and-neck cancer patients undergoing radiotherapy on overall survival, locoregional control, QOL and acute and late toxicities and provided evidence that continued smoking is associated with a lower overall survival and locoregional control and a higher incidence of late toxicities resulting in reduced QOL. Khuri et al.[79] conducted a randomised phase III trial investigating the use of low-dose isotretinoin in the prevention of second primary tumours in stage I and II head-and-neck cancer patients, and reported that current smokers had a higher rate of second primary tumours compared with never or former smokers, with the major sites of second primary tumours being lung, oral cavity, larynx and pharynx. The hazard ratio of death from any cause for current smokers versus never smokers was 2·51, and for current smokers versus former smokers was 1·60, and smoking significantly increases the rate of second primary tumours and death. In another phase III trial, Gillison et al.[51] investigated tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. They studied the associations between tobacco exposure and overall survival and progression-free survival. They reported that the risk of cancer progression or death increases with pack-years or the number of years of smoking, and the increased risk of locoregional (primary site or regional nodes) failure observed in association with smoking habits also suggested a possible direct effect on treatment response and/or disease control. They concluded that the risk of oropharyngeal cancer progression and death increases directly as a function of tobacco exposure at diagnosis and during therapy and is independent of p16 status and treatment.

As one of the most important disease and treatment outcome factors, tobacco smoking can potentially impact the QOL of cancer patients. Chen et al.[73] have investigated the relationship between tobacco smoking and QOL profiles (e.g., overall QOL, pain, fatigue, cough, dyspnoea, appetite change and performance status) in patients with small-cell lung cancer. A total of 223 survivors were involved and were classified into never smokers, former smokers (quitted >1 year prior to diagnosis), recent quitters (quitted <1 year around the period of diagnosis), late quitters (quitted after 1 year post diagnosis) and never quitters. They observed that former smokers reported the best QOL profile, while late or never quitters reported the worst.[73] Recent quitters showed an improved trend in QOL profile and lower reduced appetite compared with late or never quitters, which affirmed the negative impact of smoking on the survivors' QOL and that smoking cessation around the time of diagnosis improves overall QOL and decreases symptoms.[73] Duffy et al.[74] have examined the relationship between depressive symptoms, smoking, problem drinking and QOL among 973 head-and-neck cancer patients. They observed that smoking was negatively associated with patients' QOL and that many patients who smoked showed depressive symptoms and abuse of tobacco use and/or alcohol, which adversely impacted their QOL and survival.[74] In a similar study, Peppone et al.[29] investigated the influence of tobacco smoking on treatment side effects among 947 cancer patients during and 6 months after treatment. They observed that smokers had a higher total symptom burden than non-smokers during cancer treatment, which persisted at 6 months after treatment. Smoking at 6 months after treatment was also associated with higher odds of having severe levels of a number of side effects, including fatigue, concentration problems and depression, which impacted the QOL of participants. However, those who quit smoking had significantly lower symptom burden scores compared with smokers. The authors concluded that patients who continue to smoke throughout cancer treatment are more likely to report a greater symptom burden and poorer QOL.

Health Effects of Smokeless Tobacco

Smokeless tobacco is that which is orally consumed and not burned, and there are a variety of different types being consumed throughout the world, constituting an important worldwide public health issue.[14] In the United States, the principal types of smokeless tobacco are chewing tobacco (cut tobacco leaves) and snuff (moist ground tobacco),[15] while in Sweden, 'snus' tobacco (finely ground moist tobacco) is most commonly used. In India, smokeless tobacco contains tobacco leaf mixed with ingredients such as betel leaf, areca nut and lime (i.e., *gutkha*).[15] In Sudan, the natives use local *Nicotiana rustica* (a tobacco species with high levels of nicotine and nornicotine) to prepare their own snuff, known as *toombak*, which is made from fermented ground powdered tobacco mixed with sodium bicarbonate.[16] Smokeless tobacco is used by over 300 million people in at least 70 countries worldwide, and most of the users (89%) are in Southeast Asia.[14,17] In 2012 about 3·5% of individuals aged ≥12 years (i.e., about 9 million people) in the United States used smokeless tobacco in a month,[15] and in India and Sweden, smokeless tobacco remains by far the most prevalent form of tobacco used.[18,19]

Available literature[14–18] suggests that adverse health consequences of smokeless tobacco vary by the type used. According to a report from the US Surgeon General, the use of smokeless tobacco products can lead to nicotine addiction.[20] Smokeless tobacco consumption has been associated with periodontal diseases, precancerous oral lesions, oral cancer and cancers of the kidney, pancreas and the digestive system.[21,22] Smokeless tobacco has been shown to act as an autonomic and haemodynamic stimulus by increasing the heart rate, blood pressure and epinephrine levels and is associated with death from cardiovascular disease, cerebrovascular disease and cancers.[23,24] A recent systematic

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review concluded that betel quid and tobacco use in India are associated with substantial risks of oral cancer, although studies from the United States and Scandinavia do not show a consistent association.[15]

The Need to Integrate Smoking Cessation into Oncology Programs

Although tobacco smoking is a universal concern, there are unique considerations for tobacco use and patients undergoing cancer treatment. A growing number of studies[26–74] have demonstrated that active tobacco use after a diagnosis and during treatment of cancer can negatively impact treatment outcome, treatment efficacy and the QOL of patients. These existing evidence strongly suggests that it is imperative to support patients undergoing cancer treatment to quit smoking. Though smoking cessation at the time of cancer diagnosis is associated with significant health and treatment benefits, it was estimated that up to 50% of patients who are smokers before a cancer diagnosis continue to smoke during treatment.[80] Therefore, it is essential that patients, their partners and families are counselled on the health and treatment benefits of smoking cessation, and programs should be available to support patients to quit smoking. It is imperative that oncology programs should consistently identify and document the smoking status of cancer patients and support those patients who use tobacco at the time of diagnosis to quit. Although it is not clear whether smoking cessation interventions designed for the general population would have similar efficacy in a cancer patient population, smoking cessation programs should be sustainably integrated into any comprehensive cancer program, and the information should be targeted to the specific benefits of cessation in cancer patients.

In order to provide optimal quality of care to cancer patients, it is imperative that every interaction with a patient and his or her family should be an opportunity to discuss positive lifestyle choices, including tobacco cessation. Such discussions have the potential to help improve treatment outcomes since brief advice given in the context of medical care stands to be an effective cessation tool. A cancer diagnosis also can provide the motivation for smoking cessation (this is particularly true for patients diagnosed with smoking-related cancers), and hence all newly diagnosed cases should be screened for tobacco use and those identified as active smokers should be counselled on the benefits of cessation and encouraged to engage in a tobacco cessation program. Health professionals, including oncologists, nurses and radiation therapists, should play an integral role in assessing smoking cessation since interventions by health care professionals have been shown to be effective in increasing the rate of abstinence in cancer patients.[81] It is important for both health care professionals and patients to recognise that nicotine dependence is a chronic disease that often requires repeated interventions and multiple quit attempts to be successful. Moreover, cancer patients often face challenges (increased psychological distress including depression, anxiety or stress as a result of their diagnosis) that often makes smoking cessation more difficult, especially if the underlying condition is not recognised and treated. Therefore, in order to optimise clinical outcomes, smoking cessation interventions should be an integral component of a standard cancer care continuum from prevention through diagnosis, treatment, survivorship and palliative care. It should involve individual counselling or hospital- or community-based programs to support patients through the process of smoking cessation and maintaining abstinence.

Conclusions

The adverse health effects associated with smoking tobacco have been well demonstrated over the past few decades, and its detrimental effects on treatment outcomes, efficacy and QOL of cancer patients have also been well documented. Cancer patients who continue to smoke during radiation therapy experience reduced treatment efficacy, lower response rate and increased toxicity and side effects. Patients with a history of smoking have poorer prognosis compared with non-smokers. Tobacco smoking during cancer treatment has the potential to adversely affect the overall survival, disease-free survival and disease recurrence. Tobacco smoking has also been shown to negatively impact the outcomes of surgical procedures in general, including increased postoperative complications, reduced QOL, increased length of hospital stay and increased mortality. Tobacco use has been shown to have a direct impact on cellular function by inhibiting apoptosis, stimulating proliferation and decreasing the efficacy of cancer treatment; therefore, quitting tobacco use has the potential to improve treatment response rates and survival, as well as reduces the risk of developing second cancers. Smoking cessation is one of the most important interventions to prevent cancer and is also essential after a diagnosis of cancer to improve clinical outcomes. However, most patients may not be aware of the benefits of cessation; and therefore, all newly diagnosed cases should be assessed for tobacco use, and those identified to be active smokers should receive counselling on the numerous benefits associated with smoking cessation. Smoking cessation programs should be sustainably integrated into any comprehensive cancer program, and the information should be targeted to the specific benefits of cessation in cancer patients. This can potentially reduce symptom burden after treatment, limit the likelihood of treatment interruptions, and improve patients' QOL following treatment.

Statement of Search Strategy

The following databases were searched from January to March 2019 for relevant studies published between 2003 and 2018: Gale Cengage Academic OneFile, PubMed, Scopus, JAMA, Cochrane, Science Direct, American Chemical Society Journals, MEDLINE, SpringerLink, Wiley Online Library. The literature search used the following terms: 'smoking and cancer', 'effect of smoking on cancer treatment', 'effect of smoking on radiation therapy', 'effect of smoking on surgery', 'effect of smoking on cancer chemotherapy', 'smoking and quality of life'. The searches were not limited by study design or language of publication. The full list of sources and the search strategy are available with the authors.

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